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Recent Advancement In Treatment of Prostate Cancer

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ABSTRACT :

Radiotherapy is an appealing treatment option for prostate cancer and has a definite role in all stages of the disease. Over the last decade, breakthroughs in technology, imaging capabilities, and greater radiobiological understanding have profoundly revolutionized prostate cancer radiation, permitting dose escalation and widespread use of hypofractionation. Furthermore, the incorporation of magnetic resonance imaging (MRI) and enhanced physical accuracy of dose administration have offered an impetus to target intraprostatic tumor lesions, which were previously agnostic to the standard radiation target definition concept.

The accumulating results from randomised clinical trials and observational studies demonstrate that ultra-hypofractionation is a safe strategy, but further study is needed to evaluate its efficacy to normal fractionation. Since hypofractionation has yet to produce the theoretically envisioned enhanced biochemical control outcomes, there is continuous uncertainty about the correct alpha/beta ratio for prostate cancer. Finally, a newly published randomised experiment resolved an ongoing debate on the role of elective pelvic lymph node radiotherapy in patients with high-risk prostate cancer, demonstrating a definite advantage when pelvic nodes were treated to 50 Gy. The significance of partial gland dosage escalation/tumor boosting is developing, and additional data is required before this strategy can be used in routine clinical care. In the future, molecular imaging will be critical for assessing disease biology, potentially predicting response, and optimally personalising radiation treatment decisions. We critically reviewed the published literature and offered a practical summary of current prostate radiation advances for busy doctors in this narrative review.

KEY WORDS : Prostate Cancer, Radiotherapy, Hypofractionation, Stereotactic Body Radiotherapy, Dose Escalation, Boost, Clinical Trials.

INRTRODUCTION :

The fifth highest cause of cancer death in males worldwide and the most frequently diagnosed male malignancy is prostate cancer.[1].[2]

Radiation therapy and radical prostatectomy, as the principal treatments for localized prostate cancer, could not be directly compared in terms of their efficacy and side-effect profiles due to the lack of randomised data. Thankfully, this has changed since the UK PROTECT research, a significant randomised trial that found that radiation and radical prostatectomy are equally effective treatments for localized prostate cancer diagnosed by a PSA test, was published in 2016 [3].

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After a median follow-up of 10 years, patients who took part in the experiment saw very low observed rates of disease progression, with no discernible difference between radiation, surgery, and active monitoring. The updated analysis revealed that there was no difference in the rates of distant metastasis between individuals treated surgically and with radiotherapy and that the patients who were observed at the first stage had a marginally but considerably elevated risk of distant metastasis. [4]

PATHO-PHYSIOLOGY :

The prostate gland is positioned in the male pelvis at the base of the penis It is located beneath (in front of) the urine bladder. The prostate is around 3 centimeter long, the size of a walnut, and weighs about 20 gram. Its job is to generate approximately one-third of the total seminal fluid.

The prostate gland requires androgen (testosterone) to operate properly. This is why hormonal therapy (testosterone suppression) works so well. Castrate-resistant tumors are thought to produce androgen intracellular. Cancer starts with a mutation in normal prostate glandular cells, most commonly the peripheral basal cells.

Prostate cancer is most usually diagnosed in the peripheral zone, which is the area of the prostate that may be palpated using a digital rectal examination (DRE).[5]

- Prostate cancer is include in adenocarcinoma . Because it arises largely from the glandular portion of the organ and has characteristic glandular patterns on microscopic examination.
- The cancer cells multiply and expand, initially spreading to the surrounding prostate tissue and producing a tumor nodule.
- A tumor of this type might grow outside the prostate (extra capsular extension) or stay within the prostate for decades.
- Prostate cancer shows metastasis towards bones and lymph nodes. The pro-static venous plexus draining into the vertebral veins is hypothesized to play a role in bone metastases.

STAGES OF PROSTATE CANCER :

Staging describes where the cancer is located, whether it has spread or not, and whether it is impacting other sections of the body or not. the TNM system developed by the American Joint Committee on Cancer is the basis for widely used staging criteria.

