# Adjuvant radiotherapy controversies in localized prostate cancer

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**Abstract**

The choice of the most appropriate moment to perform radiotherapy in the treatment of prostate cancer is controversial since it can be performed immediately after prostatectomy or as rescue treatment in case of relapse. In this article, a search for the topic is carried out, the clinical trials with the best evidence are selected and the results are analyzed. Although there is benefit in adjuvant radiotherapy, this result is not found in all patients and it is associated with greater late genitourinary toxicity, therefore, the key is in the selection of treatment according to the specific patient.

**Keywords:** Radiotherapy, adjuvant, prostate cancer, prostatectomy.

**Resumen**

La elección del momento más adecuado para realizar radioterapia en el tratamiento del cáncer de próstata es controversial ya que puede ser realizada inmediatamente posterior a la prostatectomía o como tratamiento de rescate ante una recaída. En este artículo, se realiza una búsqueda del tema, se seleccionan los ensayos clínicos con mayor evidencia y se analizan los resultados. Si bien existe beneficio en la radioterapia adyuvante, este resultado no se encuentra en todos los pacientes y sí se asocia a mayor

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toxicidad genitourinaria tardía, por lo tanto, la clave está en la selección del tratamiento según el paciente específico.

**Palabras clave:** Radioterapia, adyuvancia, cáncer de próstata, prostatectomía.

**Introduction**

The ideal moment to perform radiotherapy after Radical Prostatectomy (RP) in patients with risk factors in the pathological anatomy is a matter of multidisciplinary discussion. Historically, one third of patients develop recurrent disease, although with better selection and contemporary surgical techniques, the proportion could be lower (1). The risk of recurrence is higher among men with high-risk features: extra prostatic extension, seminal vesicle invasion, positive surgical margins, and Gleason Scores > 7.

Three randomized controlled trials have reported a reduction by half in biochemical progression with surgery and adjuvant radiotherapy versus surgery alone in patients with high-risk features after RP (2,3,4). One of these trials also showed benefit in metastasis-free survival and overall survival (4). However, it also found increased late genitourinary toxicity and a group of patients who do not benefit from adjuvant radiotherapy, possibly overtreated. This has opened the door to the possibility that early salvage radiotherapy to the prostate bed may provide equivalent control to adjuvant radiotherapy, and one could avoid treating patients with no evidence of disease progression despite risk factors (5).

**Methodology**

A search was performed in PubMed for articles in English, from 2012 to 2022, using the words "Adjuvant Versus Early Salvage Radiation Therapy for Prostate Cancer", selecting those with the highest scientific evidence, according to the number of patients included, prospective trial and follow-up time.

**Results**

In 2020, 3 randomized phase 3 studies were published comparing adjuvant radiotherapy (aRT), i.e., radiotherapy applied after RP, with an undetectable PSA but with risk factors in the pathological anatomy, versus early

salvage radiotherapy (sRT), i.e., that applied once a biochemical relapse is ascertained, with it being essential that this salvage be "early", defined by a PSA greater than 0. 1 or 0.2 ng/ml according to the criteria of each study (6,7,8).

The RAVES trial (6) hypothesized that for patients with pT3 disease or with positive margins after RP, observation and sRT is non-inferior to aRT with respect to avoiding biochemical progression. They performed RT 64 Gy in 32 fractions in the prostate bed, without androgen deprivation therapy. RTTA was administered within 6 months post RP and salvage when PSA was 0.20 ng/ml or more. Patients with positive nodes were not admitted. Freedom from biochemical progression at 5 years was 86% (95% CI: 81-92) for aRT vs. 87% (82-93) in the sRT group (stratified HR 1.12, 95% CI, p= 0.15).

The French GETUG-AFU 17 trial (7) included patients pT3-pT4a, pN0-pNx, and/or positive surgical margins. All patients received 6 months of triptorelin. The primary endpoint was event-free survival. In the sRT group, 115 (54%) of 212 patients initiated study treatment after biochemical relapse. 205 (97%) of 212 patients started treatment in the adjuvant group. The 5-year event-free survival was 92% (95% CI 86-95) in the aRT group and 90% (85-94) in the sRT group (HR 0.81; 95% CI 0.48-1.36; log-rank p = 0 - 42).

In September 2020 the English trial RADICALS-RT (8) is published, which includes patients pT3- T4, Gleason of 7-10, positive margins or preoperative PSA ≥10 ng / mL. Assigned 1: 1 to aRT or sRT, the latter if PSA ≥0 ,1 ng / mL or three consecutive increases. RT to bed allowing nodal irradiation, according to medical criteria. Hormonal therapy with bicalutamide was allowed. With 169 events, biochemical progression-free survival at 5 years was 85% for those in the aRT group and 88% for those in the sRT group (HR 1.10, 95% CI 0. 81-1. 49; p = 0.56).

Regarding the three trials presented above, aRT increased the risk of urinary morbidity, and its authors propose a policy of observation with sRT as standard practice. When defining adverse pathology, according to the patient selection criteria of the Randomized Clinical Trials (RADICALS-RT,

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RAVES and GETUG-AFU), aRT vs early sRT was not significantly associated with a lower risk of All Cause Death (ACD). However, they found that among men with adverse pathology on RP, (pN1 or Gleason 8-10 and =/> pT3a), aRT was associated with a significantly reduced risk of ACD. The authors conclude that adjuvant radiotherapy should be considered in men with pN1 or Gleason score 8-10 and pT3 -pT4 given the possibility of a significant reduction in the risk of ACD.

On the other hand, in 2021 Tilki et al. published a cross-sectional cohort study (9). They included 26118 men with Prostate Cancer comparing aRT vs sRT after RP at very high risk: pN1, Gleason 8-10, pT3-pT4. Of the 26118 men, 819 (3.14%) received aRT (PSA < 0.1 ng/mL) and 4601 (17.72%) sRT with a median PSA of 0.30 ng/mL. Of the group undergoing early sRT, 655 had a persistent PSA, defined as PSA > 0.1 ng / ml postoperatively. 5.71% of patients, including both arms, had pN1 positive lymph nodes, of whom 319 (21.4%) received aRT.

The aRT was associated with a reduced risk of ACD among men with adverse pathology in RP with or without pN1 (P=0.01), whereas no significant association was observed in men without adverse pathology in RP (P=0.28).

After excluding men with adverse pathology who had persistent PSA from the early sRT cohort, we found a reduced risk of ACD with aRT compared with significant early sRT without pN1 (P=0.02) or with pN1(P=0.04), which is consistent with other studies demonstrating the benefit of performing aRT on pN1 patients, even with impact on overall survival (10,11,12).

**Conclusion**

Randomized clinical studies published in 2020 have demonstrated the safety and efficacy of salvage radiotherapy. We should keep in mind that the cutoff point for salvage radiotherapy in these studies was 0.1 or 0.2 ng/ml so we should advocate for strict PSA monitoring of patients with risk factors for relapse. In turn, in these studies the very high-risk subpopulation (Gleason >/= 8, pT4, pN1) was 8 to 18%, 1 to 4% and 1 to 4% respectively, so it could be under-represented. In this group of very high-risk patients, adjuvant radiotherapy could be the choice, we must wait for prospective studies where this patient population is represented to have higher quality evidence.

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