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Adjuvant or Immediate External Irradiation After Radical Prostatectomy with Pelvic Lymph Node Dissection for High-Risk Prostate Cancer: A Multidisciplinary Decision

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Abdollah et al. [1] selected, from a cohort of 6357 patients who underwent radical prostatectomy with extended pelvic lymph node dissection in the same institution between 1988 and 2008, a series of 1049 patients with pathologically advanced prostate cancer (PCa). The aim was to evaluate the impact of risk prognostic factors on survival with a regression analysis, and then to evaluate the relationship between adjuvant radiotherapy (ART) and survival according to the number of selected risk factors. The adjuvant treatments were based on the clinical judgment of each treating physician according to clinical and cancer characteristics after discussion with the patient. The following distribution was noted: no treatment ($n = 370$), ART ($n = 243$), ART plus androgen deprivation therapy (ADT) ($n = 288$), and ADT alone ($n = 148$). In all, only pathologic Gleason score $\geq$8, pT3b/T4 stage, and positive lymph node count $\geq$1 (pN1) were independent predictors of cancer-specific mortality ($p \leq 0.02$). The cumulative number of these predictive factors was used to develop a risk score and ranged from zero to three, with the following breakdown: zero (43.6%), one (22.1%), two (20.7%), and three (13.6%); only patients with a risk score $\geq$2 benefited from ART with lower cancer-specific mortality and overall mortality rates ($p = 0.006$).

Despite the fact that all variables have been included in the multivariable analyses, the methodology is subject to bias, which may lessen the relevance of the results and their potential clinical impact: (1) the absence of a pathologic review, since the Gleason score has changed along time and a Gleason score was a criterion of eligibility for ART and/or ADT; (2) the mixture of pN0 and pN1 patients who do not share the same outcome; (3) the lack of any clinical guidelines to tailor adjuvant treatments; (4) the difference in the choice of the planning target volume, the techniques of external irradiation, and the dose range; (5) the heterogeneity of ADT modalities and the duration of ADT; (6) the absence of a report of morbidity for adjuvant treatments, especially as the authors emphasize the potential morbidity of ART; and (7) the lack of prostate-specific antigen (PSA) values after surgery. Therefore, the comparison with randomized trials devoted to ART after radical prostatectomy with pelvic lymph node dissection [2–4] is a challenge, because those trials dealt with pT2 R1 pN0, pT3a–4 R0–1 pN0 patients with irradiation focused on the prostatic bed with conventional doses (60–64 Gy) without ADT in the experimental arm. To facilitate the comparison with daily practice, we will consider the indication of ART for patients classified as pN1 M0, who may harbor a coexistent systemic risk, and then for pN0 patients, in whom the risk of relapse is more local.

For pN1 patients, although the authors claim a benefit for ART alone, the use of ART remains controversial; the evidence of a benefit from randomized trials is needed, likely from an ART/ADT combination, as in breast cancer [5]. Indeed, Da Pozzo et al. [6] showed in a cohort of 250 pN1 patients with a median follow-up of 91.2 mo that patients treated with ART/ADT ($n = 129$) had better cancer-specific survival ($p < 0.001$) compared with patients receiving ADT. Lawton et al. [7] reported in a subset analysis of 173 patients (cT3/pT3) with biopsy-proven lymph nodes, randomly allocated between radiation therapy (RT) plus long-term adjuvant ADT with luteinizing hormone–releasing hormone agonist ($n = 98$) and RT alone ($n = 75$), a gain in overall survival ($p = 0.03$) in favor of the combined approach. At the present time, the combined approach

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with long-term ADT is considered a 2b level of evidence in the European Association of Urology guidelines [8]; the radiotherapy technique has to be optimized with intensity-modulated radiotherapy, taking into account the new definition of the pelvic lymph node areas [9].

I agree that pT3–4 pN0 patients with Gleason score 8–10 (risk score: 2) do need ART. In the randomized trials that have been mentioned, which consistently show a 50–60% reduction in the risk of PSA progression, the main eligibility criteria was pT3 (pT2R1, pT3–4 for the European Organization for Research and Treatment of Cancer [EORTC] trial). In the Southwest Oncology Group (SWOG) trial [2] that compared ART with observation in pT3 pN0 patients, ART did improve metastasis-free survival ($p = 0.016$) and overall survival ($p = 0.023$), contrary to the ARO and EORTC trials, which displayed better local control and biochemical disease-free survival. In the EORTC trial, designed 20 yr ago, the 10-yr results showed that patients with positive surgical margins seem to benefit from ART to a greater extent than patients with negative or close margins; and in terms of clinical progression-free survival, ART seems to be detrimental in patients $\geq$70 yr, without any definite reasons for this apparent negative effect [3]. This latter impact was not reported in the SWOG or ARO trials and is not seen in daily practice. The tolerance of ART is quite good; in the ARO trial with pT3 disease and undetectable PSA, tridimensional conformal radiotherapy was given with a low risk of late toxicity (0–3%) [4].

At the current time, the treatment policy for pT3–4 pN0 patients must take into account the PSA value after surgery to separate patients with undetectable PSA from patients with a detectable PSA who are at very high risk of relapse and who require a combined approach [10], with perhaps a dose escalation.

Nevertheless, no trial has shown so far that immediate RT is better than early salvage RT; thus, for R0 patients with Gleason score $<$8 and an undetectable PSA, many surgeons prefer to wait for a biochemical relapse and start RT as soon as the patient's PSA concentration reaches 0.2 ng/ml. RT can begin even earlier thanks to ultrasensitive assays that are able to detect a PSA concentration as low as 0.01 ng/ml—the lower the concentration, the better the outlook [11].

In conclusion, the decision whether to proceed with adjuvant RT for high-risk PCa (pT3–4 pN0–1 M0) after radical prostatectomy or to postpone RT as an early salvage procedure in case of biochemical relapse remains difficult. In daily practice, the urologist should explain to the patient before radical prostatectomy that adjuvant irradiation could be applied if the patient has negative prognostic risk factors. Ultimately, the decision to treat needs a multidisciplinary approach to determine the optimal timing of radiotherapy when used and to provide justification when not used, which will help in the discussion between the referent physician and the patient.

Conflicts of interest: Michel Bolla is a board member of Janssen and has received payment for lectures, including service on speakers bureaus, from Ipsen and Astellas.

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