The three main components of the TNM system are as follows:

- T (tumor), which describes the size, location, and depth to which the tumor has grown into the tissue
- N (node), which indicates whether cancer cells have spread to nearby lymph nodes or the channels that connect the lymph nodes
- M (metastasis), which indicates whether cancer cells have spread to other organs or tissues.

TNM scale is used to diagnose the types of cancer . When a doctor uses it to determine the stage of your prostate cancer, they will also consider several other factors, such as:-

- Prostate - specific antigen (PSA) levels :- PSA is a substance produced by the prostate that may be found in higher concentrations in the blood of men with prostate cancer. For checking the PSA level , PSA testing is required .[6]

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- Gleason prostate cancer score :- The most commonly used prostate cancer grading system is the Gleason scoring system. The pathologist examines the arrangement of cancer cells in the prostate and assigns a score on a scale of 3 to 5 from two different locations. Cancer cells that resemble healthy cells are given a low score.[7] Cancer cells that appear less healthy or more aggressive are given a higher score.

o Gleason X: It is impossible to determine the Gleason score.

o Gleason 6 or lower: The cells are well differentiated if they resemble healthy cells.

o Gleason 7: The cells appear moderately differentiated, which means they are similar to healthy cells.

o Gleason 8, 9, or 10: The cells appear very different from healthy cells, which is known as poorly differentiated or undifferentiated.\

- **Grade groups :-**

STAGE 1 :- When cancer cells are still localized to the prostate and have not spread outside of the prostate gland, they are classified as stage 1.

o Cancer has spread to one side of the prostate.

o Cancers typically spread slowly.

o PSA levels may be low, and cancer may not be detected during a DRE.

o There is no involvement of lymph nodes or metastasis.

o If the Gleason score is 6 or less and the PSA is less than 10, some cancers detected during a DRE may still be classified as stage 1.

STAGE 2:- Prostate cancer in stage 2 means the cancer has not spread beyond the prostate gland, but it is more likely to spread than cancers in stage 1. The three sub-stages of stage 2 prostate cancer are listed below.[8]

Stage 2A:

o Cancer has spread to both sides of the prostate gland.

o The PSA blood test level ranges from 10 to 19.

o A Gleason score of 6 or less is required.

Stage 2B:

o The cancer has spread to one or both sides.

o The PSA level is less than 20.

o The Gleason rating is 7.

Stage 2C:

o The cancer has spread to one or both sides.

o The PSA lower than 20.

o The Gleason scale ranges from 7 to 8.

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STAGE 3:- Stage 3 prostate cancer is a locally advanced cancer, which means that the cancer cells have spread beyond their original location. With a high Gleason score and elevated PSA levels, the tumor has progressed and is more likely to grow and spread. This stage has three sub-stages, which are listed below.

Stage 3A:

- Cancer has spread to one or both sides of the prostate.
- The PSA is at least 20.
- The Gleason score could reach 8.

Stage 3B:

- The cancer has spread outside the prostate gland, but not to the lymph nodes.
- The PSA could be at any level.
- The Gleason score can range from 1 to 8.

Stage 3C:

- Similar to 3B, but the cancer may not be spreading beyond the prostate.
- The Gleason rating is between 9 and 10.

STAGE 4:- Stage 4 prostate cancer is a form of advanced prostate cancer that has spread (metastasized) to distant sites or lymph nodes. It is further subdivided into two sub-stages, which are listed below.

Stage 4A:

- The cancer has spread to nearby lymph nodes but has not yet spread to surrounding tissues.
- The cancer has spread to another part of the body, such as the bones or distant lymph nodes, at this stage.

TRETMENT SELECTION:- The best available data show that there is no significant difference in overall survival in the majority of instances with possibly curable, localised prostate cancer treated with:-

- Radiation therapy using an external beam
- Stereotactic radiotherapy (SRT)
- Brachytherapy (implantation of radioactive seeds)
- Prostatectomy procedure that is radical.
- Hormone Replacement Therapy
- Particle Beam Therapy

RISK FACTORS:- Major risk factors include age, ethnicity, obesity, and family history. Cancer incidence increases with age, while cancer aggressiveness decreases with age. [9] Prostate cancer risk factors include male gender, advanced age, a positive family history, increased height, obesity,

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hypertension, a lack of exercise, consistently raised testosterone levels, Agent Orange exposure, and ethnicity.

