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A Short Review on Advanced Radiotherapy Techniques for Prostate Cancer

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Introduction

Prostate cancer is the second-leading cause of cancer-related death among males in the United States. The three most prevalent contemporary methods surgery, radiation therapy (RT), and follow-up-were not compared in two treatment trials that examined treatment efficacy [1, 2]. The most frequent non-skin cancer in males is prostate cancer (PCa), with an estimated 161,360 cases and 26,730 fatalities in the United States in 2017 [3]. Surgery, RT, and androgen deprivation therapy are all possible treatments for localized PCa (Figure 1) [4]. Using intensity modulated radiation treatment, new developments in RT planning and delivery have made it possible to provide a highly uniform radiation dose distribution (IMRT). With cure rates comparable to those of radical prostatectomy, external beam radiation treatment (EBRT) is regarded as the standard treatment for organ confined PCa.

Nevertheless, it has been shown that cutting-edge systemic radiation treatments significantly improve patient outcomes and survival in cases of metastatic sickness. RT has traditionally been employed primarily for palliation in metastatic disease. Three broad categories may be used for category RT, which is used for both local and advanced disease: X-ray equipment (a linear accelerator) is used in EBRT to generate high-energy photons that are directed at cancer cells outside the body.

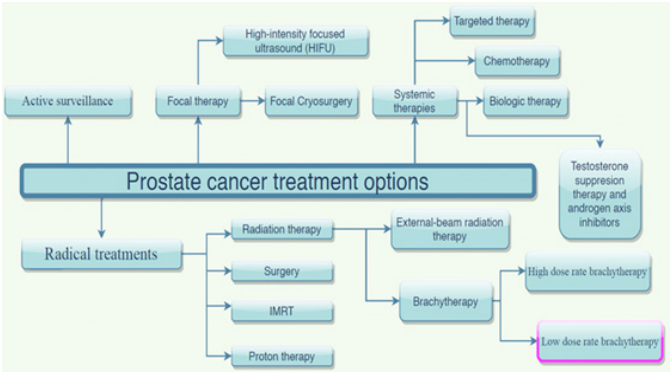

Figure 1: Treatment options available for prostate cancer [4].

Brachytherapy and targeted radionuclide therapy, which employs radionuclides connected to drugs that target cancer to irradiate tumor cells and administer radioactive seeds inside. As PCa is α/β lower than nearby healthy tissue, hypofractionation employs a higher dosage of radiation, reducing the number of fractions and the total amount of time needed for therapy, providing a therapeutic benefit in terms of tumor management and toxicity, increasing patient comfort, and reducing costs [5]. The expanding use of severe hypofractionation has been made possible by recent technological developments in radiation treatment, including intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and stereotactic radiation therapy (SBRT) in several local PCa therapy settings. PCa diagnosis and treatment have dramatically increased as a result of the widespread use of PSA testing. Unfortunately, due to the loss of weight or spread at the time of diagnosis, many men do not benefit from treatments. Sexual, urinary, and bowel function may be adversely affected by prostate cancer therapy [6–11]. The success of two treatment studies was assessed, but they did not compare the three most popular contemporary approaches—surgery, RT, and follow-up [1, 2, and 12]. Additionally, recent developments in RT technology, such as IGRT, IMRT, and SBRT, have gradually made it possible to use extreme hypofractionation (defined) in a variety of local PCa treatment scenarios. SBRT, also known as stereotaxic ablative radiotherapy (SABR), has shown in prospective randomized trials comparable biochemical control and morbidity to traditional fractionated regimens [13,14]. SBRT can also deliver higher doses in hypofractionated regimens.

