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Clinical-Prostate cancer

# Prostate cancer patients with lymphatic node involvement detected by immunohistochemistry. Is the effort worthwhile?

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**Abstract**

**Introduction:** Lymph node (LN) status is one of the main prognostic factors in localized prostate cancer (CaP) patients after surgery. Examining palpable lymph nodes with hematoxylin and eosin (HE) is the most common approach in clinical practice; however, immunohistochemistry (IHC) has been reported to increase the LN detection rate. We reviewed the oncological results of patients with LN metastasis detected by IHC.

**Methods:** Retrospective study of CaP patients who underwent lymphadenectomy at the time of the prostatectomy. Extended lymphadenectomy was performed with complementary indocyanine green (ICG) guidance. Three groups were considered according to LN status. Definition of the pN+ group was made if LNs were detected by HE, occulted lymph node-positive (OLN+) was considered when ≥ 1 LN was identified with IHC and occulted lymph node-negative (OLN-) if no metastatic nodes were found. Oncological outcomes were reported regarding PSA kinetics, biochemical recurrence (BCR), need for secondary treatments and metastasis-free survival (MFS).

**Results:** A total of 283 patients with a median follow-up of 69 months were included in the study. Immunohistochemical assessment revealed metastatic LNs in 8.9% of patients. The rate of locally advanced disease and positive surgical margins was higher in the OLN + and pN + groups vs the OLN − group ($P < 0.05$). At the end of follow-up, 19%, 44% and 52% of patients from the OLN -, OLN + and pN + groups experienced BCR ($P < 0.001$), respectively. Additionally, 2.6%, 17% and 22% of patients developed metastatic progression from the OLN -, OLN + and pN+ group ($P < 0.001$), respectively. In the multivariate analysis, the OLN + group had a higher risk HR: 12 (95% CI, 2.4-56; $P = 0.002$) of metastatic progression in comparison with OLN − patients. This difference was not observed in the risk of biochemical recurrence HR 1.8 (95% CI, 0.9-3.8; $P = 0.09$).

**Conclusion:** Conventional HE histological analysis underdiagnosed nearly 10% of patients. IHC-detected patients were at higher risk of metastasis development than OLN - patients. This report highlights the importance of optimizing the anatomopathological analysis properly. 

*Keywords:* Prostate cancer; Lymph node assessment; Pathological evaluation; Immunohistochemistry

## 1. Introduction

Lymph node (LN) invasion is one of the main prognostic factors in a priori localized prostate cancer (CaP) patients after surgery. It is widely known that patients with 3 or

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more metastatic lymph nodes significantly decrease overall survival (OS) [1,2]. Detecting lymphatic metastasis depends mainly on the extension of the lymphadenectomy and the histological evaluation of the specimens.

Extended pelvic lymph node dissection (PLND) at the time of the prostatectomy comprises the goal standard for lymphatic assessment in patients at high risk for nodal metastasis. Around 10%-30% of patients are unnecessarily exposed to develop complications, which is the main drawback of this procedure [3]. Several techniques are being investigated to guide a more accurate dissection with a lower complication rate [4].

There is no standardized recommendation for the pathological handling or sampling of PLND specimens. The variability in the histological evaluation influences the final LN status and subsequent risk stratification of patients. Examination of palpable LNs with Hematoxylin and eosin (HE) is the most common approach in clinical practice; however, immunohistochemistry (IHC) has been reported to increase the LN detection rate [5−7]. Additionally, patients with metastatic LN detected by IHC seem to have a worse prognosis than "real" pN0 patients [5]. The evidence on this topic is limited due to the high expenses related to the technique and its uncertain benefits.

In this study, we reviewed the oncological results of patients with LN metastasis detected by HE or IHC.

## 2. Methods

We conducted a retrospective study at Instituto Valenciano de Oncología from February 2014 to December 2019 involving CaP patients who underwent lymphadenectomy at the time of the prostatectomy. Data was extracted from "FIVO SEREXTHO," a structured query language ambispective prostate cancer register approved by the ethical committee (Institutional Review Board approval CaP-ROS-IVO). The study was completed in accordance with the principles of the Declaration of Helsinki.

Consecutive cases of CaP patients eligible for prostatectomy and lymphadenectomy were included in the study. Surgery started with an ultrasound-guided injection of indocyanine green (ICG) into both lobes of the prostate. PLND encompassed the removal of ICG-stained nodes within the small pelvis (obturator, internal, external, presacral and common iliac) and was completed with an extended template for these regions. A more comprehensive description of this technique has been previously published [8]. Patients who underwent radiotherapy or hormonotherapy prior to surgery were excluded from the study. The surgery was performed laparoscopically by three experienced urologists.

