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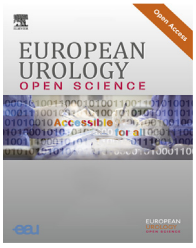

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High-risk Locally Advanced Prostate Cancer: Multimodal Treatment Is the Key

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While prostate-specific antigen (PSA) screening is not recommended in the general male population and its use is declining, an increasing number of patients are being diagnosed with high-risk and/or locally advanced prostate cancer (HRLAPC). Locally advanced tumors, for which there is no consensus definition, represent an intermediate entity between localized and metastatic stages, with a high propensity for biochemical or clinical progression and cancer-related death [1]. Treatment intensification is essential to reduce mortality in this subgroup of patients. The ideal strategy should achieve both local control and treatment of microscopic disease, and only a multimodal approach can meet these requirements. The need for such a strategy is first suggested by the poor biochemical and clinical outcomes for patients with HRLAPC when treated with monotherapy (radical prostatectomy [RP], external beam radiation therapy [EBRT], or brachytherapy [BT]) despite curative intent [2]. In this regard, several large randomized controlled trials (RCTs) and prospective series have shown prolonged biochemical progression-free survival (PFS) and overall survival with the combination of (neo-) adjuvant androgen deprivation therapy (ADT) and RT compared to either treatment alone, thus consolidating this as a level-one proven standard of care in major guidelines for high-risk disease (Table 1). It has been shown that dose escalation is associated with better biochemical outcomes (even when combined with ADT) and recent developments in RT techniques, such as intensity-modulated RT and stereotactic body RT, result in more efficient sparing of organs at risk. In addition, subgroup analyses have indicated that patients with high Gleason score (GS) and high clinical T stage appear to achieve better survival with RT than with RP [3]. In this context, the combination of BT boost with EBRT has shown promising results and probable superiority to EBRT dose escalation, especially for patients with unfavorable pathological features. In a large retrospective study by Kishan et al [4] that included patients with GS 9–10 disease, EBRT + BT with ADT was associated with better prostate cancer–specific mortality (PCSM) and distant metastasis outcomes compared to EBRT + ADT or RP.

Otherwise, with advances in surgical techniques, urologists are increasingly inclined to offer surgery to patients with HRLAPC to reduce the tumor burden and for accurate staging to better identify patients for adjuvant strategies. No study has directly compared this strategy to RT + ADT. It is undeniable that recent large observational series have shown the efficacy of RP with extended pelvic lymph node dissection for patients with HRLAPC in terms of survival, approaching or even exceeding the outcomes obtained with EBRT + ADT. However, it seems important to keep in mind that these series have significant weaknesses: most have a retrospective design with inherent selection bias, while EBRT is more often offered to patients with comorbidities or unfavorable factors (in terms of biopsy GS, PSA, and

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Table 1 – Selected prospective data from trials evaluating a multimodal strategy for patients with high-risk locally advanced prostate cancer

Trial	Population	Median FU (yr)	Arms	Outcomes
Addition of RT to ADT				
Intergroup T94-0110	*n* = 1205 (1057 stage T3–4)	8	ADT vs ADT + RT ADT: lifelong LHRH agonist or bilateral orchiectomy	10-yr OS: 45% vs 55% ($p = 0.001$)
SPCG-7	n=875 T1b–2 G2–3 or T3 (78%), PSA < 70 ng/ml, N0	7.6	ADT vs ADT + RT ADT: GnRH agonist for 3 mo followed by continuous antiandrogen	10-yr OS: 61% vs 70% ($p = 0.004$) 10-yr DSS: 76% vs 88% ($p < 0.001$)
Addition of long-term ADT to RT				
RTOG 85-31	*n* = 945 T3 (82%) or N1 (18%)	7.6	RT vs RT + ADT ADT: goserelin for >2 yr until progression	10-yr OS: 39% vs 49% ($p = 0.002$) 10-yr DSS: 78% vs 84% ($p = 0.005$)
EORTC 22863	*n* = 415 T1–2 N0 G3 or T3–4 N0–1	9.1	RT vs RT + 3 yr of ADT ADT: cyproterone acetate 1 mo, goserelin 3 yr	10-yr OS: 40% vs 58% ($p = 0.0004$) 10-yr DSS: 10% vs 30% ($p < 0.0001$)
Addition of RT after RP				
SWOG 8794	*n* = 431 pT3 cN0 (± involved SM)	12.6	Observation vs adjuvant RT	10-yr bPFS: 30% vs 53% ($p < 0.05$) 10-yr OS: 66% vs 74% ($p < 0.023$)
EORTC 22911	*n* = 1005 pT3 (± involved SM) pN0 pT2 + involved SM pN0	10.6	Observation vs adjuvant RT	10-yr bPFS: 41% vs 60.6% ($p < 0.001$)
ARO 96-02	*n* = 388 pT3 (± involved SM) pN0	9.3	Observation vs adjuvant RT	10-yr bPFS: 35% vs 56% ($p = 0.0001$) 10-yr OS: 82% vs 86% (NS)

