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## The Moving Landscape of Locally Advanced Prostate Cancer: Combination of External Irradiation and Endocrine Treatment and/or Multimodal Approach

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The pioneering results of the European Organization for Research and Treatment of Cancer [1] and the Radiation Therapy Oncology Group [2] trials devoted to locally advanced prostate cancer (PCa) have shown a significant gain in overall survival in favor of the combination of external irradiation and long-term androgen deprivation therapy (ADT) and raised the question of whether the gain was due to ADT alone rather than to the combined approach. Many trials were launched to assess the value of a long-term ADT plus or minus irradiation.

Mottet and al [3] report on the results of a phase 3 multicentric randomized trial devoted to 264 N0–X M0 patients classified as cT3–4 ( $n = 254$ ) or pT3 with positive biopsies of the capsule ( $n = 10$ ), randomly allocated between long-term (3-yr) ADT alone or combined with three-dimensional conformal radiotherapy (3D-CRT). ADT was administered with a luteinizing hormone-releasing hormone (LHRH) agonist (leuprorelin) given subcutaneously with a 3-monthly depot and an oral antiandrogen (flutamide) for 1 mo to inhibit flare-up. In the ADT arm alone, 33 patients received salvage radiotherapy (RT) for local progression. Irradiation was focused on the pelvis with a four-field box technique ( $46 \pm 2$  Gy) followed by a boost on the prostate and periprostatic tissue ( $22 \pm 2$  Gy). The patients were <80 yr old with a World Health Organization (WHO) performance score (PS) <2. There was no pathologic central review. Of this sample, 49% had Gleason score 4–6, and 22.5% of the patients had a baseline PSA  $\geq 20$  ng/ml. With a median follow-up of 67 mo, there was a significant difference in favor of the combined approach with regard to local-regional control ( $p < 0.0001$ ), metastatic progression ( $p = 0.018$ ), and progression-free survival ( $p < 0.001$ ), but there was no improvement in overall survival or disease-specific survival

because of an insufficient target sample size and/or not mature enough results. With the same concept, a life-long ADT, and a greater target sample size, the trials of Warde et al. [4] and Widmark et al. [5] shared these results but with added value for survival.

Warde et al. [4] reported on a cohort of 1205 N0–X patients (T3–4 [ $n = 1057$ ], T2 prostate-specific antigen [PSA] >40 ng/ml [ $n = 119$ ], or T2 PSA >20 ng and Gleason >8 [ $n = 25$ ]) randomized between life-long ADT (bilateral orchidectomy or LHRH agonist) with or without RT (65–70 Gy to prostate  $\pm 45$  Gy to pelvic lymph nodes). With 6-yr median follow-up, the combined approach significantly reduced the risk of death ( $p = 0.033$ ) and of specific death ( $p = 0.001$ ). The SPCG-7/SFUO 3 trial [5] accrued a cohort of 875 N0–X M0 patients (T3, any WHO grade [ $n = 682$ ]; T1b–T2 G2–3 [ $n = 168$ ]; unknown [ $n = 5$ ]). Patients were randomly assigned to endocrine treatment alone (3 mo of total androgen blockade followed by continuous endocrine treatment using flutamide) or to the same endocrine treatment combined with 3D-CRT (70 Gy to the prostate): With 7.6-yr median follow-up, the combined approach halved the 10-yr PCa-specific mortality ( $p < 0.0001$ ) and decreased overall mortality ( $p < 0.004$ ). These results mimic what was observed for locally advanced breast cancer, with the greatest effect being achieved with the combination of RT and endocrine treatment given concomitantly [6]. Nevertheless, these findings issued from trials conceived during the 1990s, and they needed to be put in the present context: Is the staging of locally advanced PCa today the same as yesterday? Do we need life-long ADT? How can irradiation be improved? What is the room of a multimodal treatment?

Waiting for a better classification of high-risk PCa thanks to a genomic approach, high-risk PCa still represents a

heterogeneous group, including high-risk localized PCa T1–2 NO–X M0, Gleason score 8–10, or PSA >20 ng/ml, and locally advanced PCa. We would like to focus our attention on locally advanced PCa cT3–T4 NO–X M0. First, the cT staging based on the endorectal examination has to be completed by multiparametric magnetic resonance imaging to evaluate the alteration of the capsule and/or the seminal vesicles. If capsular extension is confirmed, or even seminal vesicle invasion, two options could be discussed theoretically within the frame of a multidisciplinary approach, depending on the physiologic age of the patient, WHO PS, comorbidities, life expectancy, International Prostate Symptom Score (IPSS) and uroflowmetry data, and the patient's own feeling.

If the combined approach is chosen, as in the trials mentioned previously [3–5], an extended pelvic lymph node dissection (ePLND) has to be proposed beforehand to young patients. Provided a sufficient number of nodes is removed, such a procedure has prognostic and therapeutic value [7] and has a real impact on the determination of the planning target volume and the duration of ADT. Patients with negative pelvic lymph node status (pN0) or no more than two nodes involved without capsular rupture (pN1 to <3) will not receive pelvic lymph node irradiation, whereas those with more than two nodes will. The technique of irradiation is image-guided intensity-modulated RT [8] with prostate dose escalation delivering 78 Gy over 39 fractions, to improve local control without increasing the risk of acute and late toxicity, and 50–56 Gy to the pelvic lymph nodes during the same treatment time. Although there are no phase 3 randomized trials, life-long ADT is no longer needed because of its potential morbidity, its impact on health-related quality of life, and the difficulty of compliance; a 3-yr ADT will be administered with an LHRH analog [9] or more for patients pN1 to >2.

The surgical option, taking into account the expertise of the surgical team, is radical prostatectomy with an ePLND. Patients should be informed that should there be poor prognostic factors, such as capsule perforation and/or involvement of seminal vesicles on the pathology report, adjuvant RT could be discussed, knowing that 20% of the patients not need adjuvant irradiation because of downstaging (pT2 R0–1 pN0). For patients classified as pT3a–c R0–1 pN0 with an undetectable PSA, adjuvant irradiation of the prostatic bed (66 Gy) or entrance into a phase 3 randomized trial assessing the value of adjuvant RT +/- ADT will be proposed [10], whereas pN1>2 patients will be treated like locally advanced PCa.

In the individual screening era, with PCa with less tumoral burden and the evolution of surgical and radiation techniques, the practice and the exchanges offered through multidisciplinary dialogue contribute to the therapeutic

strategy, providing physicians and patients with more choices. In addition to with the eclecticism of loco-regional treatments, it is likely that other endocrine manipulations based on new biochemical pathways will be offered in the near future.

**Conflicts of interest:** The author has received honoraria from Janssen for attending advisory board meetings and from Astellas and IPSEN for conference participation.

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