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Commentary: Current Status of Prophylactic Nodal Irradiation in Ultra - Hypofractionated/ Stereotactic Body Radiotherapy for High - Risk Prostate Cancer

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Abstract: ***Ultra - hypofractionated radiation therapy, particularly Stereotactic Body Radiation Therapy (SBRT), has emerged as a promising treatment for localized prostate cancer. However, its role in high - risk prostate cancer, especially when combined with elective nodal irradiation (ENI), is still under investigation. This commentary explores the current evidence supporting the use of ultra - hypofractionated regimens and ENI in high - risk cases. While trials such as HYPO - RT - PC and PACE - B confirm the efficacy of SBRT in intermediate - risk prostate cancer, data on high - risk settings remain limited. Studies, including those by SHARP and Glicksman, highlight promising oncological outcomes with manageable toxicity profiles, though results also indicate variability in genitourinary (GU) and gastrointestinal (GI) toxicities. Ongoing trials like HOPE, SHARP, and PACE - NODE are anticipated to provide further clarity on toxicity and disease control with pelvic nodal irradiation. In conclusion, while SBRT with ENI shows potential, it cannot yet be considered the standard of care for high - risk prostate cancer until more robust, long - term evidence emerges.***

Keywords: Ultra - hypofractionation, Stereotactic Body Radiation Therapy (SBRT), High - risk prostate cancer, Elective nodal irradiation

1. Introduction

Over the past three decades, primary radiation therapy has become a cornerstone in the management of prostate cancer. External beam radiation therapy has evolved into a safe and effective curative option, traditionally involving prolonged treatment courses with conventional 2 Gy per fraction doses over nearly seven weeks. However, a deeper understanding of prostate cancer radiobiology with its low alpha/beta ratio, along with advancements in radiation delivery systems and the integration of advanced imaging modalities in treatment planning and delivery, has enabled the adoption of more abbreviated regimens, employing higher doses per fraction for prostate cancer treatment. (1)

Multiple large, randomized trials have consistently demonstrated that moderately hypofractionated radiation therapy is just as effective as conventional fractionation for treating low - and intermediate - risk prostate cancer. Additionally, emerging evidence suggests that this approach may also be beneficial in high - risk disease, offering a more efficient and equally potent treatment option across risk groups. (2–5) Addressing the pelvic lymph nodes in an elective manner has shown to improve progressive free survival while not increasing the risk of toxicities in certain studies. (6)

Ultra - hypofractionated radiation therapy, delivering more than 5 Gy per fraction, has now become more popular and being practised widely for localized prostate cancer, particularly for low to intermediate - risk cases. Stereotactic Body Radiation Therapy (SBRT), a form of ultra - hypofractionated RT, leverages advanced imaging, planning, and treatment technologies to deliver high - dose radiation in five or fewer sessions. This approach has revolutionized prostate cancer treatment, offering a precise, safe, and convenient alternative to traditional longer courses of radiation. With treatment typically completed in about a week and a half, SBRT is emerging as a cost - effective and efficient option for patients. (7)

While this approach has shown significant promise in treating low to intermediate - risk prostate cancer, its role in managing high - risk prostate cancers remains an area of active investigation. The use of elective nodal irradiation in ultra - hypofractionation for prostate cancer is not yet well established and requires further discussion and research. We explore two aspects in this commentary –The role prophylactic nodal irradiation in ultra - hypofractionated radiotherapy for the treatment of high - risk prostate cancers and status of treatment of high - risk prostate cancer with ultra - hypofractionated regimens.

Role of SBRT in High - Risk Prostate Cancers:
The HYPO - RT - PC and PACE - B trials, both large Phase 3 randomized studies, have highlighted that ultra - hypofractionated radiation therapy is a viable alternative to conventional radiation regimens for prostate cancer, particularly benefiting patients with intermediate - risk disease. These trials demonstrate that this approach can effectively maintain treatment efficacy while reducing the overall treatment burden, making it an attractive option for patients seeking more efficient therapy. (8, 9)

The 2024 AUA/ASTRO guidelines provide a conditional recommendation for the use of ultra - hypofractionation in prostate cancer, specifically for patients with low - or intermediate - risk disease who opt for external beam radiation therapy (EBRT). This recommendation is supported by a Grade B level of evidence. (10)

At present, there is a paucity of Level I evidence to establish the role of SBRT in High - Risk Prostate Cancers.

The SHARP consortium conducted a prospective analysis involving 344 patients with high - risk prostate cancer who were treated with Stereotactic Body Radiation Therapy of which 19% patients received elective pelvic nodal irradiation. With a median follow - up of 49.5 months, the study showed that the estimated four - year biochemical recurrence - free survival rate was 81.7%, while the distant metastasis - free survival rate was 89.1%. Furthermore, the reported crude incidence of late genitourinary and late gastrointestinal toxicities were 2.3% and 0.9%, respectively. (11)

A systematic review conducted by Foerster, and colleagues identified 18 individual studies that met the established criteria for further analysis, along with five additional studies considered relevant. Among these, three trials focused on prostate SBRT that included pelvic nodes: two utilized elective nodal irradiation (ENI), and one concentrated on positive pelvic nodes alone. The other studies examined SBRT solely for the prostate. The results indicated that Grade 2+ acute genitourinary (GU) toxicity rates varied from 12% to 46.7% in studies that involved pelvic node irradiation, while prostate - only studies showed a wider range, from 0% to 89%. For chronic GU toxicity, rates were reported between 7% and 60% for those with pelvic nodes compared to 2% to 56.7% for studies focusing on the prostate. Chronic GI toxicity rates varied from 4% to 50.1% for pelvic nodes and 0% to 40% for prostate - only studies. Biochemical control rates were high, ranging from 82% to 100% after two years and 56% to 100% after three years, although only a limited number of studies provided longer follow - up data. Overall, the findings suggested that SBRT with or without pelvic ENI cannot yet be considered the standard of care for high - risk prostate cancer due to insufficient Level 1 evidence, but it may be suitable for selected patients at specialized centres with access to advanced radiation therapy technologies or in a clinical trial setting. (12)