Methods

Prostate Cancer Immunotherapy

After anecdotal reports of metastatic PCa that improved following local cryotherapy, the concept of immunotherapy for PCa emerged. Immune checkpoint inhibitors and adjuvant treatment are major components of the growing immunotherapy landscape for patients with PCa. The qualities and launching points of possible discoveries are critical to enhancing future results in a landscape with several current studies. After lung cancer and bronchial cancer, the condition is the second greatest cause of cancer death in the US, accounting for 345,000 fatalities annually. This abscopal-type reaction may have

been immune-mediated, based on the identification of autologous antibodies to prostatic tissue [15]. This has greatly increased interest in the development of immune-based PCa therapy methods. At the beginning, research centered on vaccines intended to trigger T-cell and antibody responses in the prostate. The prostate gland is a small organ, so this idea is best suited for PCa. As a result, the immune response to the prostate does not only target malignant cells but also includes autologous antigen-presenting cells that have been *ex vivo* loaded with the tissue-specific antigens prostate acid phosphatase (PAP) and GM-CSF fusion proteins. Although, Sipuleucel-T clearance showed the potential of vaccine treatments for the treatment of PCa, there are currently no approved vaccinations against this illness. Substantial changes in serum prostate-specific antigen (PSA) with sipuleucel-T or other vaccinations when administered as monotherapy or remarkable objective radiography responses have been observed; combination therapies that include vaccines have been developed that include vaccines. In early metastatic PCa patients, PD-1/L1 blocker clinical studies have also found scant evidence of a single impact [16, 17]. As the combination of PD-1 and CTLA-blockade has shown much higher clinical toxicity against advanced PCa but modestly improved clinical efficacy, it will no longer be continued [18]. Enzalutamide's phase III study with or without atezolizumab revealed no change in overall survival [19]. Most of the vaccination regimens used in phase III studies, when used alone to treat advanced PCa, did not improve medical outcomes, despite the fact that all of them were successful in activating antigen-specific T cells. Like immune checkpoint blockade therapy, which is successful against many different cancer types, advanced PCa has not responded well to these treatments when used alone. All these data point to immune suppression mechanisms being at play in PCa. The microenvironment of PCa may be immunologically "cool," as shown by its little invasion of CD8 T-cell effectors and low mutational load. Hence, these immunotherapeutic strategies may work best when combined with drugs that aim to undermine the processes causing immunological and tumor-associated resistance.

Techniques

Radiation Therapy using an External Beam

With the emergence of numerous alternative IGRT procedures, treatment accuracy has considerably increased, enabling both treatment margin optimization and dosage escalation. One of the mainstays of the first therapy for PCa is EBRT, which is also a known risk factor for developing a second primary cancer (SPC). The standard of treatment for low-risk illness is 75–80 Gy, and EBRT is frequently coupled with short-term androgen deprivation for intermediate- and high-risk PCa [20, 21]. SPC is more likely to occur in pelvic organs, including the bladder and rectum [22, 23], and it is generally accepted that EBRT modifications can impact SPC risks, which some have proven. Cohort studies in tumors, despite the fact that previous research has not clearly demonstrated a relationship between improved radiation procedures and SPC hazards. Patients who do not undergo a prostatectomy and/or who have poor pathologic characteristics are typically preferred for EBRT, a possibly curative treatment for metastatic PCa [24, 25]. IMRT, an upgraded version of conformal therapy, was invented in the middle of the 1990s as a result of the development of more complex treatment planning software. IGRT is a crucial adjunct to IMRT in controlling daily changes in target anatomy [26]. Proton radiotherapy (PBT), in contrast to traditional photon (X-ray) therapies, can offer a number of benefits in terms of tumor targeting and dosage exposure.

