

available at www.sciencedirect.comjournal homepage: www.eu-openscience.europeanurology.com

European Association of Urology



Open to Debate: For

Pelvic Lymph Node Dissection at the Time of Radical Prostatectomy: Extended, of Course

Giorgio Gandaglia^{*}, Francesco Barletta, Francesco Montorsi, Alberto Briganti

Unit of Urology/Division of Oncology, Gianfranco Soldera Prostate Cancer Lab, IRCCS San Raffaele Scientific Institute, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy

Article info

Article history:

Accepted May 26, 2022

Associate Editor:

Guillaume Ploussard

Clinical guidelines recommend performing an extended pelvic lymph node dissection (ePLND) at the time of radical prostatectomy (RP) in patients with prostate cancer (PCa) at higher risk of lymph node invasion (LNI) according to preoperative stratification tools [1]. Of note, ePLND is associated with a longer operative time and the risk of complications associated with this procedure can be as high as 15% [2]. The likelihood of experiencing adverse perioperative outcomes varies according to the extent of the procedure itself [2]. That being said, an anatomically defined ePLND that includes removal of at least the external iliac, obturator, and internal iliac nodes plays a key part in the surgical management of selected PCa patients for the following reasons.

First, ePLND represents the only available procedure that allows for reliable nodal staging. Despite the great enthusiasm for the use of prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) as an upfront staging procedure, this imaging modality has low sensitivity for detection of microscopic nodal metastases [3]. This is key, since in approximately

60% of all contemporary patients with pN1 disease treated at our institution the maximum diameter of nodal metastases is ≤ 5 mm. Therefore, negative PSMA PET/CT imaging cannot replace ePLND, especially in men with higher-risk disease, since the accuracy of PSMA PET/CT decreases as the risk of LNI increases [4]. PSMA PET/CT can instead be used in addition to LNI risk tools to further optimize candidate selection and the anatomical extent of ePLND [5]. Moreover, PSMA radioguided ePLND has also shown suboptimal sensitivity in detecting all micrometastatic nodal disease [6]. For all these reasons, there is no imaging-based approach that can currently replace ePLND as far as nodal staging is concerned.

Second, exact knowledge of the true nodal status and of the number of positive lymph nodes gleaned from ePLND has crucial implications for the selection of patients who should be considered for additional therapies [1,7,8]. Men with pN1 disease represent a heterogeneous patient group who may undergo different postoperative approaches, provided reliable and accurate nodal staging is obtained at the time of surgery. In this context, it should be highlighted that results from the RADICALS, GETUG-AFU 17, and RAVES trials testing the role of adjuvant versus early salvage radiotherapy (RT) cannot be extrapolated to men with pN1 disease since this population was almost not represented in these studies [9–11]. Therefore, for optimal use of RT in these patients we need to mainly rely on retrospective evidence, which invariably involved heterogeneous outcomes. For example, while some of these men can be initially observed after surgery (namely, those with a limited burden of nodal invasion and undetectable postoperative prostate-specific antigen), as also recommended by current guidelines, in others (namely, those with higher nodal burden) a “wait

^{*} Corresponding author. Department of Urology and Division of Experimental Oncology, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. Tel. +39 02 26435663; Fax. +39 02 26437298. E-mail address: giorgio.gandaglia@gmail.com (G. Gandaglia).

and see” protocol, even if followed by timely administration of early salvage RT, is associated with a detrimental effect on survival [12]. Similarly, the use of androgen deprivation therapy immediately after surgery improves patient outcomes, especially in those with more adverse features [8]. Therefore, the exact knowledge of the true nodal status and of the extent of nodal dissemination given by ePLND is essential for tailoring the optimal management for these men [13].

Third, it has been hypothesized that ePLND might even have oncological benefits [14]. However, two randomized controlled trials (RCTs) failed to prove a significant impact of ePLND over limited PLND on early oncological outcomes [15,16]. Despite the scientific validity of both studies, issues related to significant variability in the anatomical extent of PLND, relatively short follow-up, and the inclusion of a high proportion of men with low probability of experiencing LNI and adverse outcomes could have undermined the effect of ePLND over a limited approach. To support this hypothesis, it is worth reporting that Lestingi et al. [15] observed better oncological control in the ePLND arm for patients with pre-operative biopsy grade group 3–5, with a 52% reduction in the risk of biochemical recurrence. This is also indirectly confirmed by the POP-RT trial, in which RT treatment of nodal areas in men with LNI risk $\geq 20\%$ and adequate follow-up was associated with significantly better biochemical- and metastases-free survival rates [17]. Moreover, previous retrospective studies demonstrated that removal of a higher number of nodes was associated with better disease control among patients with pN1 disease [14]. Thus, it is plausible that the benefit from ePLND may mainly be experienced by patients with a higher risk of LNI. Finally, it has been suggested that more extensive dissection at the time of RP reduces the risk of salvage RT failure for men with biochemical recurrence, thus supporting the importance of maximizing pelvic disease control to improve outcomes [18].