GENETICS :-

- The exact cause of prostate cancer is unknown, but genetics is almost certainly involved.
- Prostate cancer risk is known to be influenced by genetics, ethnicity, and family history.[10]
- Patients with genetic or hereditary prostate cancer tend to develop the disease at a younger age, progress more quickly, are more likely to be locally advanced, and have a higher risk of recurrence after surgery.[11]
- Hereditary prostate cancer is the most heritable of any major male cancer.[12] A family history of hereditary breast and ovarian cancer, also known as Lynch syndrome, increases the risk of prostate cancer, indicating a genetic link.

DIET :-

- Alcohol appears to have little or no effect on the risk of prostate cancer. However, there is some evidence that suggests that drinking red wine in moderation may be beneficial.
- Vitamin supplements do not reduce the risk, and some may even increase it.[14]
- Reduced vitamin D levels in the blood may increase the risk of developing prostate cancer.
- Patients with prostate cancer who are vitamin D deficient have a higher overall and cancer-specific mortality.[16][17]
- This suggests that vitamin D supplements may be beneficial in prostate cancer patients who are vitamin D deficient.

CHEMICAL EXPOSURE AND, EDUCATIONS :-

- The use of statins, metformin, and NSAIDs, particularly those with anti-COX-2 activity, may reduce the risk of prostate cancer.[18]
- Regular aspirin, which is now taken by an estimated 23.7 million men, appears to reduce the risk of prostate cancer.[19] This effect could be due to anti-inflammatory activity as well as decreased angiogenesis.[20]
- Aspirin and NSAIDs appear to be more effective in aggressive prostate cancer patients and those with prostatitis.

SEXUAL ACTIVITY :-

- Multiple lifetime sexual partners or beginning sexual activity at a young age both raise the risk of prostate cancer.
- Although frequent ejaculation may reduce overall prostate cancer risk, lowering ejaculatory frequency is not connected with an increase in the risk of advanced illness.[21]\

INFECTIONS :-

- Infections may be linked to the occurrence and progression of prostate cancer.[22]

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- Chlamydia, gonorrhea, and syphilis infections appear to increase the risk of developing prostate cancer.[23]
- The Human Papillomavirus (HPV) has been proposed to play a role in the occurrence of prostate cancer, but the evidence is inconclusive.

OVERVIEW OF RADIOTHERAPY OPTIONS IN LOCALIZED DISEASE :-

The most recent NCCN (National Comprehensive Cancer Network) guidelines clearly outline the indications for radiation and emphasize the crucial role radiotherapy plays in treating patients from all risk groups.[4] The active surveillance option is preferred in the low-risk category, and radiation is the treatment of choice for patients who are not suitable for surveillance or who chose active treatment. [5]. Radiation therapy combined with short-course androgen deprivation therapy (ADT) appears to improve outcomes in the intermediate-risk subcategory of patients, while radical prostatectomy is equally appropriate for favorable patients in the intermediate-risk category as is image-guided radiotherapy. [6] The most important treatment strategy for high-risk illness is a combination of either radiation with long-term ADT or radical prostatectomy followed by adjuvant or early salvage. When it comes to radiation fractionation, a practising oncologist is confronted with an array of alternatives supported by varying levels of evidence. Prostate cancer was the first site to use hypofractionation in clinical radiation. Hypofractionation uses a larger (conventional) dose per fraction (1.8-2 Gy) than usual.

Prostate cancer radiobiology favors larger doses per fraction due to its unique low alpha/beta ratio, specifically lower than the alpha/beta ratio of surrounding organs-at-risk, resulting in an increased therapeutic ratio when high(er) dose per fraction (i.e. hypofractionation) is used [15]or could be improved. Materials and Methods: We analyzed two mature data sets on radio therapeutic tumor management for prostate cancer, one utilising EBRT and the other permanent seed implants, to determine the susceptibility of prostatic tumors to changes in fractionation.