Intraprostatic Radiopaque Markers

The most often employed technology for the routine localization of prostate cancer in contemporary radiotherapy is cone-beam computed tomography (CBCT). CBCT can be supplemented with intraprostatic radiolucent fiducials (FM). The mean values of recorded movements were compared across groups using analysis of variance and t-tests ($p < 0.05$, significance level). According to the researchers, no statistically significant difference between operators was discovered when comparing photos with and without FM. We noticed a potential reduction in the clinical target volume and target threshold planning using the Van Herk formula, and the use of intraprostatic FMs in daily CBCT appears to be helpful to identify and rectify small rotation mistakes. Daily volume or portal imaging is used to scan FMs, and rigid registration by a radiation therapist is necessary. Using a transrectal or transperineal technique, three radioactive markers, gold seeds, or coils were inserted at the border of the prostate. Only translational displacements may be calculated when utilizing one or two FMs. As the markers essentially act as stand-ins for the prostate's location, the prostate-rectal interface may be reliably determined even when the prostate rotates and deforms. FMs stay stable within the prostate with an average movement of 1.01–2.8 mm, and while two markers are typically put beneath the prostate, one marker is inserted apically [27,28]. There are slight variations in the dosage coverage of pelvic nodules when FM markers and CBCT are used for localization [29,30].

Brachytherapy

Propensity score analysis combined with radical prostatectomy (RP) and low-dose brachytherapy (LDR-BT) for patients with clinically localized, intermediate-risk PCa. The three most often used isotopes for EBRT are currently iodine-125, palladium-103, and cesium-131. LDR-BT has now replaced RP as one of the standard treatment choices for tinier irregularities [31]. No isotope appears to be more efficient than the others, according to the data provided [32]. A therapeutic option for intermediate- or high-risk PCa is high-dose-rate brachytherapy (HDR-BT) boost; however, there aren't many long-term clinical outcomes. In individuals with intermediate- or high-risk prostate cancer, LDR-BT is combined with EBRT [33]. In addition to being used alone and in conjunction with EBRT, dosage escalation using HDR-BT using iridium-192 has also been used to treat locally advanced PCa.

MRI-Guidance

The most frequent cancer in males and the second-leading cause of cancer-related mortality is PCa [34]. MRI offers high-resolution images of the prostate and adjacent structures with good soft tissue distinction [35,36]. Prostate motion was observed using MRI; this further included information on the quantity and quality of prostatic intrafraction motions. Using MRI, the report demonstrated that the prostate's intrafraction mobility and the seminal vesicles' mobility both increased over the duration of treatment. It was shown that intrafractional movement inside the prostatic and seminal vesicles both increased using MRI. During the course of therapy, the seminal vesicles and the prostate gland did not migrate within the same fraction. The seminal vesicle moves anywhere between 4 and 7 millimeters in the AP direction at 15 minutes, 4.7 to 7.2 millimeters in the SI direction at 15 minutes, and 2.7 to 3.4 millimeters in the left-right direction at 10 minutes. Radiation treatment using an MRI has a number of technical difficulties. Due to electromagnetic interference from the linear accelerator and changes in intended transmission, the existence of a magnetic field might make RT transmission more difficult [37]. The first commercial system for MR-guided RT, the magnetic resonance system, was created to lessen these

effects by employing three 60Co sources and a low-field magnet in place of a linear accelerator [38]. This method might make adaptive planning and tumor tracking during radio transmission possible [39–41]. The amount of Watch Ray experience is increasing, and the introduction of the MRI-LINAC system is anticipated to increase the visibility of MRI-based IGRT by supplying better dosimetry.

Conclusion

RT is a popular, secure, and efficient PCa treatment. Radioactive doses to healthy tissue have dropped, harmful effects of RT have lessened, and EBRT planning and delivery have improved. With the advent of these methods, it was feasible to boost radiation exposure without raising toxicity. Although these treatments clearly have a place in treating locally advanced PCa, they have only been applied palliatively to patients whose illness has spread to distant tumor locations. PCa definitively treated with an EBRT has advanced significantly over the years thanks to cutting-edge methods like IMRT or SBRT. Moreover, image guidance permitted a reduction in the toxicity profile and the PTV margin, which led to an increase in the quality of life as indicated by patients. Interaction and fractional internal motion control are both made possible by MRI control.

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