In conclusion, although available RCTs failed to show an oncological benefit associated with ePLND at the time of RP in PCa patients, this procedure still represents the only staging procedure able to accurately identify LNI. The accurate knowledge of the real number of positive lymph nodes that can be obtained only by performing an anatomically defined ePLND has important implications for postoperative management and patient counseling. Indeed, information gained via staging may ultimately translate to better patient outcomes because of timely administration of postoperative treatments. Similarly, in men with more favorable characteristics, ePLND might also play a therapeutic role by maximizing local disease control while decreasing postoperative treatment intensification at the same time.

Conflicts of interest: The authors have nothing to disclose.

References

- [1] Mottet N, Cornford P, van den Bergh RCN, et al. EAU guidelines: prostate cancer. Arnhem, The Netherlands: European Urology Association; 2021.
- [2] Cacciamani GE, Maas M, Nassiri N, et al. Impact of pelvic lymph node dissection and its extent on perioperative morbidity in patients undergoing radical prostatectomy for prostate cancer: a comprehensive systematic review and meta-analysis. *Eur Urol Oncol* 2021;4:134–49.
- [3] van Leeuwen PJ, Emmett L, Ho B, et al. Prospective evaluation of 68Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer. *BJU Int* 2017;119:209–15.
- [4] Stabile A, Pellegrino A, Mazzone E, et al. Can negative prostate-specific membrane antigen positron emission tomography/computed tomography avoid the need for pelvic lymph node dissection in newly diagnosed prostate cancer patients? A systematic review and meta-analysis with backup histology as reference standard. *Eur Urol Oncol* 2022;5:1–17.
- [5] Meijer D, van Leeuwen PJ, Roberts MJ, et al. External validation and addition of prostate-specific membrane antigen positron emission tomography to the most frequently used nomograms for the prediction of pelvic lymph-node metastases: an international multicenter study. *Eur Urol* 2021;80:234–42.
- [6] Gondoputro W, Scheltema MJ, Blazeovski A, et al. Robot-assisted prostate-specific membrane antigen-radioguided surgery in primary diagnosed prostate cancer. *J Nucl Med*. In press. <https://doi.org/10.2967/jnumed.121.263743>.
- [7] Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol* 2014;32:3939–47.
- [8] Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7:472–9.
- [9] Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet* 2020;396:1413–21.
- [10] Sargos P, Chabaud S, Latorzeff I, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol* 2020;21:1341–52.
- [11] Kneebone A, Fraser-Browne C, Duchesne GM, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol* 2020;21:1331–40.
- [12] Tilki D, Chen MH, Wu J, et al. Adjuvant versus early salvage radiation therapy for men at high risk for recurrence following radical prostatectomy for prostate cancer and the risk of death. *J Clin Oncol* 2021;39:2284–93.
- [13] Vale CL, Fisher D, Kneebone A, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet* 2020;396:1422–31.
- [14] Abdollah F, Gandaglia G, Suardi N, et al. More extensive pelvic lymph node dissection improves survival in patients with node-positive prostate cancer. *Eur Urol* 2015;67:212–9.
- [15] Lestingi JFP, Guglielmetti GB, Trinh QD, et al. Extended versus limited pelvic lymph node dissection during radical prostatectomy for intermediate- and high-risk prostate cancer: early oncological outcomes from a randomized phase 3 trial. *Eur Urol* 2021;79:595–604.
- [16] Touijer KA, Sjoberg DD, Benfante N, et al. Limited versus extended pelvic lymph node dissection for prostate cancer: a randomized clinical trial. *Eur Urol Oncol* 2021;4:532–9.
- [17] Murthy V, Maitre P, Kannan S, et al. Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): outcomes from phase III randomized controlled trial. *J Clin Oncol* 2021;39:1234–42.
- [18] Fossati N, Parker WP, Karnes RJ, et al. More extensive lymph node dissection at radical prostatectomy is associated with improved outcomes with salvage radiotherapy for rising prostate-specific antigen after surgery: a long-term, multi-institutional analysis. *Eur Urol* 2018;74:134–7.