For the analysis, the usual linear-quadratic model was applied. Prostatic malignancies appear to be substantially more sensitive to fractionation alterations than most other tumors. The value is anticipated to be 1.5 Gy [0.8, 2.2]. This finding is not surprising given that there is an established link between cellular proliferative status and sensitivity to fractionation changes, and prostatic tumors have extremely low percentage of proliferating cells. Conclusions: HDR stands for high dosage rate.

This idea sparked a flurry of clinical research; a number of significant trials [16-20] have been conducted, including a phase 3, non-inferiority trial that enrolled men with localized prostate cancer (pT1b-T3aN0M0, some of which are still ongoing [21, 22]. In contrast to normal fractionation (usually 2 Gy each fraction to a total dose of 74-78 Gy), hypofractionation can be either mild (a dose per fraction 2.5-3.5 Gy to a total dose of 57-60 Gy) or extreme (a dose per fraction 4-10 Gy to a total dose 37.5-40 Gy). Stereotactic body radiation (SBRT) is the only way to accomplish extreme fractionation [23]. Brachytherapy with either high-dose-rate (HDR) or low-dose-rate (LDR) isotopes is one method for increasing the dose to the prostate.

Both brachytherapy methods, which have an advantage of quick dose fall-off, could be employed as monotherapy or in combination with external beam radiation [24-26].

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Finally, one way to improve radiotherapy cure rates in patients with more advanced localized disease was to use elective pelvic radiotherapy, which was controversial for a long time until the randomised trial was published, which likely solved the pelvic radiotherapy issue in prostate cancer [27, 28]. The overarching question is how to choose the proper dose and fractionation in everyday practice, given the quantity of viable alternatives.

OVERVIEW OF LANDMARKS MODERATE HYPOFRACTIONATION STUDIES :-

So far, 6339 individuals have been enrolled in four major contemporary randomised trials that compared moderate hypofractionation to traditional fractionation. CHHIP (UK) (16), RTOG 0415 (US) (19)115 men with low-risk prostate cancer were randomly assigned 1:1 to C-RT (73.8 Gy in 41 fractions over 8.2 weeks), PROFIT (Canada, Europe) (17), and HYPRO (Dutch) trial (20), implying that hypofractionation could increase the biological tumor dose without increasing genitourinary and gastrointestinal toxicity. Hypofractionated irradiation for Prostate cancer (HYPRO.

The CHHIP trial was a randomized, phase 3, non-inferiority trial conducted in the United Kingdom that enrolled patients with prostate cancer from all risk groups and randomly assigned them to one of three arms: conventional fractionation (74 Gy delivered in 37 fractions over 7.4 weeks), the first hypofractionated schedule (60 Gy in 20 fractions over 4 weeks), and the second hypofractionated schedule (57 Gy in 19 fractions over 3.8 weeks). ADT was administered to intermediate and high-risk patients for 6 months. The PROFIT trial, which was conducted in Canada, enrolled 1206 patients with low- and intermediate-risk prostate cancer and randomly assigned them to either normal treatment of 78 Gy in 39 fractions or hypofractionated treatment of 60 Gy in 20 fractions.

RTOG 0415 was a US-based trial that randomly assigned 1115 patients with low-risk prostate cancer to the standard arm, which received 73.8 Gy in 41 parts, or the experimental arm, which received 70 Gy in 28 fractions. Finally, the HYPRO trial was a Dutch study that randomised 820 patients with intermediate-risk (26%) and high-risk (74%) prostate cancer to hypofractionated radiation of 64.6 Gy in 19 fractions (EQD2 90.4 Gy) or conventionally fragmented radiotherapy of 78 Gy in 39 fractions. The vast majority of patients (67%) were given long-term concurrent ADT (median duration 32 months). The majority of patients were treated with 3D-conformal radiation. This was a superiority trial for the hypofractionated treatment group. In a subgroup analysis, patients with high-grade disease (Gleason score 7 and 8-10 patients) did not gain as much with hypofractionation as patients with low-grade disease (Gleason score 6). The overall p-value on the Forrest plot, however, was non-significant (0.16).