FU = follow-up; RT = radiation therapy; ADT = androgen deprivation therapy; RP = radical prostatectomy; SM = surgical margin; LHRH = luteinizing hormone–releasing hormone; GnRH = gonadotropin-releasing hormone; OS = overall survival; DSS = disease-specific survival; bPFS = biochemical progression-free survival; NS = not significant.

clinical stage). Patients treated with surgery have traditionally received earlier and more frequent salvage treatment after failure [5], and it is now accepted that earlier salvage treatment is associated with better PFS [6]. Salvage therapy after local RT failure rarely has curative intent and typically consists of ADT, which has only palliative intent. It should be noted that the majority of patients included in the RP series also received adjuvant treatment (RT ± ADT) because of pathological features, which is another argument for a multimodal approach. It is therefore clear that a surgical strategy can achieve comparable results to RT + ADT only in combination with adjuvant treatments (Table 1). Indeed, Tilki et al [7] have shown that RP + adjuvant RT and ADT (called *MaxRP*) and RP + BT + ADT (called *MaxRT*) achieve similar PCSM rates among men with GS 9–10 disease.

However, use of multimodal strategies may result in a higher risk of toxicities, as reported by Jarosek et al [8]. The combination of two treatments (RP + EBRT or BT + EBRT) increased the risk of late urinary adverse events in elderly patients. In the decision-making process, the use of adjuvant treatment (and its inherent toxicities) should be discussed with patients.

Recent data indicate that patients with HRLAPC represent a heterogeneous group with different outcomes depending on baseline characteristics, and it is conceivable that monotherapy may be sufficient for a (small) subgroup of patients. It should not be forgotten that some series of high-risk patients have shown that nearly 40% treated with RP alone [9] and nearly 30% treated with EBRT alone [10] had no evidence of relapse at 5 yr. These results suggest that patients with (very) good prognosis might benefit from surgery or RT alone, with excellent long-term survival. Conversely, patients in the poorest prognosis subgroup (GS >7 and stage cT3–4 and/or PSA >20 ng/ml) needed a multimodal strategy. This argues for careful patient selection in decision-making and the need to develop new treatment strategies to improve survival outcomes. Several studies testing chemohormonal or second-generation antiandrogen therapy as part of neoadjuvant treatment have shown promising results in terms of pathological response, but long-term outcomes are still lacking.

In conclusion, the strong data available indicate that a multimodal strategy remains the backbone of treatment for patients with HRLAPC. RP (in a multimodal approach) and long-term ADT with EBRT are currently recommended as first-line treatments. Initial tumor characteristics (GS, T stage) and the toxicity profiles of the treatments should be part of the decision. Patients should be well informed on the basis of current data and possibly included in RCTs. Future directions should focus on identifying the highly selected subgroup of patients for whom monotherapy would be sufficient, as suggested by several series. Therapeutic decision-making will certainly be redefined in light of recent advances in imaging (prostate-specific membrane antigen positron emission tomography/computed tomography), genomic biomarkers, and new drug developments.

Conflicts of interest: The authors have nothing to disclose.

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