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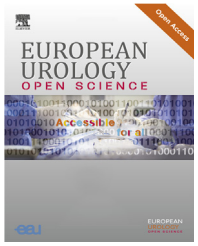

European Association of Urology

Opinion: Open Science

Sentinel Lymph Node Biopsy: A Great Opportunity for Personalized Radiotherapy in Prostate Cancer

Stéphane Supiot [a,b,*], *Loic Ah-Thiane* [a], *Caroline Rousseau* [c,d]

[a] *Department of Radiotherapy, ICO René Gauducheau, Saint-Herblain, France;* [b] *Nantes University, Nantes, France;* [c] *Department of Nuclear Medicine, ICO René Gauducheau, Saint-Herblain, France;* [d] *CRCI2NA, UMR 1307 Inserm-UMR 6075 CNRS, Nantes University, Nantes, France*

In intermediate- and high-risk prostate cancer (PCa) without clinical node involvement, whole-pelvis radiotherapy (WPRT) is a matter of debate. The benefits of WPRT compared to prostate-only radiotherapy (PORT) did not seem significant according to results from the GETUG-01 and RTOG 9413 randomized trials [1]. By contrast, the POP-RT trial showed significant improvements in biochemical recurrence-free survival (RFS), disease-free survival, and distant metastases–free survival, despite no significant difference in overall survival [2]. The literature is also mixed regarding the toxicity of pelvic radiotherapy. An excess of late genitourinary toxicities (grade II or higher) after WPRT was observed in the POP-RT trial [3], while a population-based study involving thousands of men did not reveal a meaningful difference in toxicity between WPRT and PORT [4].

Similarly, the therapeutic value of extended pelvic lymph node dissection (ePLND) remains unclear [5] but the procedure may increase the accuracy of initial staging. The European Association of Urology guidelines recommend use of a probability cutoff of 7% for the updated Briganti nomogram for intermediate- or high-risk PCa to guide decisions on whether or not to perform ePLND [6]. Sentinel lymph node (SLN) biopsy (SLNB) has a main aim of reducing eventual morbidity associated with ePLND while preserving maximal sensitivity for diagnosis of metastatic disease [7].

In this issue of *European Urology Open Science*, de Barros and colleagues [8] suggest a new way to address the question of WPRT in PCa. The authors hypothesized that SLNB could help in selecting patients with clinically node-negative (cN0) disease with a risk of nodal involvement of >5% estimated using the Briganti nomogram who might benefit from WPRT. They conducted a retrospective comparison of two groups: patients in the non-SLNB group were treated with PORT, while patients in the SLNB group were treated with WPRT in cases of pathological involvement (pN1) or with PORT otherwise (pN0). In comparison to the non-SLNB group, the SLNB group had a higher rate of biochemical RFS (hazard ratio 0.38, 95% confidence interval 0.25–0.59; $p < 0.001$), which was the primary outcome, and a higher rate of radiological RFS, but there was no difference in disease-specific survival. Caution is required when interpreting these results: the benefits observed might not be due to the SLNB intervention, which could be a major confounding bias, but to the effect of pelvic irradiation instead, and could thus support the benefits of WPRT for all patients. Despite not being a validated standard, WPRT is currently prescribed in many centers, and SLNB should then be seen as a way to safely de-escalate nodal irradiation. Another limitation mentioned in the study and important to remember is that patients were selected if they had cN0 status on the basis of findings on conventional imaging (computed tomography [CT] scan), which could lead to underestimation of the disease stage in patients treated only by PORT, whereas patients in POP-RT may have been more accurately selected according to negative positron emission tomography (PET)/CT imaging. This could at least partly explain why the 7-yr rates for biochemical and radiological RFS seemed lower than expected in the non-SLNB group. However, molecular imaging is now widely used for more accurate disease staging, notably given the good performance of prostate-specific membrane antigen (PSMA) PET/CT, and should become a recommended standard of care, which may limit the need for invasive SLNB [9]. The authors state

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* Corresponding author. Service de Radiothérapie, Institut de Cancérologie de l'Ouest René Gauducheau, Boulevard du Professeur Jacques Monod, 44800 Saint-Herblain, France. Tel. +33 2 4067 9913.
E-mail address: stephane.supiot@ico.unicancer.fr (S. Supiot).

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that a further study is needed to better address the relevance of SLNB in patients undergoing PSMA PET/CT, as one of their previous publications suggested combining both modalities in order to achieve accuracy of >90% for nodal staging in newly diagnosed intermediate- and high-risk PCa [10]. In addition, mild to moderate toxicity was surprisingly high in the SLNB group of patients undergoing prostate-only radiotherapy, with no clear reason for this unexpected result. SLNB should therefore still be considered as an experimental staging procedure.

The study highlights that SLNB could help in personalizing treatment for individual patients. In particular, SLNB could identify the tumor drainage pattern for each patient, leading to individualized radiotherapy instead of probabilistic irradiation based on delineation atlases. The French GETUG group identified areas of drainage during SLN procedures, such as the pararectal, perivesical, perivesicular, presacral, pudendal, inguinal, and retroperitoneal drainage regions, that are not covered by standard delineation recommendations but are nonetheless at risk of invasion [11]. For instance, an in silico study showed that tailoring pelvic irradiation according to individualized SLN detection was technically feasible and was relevant in avoiding missing some unusual areas of drainage [12]. This concept can be called lymph flow–guided radiotherapy and its aim is to avoid recurrence in unexpected areas and limit the volume of irradiated healthy tissue.

In conclusion, after emerging as a breakthrough in surgery to diminish the need for extensive nodal dissection, which is responsible for a significant morbidity burden, SLNB seems to be a promising concept for precision medicine in personalized radiotherapy, especially in urological malignancies such as prostate cancer.

Conflicts of interest: The authors have nothing to disclose.

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