The pattern of relapse was analysed in the updated report of the HYPRO trial, which demonstrated a low rate of local relapse in patients with Gleason grade 8 treated with hypofractionated regimen compared to conventionally treated patients .[29]

With the exception of the 57 Gy in 19 fractions arm in the CHHIP trial, which had inferior biochemical control and was not considered an appropriate treatment [16], the main finding consistent across all four trials is a similar (not different) disease-control rate, i.e. biochemical control, in patients randomised into the hypofractionated arm versus patients randomised to conventionally fractionated treatment.

When transferring the outcomes of these studies to ordinary clinical practice, keep in mind that the majority of patients in the CHHIP, PROFIT, and RTOG 0415 trials were low- and intermediate-risk

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individuals. It needs to be shown whether hypofractionation is actually superior for truly high-risk individuals.

SMALLER SIZE HYPOFRACTIONATION PROSPECTIVE TRIALS -FOCUS ON LONG-TERM DATA:-

The updated results of the Fox-Chase hypofractionation experiment after ten years of follow-up [30] with sensitivity analysis for the National Comprehensive Cancer Network (NCCN) were recently released. In this study, 303 men with intermediate- to high-risk prostate cancer were randomly randomised to receive either conventionally fractionated IMRT (76 Gy in 38 fractions) or moderate hypofractionated IMRT (70.2 Gy in 26 fractions). All patients with intermediate- and high-risk illness got ADT for four and twenty-four months, respectively. In addition, high-risk individuals received pelvic lymph node radiation.

Although this trial was supposed to demonstrate hypo fractionation's theoretical superiority in terms of biochemical control, it failed to do so in the first 5-year analysis. In addition, unlike the HYPRO trial, this study found a trend towards a higher 10-year rate of distant metastasis in patients treated with hypofractionated radiotherapy compared to patients treated with conventionally fractionated radiotherapy (14.3% vs 6.4%, unadjusted HR 1.93, 95%CI 0.93-4.00, p=0.08). Other measures (biochemical failure, local recurrence, prostate cancer-specific mortality, and overall mortality) did not show a statistically significant difference between treatment arms (18, 30). Men with low- to high-risk prostate cancer were randomised at random to receive 76 Gy in 38 fractions of 2.0 Gy each (traditional fractionation intensity-modulated radiation).

In low- and intermediate-risk prostate cancer, mild hypofractionation is therapeutic and safe. There is no evident preference for one hypofractionation protocol over the other in terms of clinical execution. When contemplating the adoption of a specific protocol, evaluate the department's experience, capabilities, and logistics. However, there may be insufficient data on the long-term results of hypofractionation in high-risk patients, despite the fact that the HYPRO study clearly demonstrated improved local control in this risk category.

A subgroup analysis of the CHHIP trial showed the efficacy and safety of hypofractionation in the group of frail individuals over the age of 75. Both hypofractionated schedules (60 Gy in 20 fractions and 57 Gy in 19 fractions) fared similarly well in this study, with urine and bowel toxicity remaining low and comparable to the toxicity rates found in individuals younger than 75 years [31].

Men with favorable- to high-risk prostate cancer were randomly assigned to receive 76 Gy in 38 fractions at 2.0 Gy per fraction . However, with sensitivity analysis for the National Comprehensive Cancer Network (NCCN), mature trial findings broadly disputed the theoretically anticipated hypofractionation advantage (i.e. superiority) [30].

Actually, what was mostly seen was that hypofractionation was not inferior to conventional fractionation. This raised the notion that the alpha/beta ratio in prostate cancer is not as low as previously thought, as other investigations revealed higher alpha/beta ratio values, even exceeding 4 Gy [32, 33].

