# Adjuvant vs. salvage Radiation Therapy after Radical Prostatectomy: Role of Decipher® in the Era of Personalized Medicine

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Prostate cancer (PCa) is the most common and the second cause of cancer-related deaths among men, with increasing incidence and burden, nationally and globally.[1,2] Radical prostatectomy (RP) has substantially influenced PCa management, providing excellent results in treating the patients.[3] However, likelihood of biochemical recurrence (BCR) remains high, especially in patients with adverse pathological features and these patients should receive postoperative adjuvant radiation therapy (ART) according to the guidelines.

There are some uncertainties about receiving immediate ART after RP in men with adverse pathological features versus salvage radiation therapy (SRT) after BCR. Unlike ART, SRT provides time for urinary and sexual recovery, though it might be associated with undertreatment and risk of disease progression in a subset of patients. In the era of personalized medicine, molecular diagnosis has the potential to distinguish patients with higher risk of progression and metastasis who may benefit from ART.

Decipher® (GenomeDx Biosciences) is a semi-quantitative genomic classifier (GC) with the potential to predict the risk of PCa metastasis after RP in men at high risk of recurrence. The test is based on gene-expression microarray analysis of 22 RNA biomarkers and produces scores ranging between 0 and 1. Results are also classified into low-risk, intermediate-risk, and high-risk groups (for scores < 0.45, between 0.45 and 0.6, and > 0.6, respectively).[3] The probability of recurrence at 10 years after RP has been reported to be 2.6% and 13.6% in men with low risk and high risk Decipher scores respectively.[3] Analyzing data from the Leuven and GRID cohorts also revealed that for every 10% growth in Decipher test score, 10-year metastasis odds increased 53% and 31%, respectively[4] Decipher has been found to be predictive of 5-year Prostate cancer-specific mortality (PCSM) rate. Mortality rates among men with low and intermediate Decipher scores were found to be 0%, compared to 9.4% for high-risk patients.[5]

In a Recent meta-analysis,[6]10-year incidence of metastasis based on Decipher score in low-risk, intermediate-risk and high-risk patients were 5.5%, 15.0% and 26.7%, respectively.

The National Comprehensive Cancer Network (NCCN) classifies intermediate-risk PCa patients into two favorable and unfavorable intermediate risk groups (FIR and UIR respectively). Although regression-free survival is statistically comparable between FIR and low risk (LR) groups, odds of adverse pathology in FIR patients is significantly higher compared to very low (VL) and LR men.[7] Therefore, it is yet to be determined whether wait-and-see followed by SRT is beneficial in the FIR group. Herlemann et al.[8] conducted a retrospective study on 647 patients who were classified as VL/LR (427, 66%) or FIR (220, 34%) risk groups. RP was their initial treatment and Decipher analysis was performed to assess if this genomic test can predict the presence of adverse pathology. FIR patients with low or intermediate risk Decipher scores demonstrated statistically same odds for harboring adverse pathology as NCCN VL/LR groups; however, adverse pathology was observed at significantly higher rates in Decipher high risk FIR patients compared to VL/LR groups (OR = 6.8, $p < 0.001$).

One study in patients with low risk disease based on Decipher testing (score<0.4) showed that receiving SRT compared to ART is not associated with decline in 5-year metastasis free survival; however, ART decreased 5-year metastasis rate from 23% to 6% in patients with scores $\geq$ 0.4.[9]

In order to better identify the appropriate treatment for each patient, Dalela et al.[10] proposed a novel scoring system (ranging 0-4) by merging genomic and histopathology data. Based on their nomogram, when patients with high Decipher scores and aggressive disease characteristics (overall score $\geq$ 2) received ART rather than SRT, an absolute decrease of 17.3% and 32% in clinical recurrence was noted, 5 and 10 years following RP, respectively. While proposing radiotherapy is aimed for PCa relapse prevention, short- and long-term side effects and complications must be taken into account. Treatment-associated cost is also a salient criterion to consider in decision-making. In comparison with 100% adjuvant radiotherapy, Decipher engenders more QALYs and is more effective whilst being more cost-effective. Due to imperfect implementation of the guidelines (which suggest ART for all patients with adverse pathologic features), and subsequent diminished use of ART, Decipher-based treatment happens to be the superior side in QALY and outcomes of the patients, but more expensive than usual care. The incremental cost-effectiveness ratio (ICER) of GC-based care is $90,833 per QALY, which is within reasonable thresholds ($100,000 to $150,000).[11]

Decipher has shown to be capable of predicting disease recurrence, metastasis and PCSM in multiple studies and

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has the potential to predict subgroup of patients who might benefit from ART after RP; however, further investigations are required to prove Decipher's role in clinical outcome improvement in patients receiving Decipher-based treatment compared with those receiving usual care.

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