Role of Elective Nodal Irradiation in SBRT for High - Risk Prostate Cancers:

FASTR trial enrolled 15 patients of high - risk prostate cancer to be treated with SBRT. Radiation dose to the prostate was 40 Gy/15# with a simultaneous integrated boost of 25 Gy/5# to the pelvic nodes. They observed higher than anticipated late toxicities with more than 60% patients experiencing >= Grade 2 toxicities and had to be terminated before phase 2. (13)

Glicksman et. al evaluated four prospective trials examining the safety and efficacy of ultra - hypofractionated elective nodal radiation for prostate cancer, enrolling 165 patients, 59% of whom had high - risk disease. Acute grade 2 genitourinary and gastrointestinal toxicities were 48% and 7.5%, respectively, with late grade 2+ toxicities at 36 months reported as 58% for genitourinary and 11.3% for gastrointestinal, and no grade 4+ toxicities observed. Although bowel and sexual quality of life worsened for up to a year post - treatment, urinary, bowel, and sexual scores significantly improved over time ($p < 0.0001$). The 3 - year biochemical recurrence - free survival rate was an impressive 98%. (14)

Hannan et. al conducted a prospective multi - level MRI - based dose escalation trial for high - risk prostate cancers employing SBRT. The dose to the pelvic nodes ranged from 22.5 to 25 Gy, delivered in five fractions. A total of 55 patients were enrolled, with acute and late grade 2 genitourinary toxicities reported at 25% and 20%, respectively, while gastrointestinal toxicities were 13% and 7%. Late grade 3 genitourinary and gastrointestinal toxicities were observed at 2% and 0%, respectively.

Murthy et. al compared urinary and gastrointestinal toxicities in patients treated with either prostate - only stereotactic body radiation therapy (n=118) or whole pelvic stereotactic body radiation therapy (n=102, 79% node positive, and 21% high risk) for nonmetastatic prostate cancer. Patients were followed for a median of 28 months, with the radiation dose to the prostate being 36.25 Gy in 5 fractions, and 25 Gy to the pelvic nodes in the whole pelvic group. Whole pelvic treatment was associated with significantly higher rates of acute grade 2 gastrointestinal toxicity (29.4% vs.14.7%, p=0.008) and late grade 2 urinary toxicity (45.6% vs.25.0%, p=0.003) compared to prostate - only treatment. Severe late toxicities were rare, with grade 3 adverse effects observed in only 2.5% for urinary and 1% for gastrointestinal toxicities. (15)

A systematic review and meta - analysis conducted by Mohamad et. al aimed to evaluate the safety and evidence for ultra - hypofractionated pelvic nodal irradiation in prostate cancer, focusing on reported acute and late gastrointestinal and genitourinary toxicities. A comprehensive search identified 16 publications, of which 7 met the inclusion criteria, involving 417 patients with intermediate - to high - risk and node - positive prostate cancer. The median dose to the pelvic lymph nodes was 25 Gy over 5 fractions, with the prostate receiving a median dose of 40 Gy. Androgen deprivation therapy was used for a median of 18 months. Results showed that the rates of acute grade ≥2 gastrointestinal and genitourinary toxicity were 8% and 29%, respectively, while late grade ≥2 toxicities were 13% for gastrointestinal and 29% for genitourinary. (16)

The results from ongoing studies such as the HOPE trial (NCT04197141), the SHARP trial (NCT04861415), and the PACE - NODE trial in the UK, are poised to provide critical insights into the role of ultra - hypofractionated pelvic irradiation in high - risk prostate cancer. These trials are testing the efficacy and safety of combining prostate and pelvic irradiation in prostate cancer SBRT. By evaluating acute and late toxicities as well as oncological outcomes, these studies will contribute to refining treatment strategies and determining whether pelvic nodal irradiation can be safely integrated into ultra - hypofractionated regimens for better disease control. (17, 18, 19)

2. Conclusion

The AUA/ASTRO guidelines currently support the use of ultra - hypofractionated EBRT for patients with low - to intermediate - risk prostate cancer, backed by Grade B

evidence. However, when it comes to high - risk prostate cancer and the inclusion of pelvic nodal irradiation with either ultra - hypofractionated regimens or SBRT, the evidence remains less robust. Although emerging studies indicate that the occurrence of late grade 3 adverse events, especially related to genitourinary (GU) and gastrointestinal (GI) toxicity, appears to be relatively low, more comprehensive research is necessary.

Clinical trials like HOPE, SHARP, and PACE - NODE have examined ultra - hypofractionated nodal irradiation, showing promising results with manageable toxicity profiles. However, long - term data, particularly on delayed toxicity and the impact on quality of life, remain limited. Further large - scale randomized trials are needed to provide a clearer understanding of late GU and GI toxicities, which is critical to solidifying SBRT's role in elective nodal irradiation.

In summary, while SBRT shows potential in the treatment of high - risk prostate cancer, especially when paired with elective nodal irradiation, its widespread adoption should be approached cautiously. The findings of future large - scale studies will be pivotal in shaping guidelines, ensuring that SBRT can be implemented with strong, long - term evidence supporting its safety and effectiveness in these high - risk settings.

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