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If the alpha/beta ratio was actually 4 Gy, the hypofractionation-related dosage escalation advantage would be fully eliminated. According to the Widmark trial of ultimate hypofractionation (42.7 Gy in 7 fractions=6.1 Gy per fraction), the associated alpha/beta ratio on logistic regression is around 3 Gy. As a result, more data on higher doses per fraction are needed in the SBRT era to draw more strong conclusions about the true alpha/beta ratio .

This research also revealed that there could be a dose-threshold effect on the dose-response curve. With EQD2 above 80 Gy, it appears that the benefit of continued dosage escalation would be negligible at most, implying a plateau of the dose-response curve at doses of 80 Gy .

IMPROVING OUTCOMES WITH PARTIAL-GLAND DOSE- ESCALATION :-

Because there is a limit to safe whole-prostate dose escalation with external beam radiotherapy, a therapeutic advantage may be possible if we selectively target and enhance the area of the prostate carrying the bulk of the tumor known as dominant intraprostatic lesion (DIL). The widespread use of MRI allows for the dissection of prostate anatomy and the clear visibility of intraprostatic tumors, allowing for their radiation targeting .

The authors used volumetric modulated arc therapy to execute a stereotactic boost to DIL and reported early effectiveness and toxicity endpoints in a recent JCO publication. The FLAME trial authors hypothesized that external beam radiation focused on the macroscopic visible tumor would improve biochemical control in patients with localized prostate cancer. They enrolled 571 patients with intermediate- and high-risk prostate cancer and randomly assigned them to normal therapy (77 Gy in 2.2 Gy daily fractions) or integrated simultaneous tumor boosting to 95 Gy (2.7 Gy fractions, EQD2=115.8 Gy).

Interestingly, there was a numerical, but not statistically significant, improvement in distant metastasis control in patients who received focused boost, suggesting that an extra dose to the main lesion was able to remove subsequent micro metastatic clones .

NEW DATA ON THE ROLE OF ELECTIVE PELVIC LYMPH NODE RADIOTHERAPY :-

For decades, there has been debate about elective pelvic radiation. Several trials, despite a number of limitations, failed to demonstrate improved outcomes when pelvic nodes were treated [27]. POP-RT, an important trial that reassessed this problem, was recently published. In this randomised phase 3 trial, 224 PSMA-PET or MRI-staged patients with high-risk or very high-risk prostate cancer were randomly assigned to prostate only treatment (68 Gy in 2.72 Gy per fraction, EQD2=78-81 Gy) or prostate plus pelvis radiotherapy (50 Gy in 25 fractions). All patients were given long-term ADT. The primary outcome was 5-year biochemical relapse-free survival. The experiment was halted early due to a lower-than-expected incident rate after ten years of follow-up.

Patients randomised to combination treatment had significantly better biochemical control and metastasis-free survival (HR 0.23 and 0.35, respectively). When the relapse pattern was examined, it was obvious that individuals who received only prostate radiation had greater pelvic recurrences and distal metastases. Except for those above the age of 66, all other categories benefited from pelvic irradiation, according to subgroup analysis [28].

In adequately staged patients with high-risk prostate cancer, this trial established pelvic radiation as the standard of care.

CONCLUSION :-

Over the past ten years, prostate cancer radiation has changed as a result of significant trials that cleared the path for widespread acceptance of moderate hypofractionation in normal care. The COVID-19 pandemic also provided motivation for cutting the traditionally lengthy radiation regimens short in order to reduce the danger of infection and conserve clinical and human resources, which were already under a lot of strain. Regarding extreme hypofractionation, which is the focus of multiple ongoing experiments, more information is anticipated.

Prostate cancer radiation has advanced over the past 10 years as a result of important trials that paved the way for the widespread use of moderate hypofractionation in routine therapy. The COVID-19 pandemics also offered impetus to shorten the extensive radiation courses that had previously been in place in order to decrease the risk of infection and conserve clinical and human resources, which were already under a lot of strain. Extreme hypofractionation, which is the subject of multiple ongoing experiments, is anticipated to produce more information.

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