Tissue from ICG-stained LNs was sectioned into two slides, each 4$\mu$m wide, at intervals of 250 $\mu$m until the specimen was fully examined. The first pair of slides underwent HE staining. If no metastasis was found, IHC was performed on the remaining sample using cytokeratins AE1/AE3, FLEX RTU, Dako Omnis. ePLND nodes were only tested with HE for metastasis detection. Following a prior report [5], three groups were defined based on histopathological analysis. pN+ patients: 1-2 LNs detected by HE. Occulted lymph node-positive (OLN+): ≥ 1 LN identified with IHC that HE did not initially detect. Occulted lymph node-negative (OLN-): No metastatic node was found, neither by HE in the ePLND specimen nor by HE/IHC in the ICG-PLND specimen. This distribution is simplified in Fig. 1. pN+ patients with ≥3 positive nodes were excluded from the study to ensure group comparability.

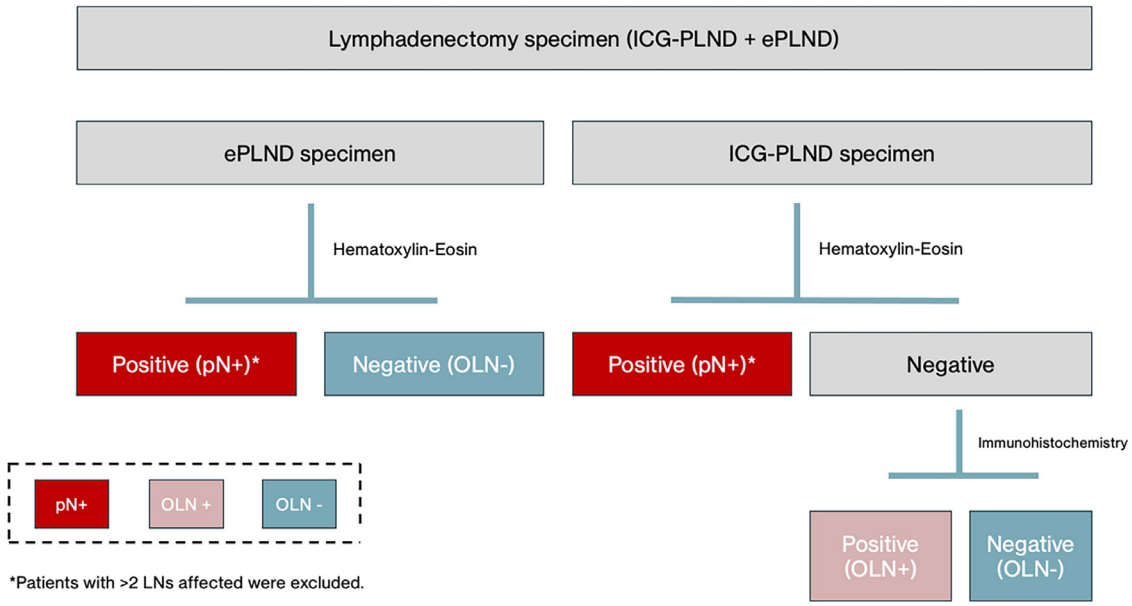


Fig. 1. Group distribution according to histological analysis.

Regular follow-up visits were scheduled at week 6th after surgery and every 3-6 months according to the patient's characteristics. Biochemical recurrence (BCR) was awaited before planning secondary treatments, which were determined at the discretion of an uro-oncological committee.

The endpoints of the study included the rate of PSA persistency after surgery, the rate of patients that required secondary strategies, the rate of patients that remained with undetectable PSA, the analysis of BCR-free survival and the metastasis-free survival (MFS). Persistent PSA was considered if the first postoperative PSA exceeded 0.1 ng/ml. BCR was defined as 2 consecutive PSA ≥0.2 ng/ml during follow-up, and undetectable PSA was considered a PSA <0.1 ng/ml without the need for secondary strategies

### 2.1. Statistical analysis

A comprehensive statistical analysis using R software was conducted to assess the relation between 3 groups defined by the LN status: OLN -, OLN +, and pN +. The chi-square test was used to analyze categorical variables, and the t-test for continuous variables. BCR and MFS were estimated using the log-rank test and presented as Kaplan-Meir curves. Univariate and multivariate analysis was performed for LN status, Gleason Score, clinical stage, and surgical margins to detect the association of each variable with BCR and MFS.

## 3. Results

A total of 283 patients with a median follow-up of 69 (51-83) months were included in the study. IHC assessment revealed metastatic LNs in 23 out of 256 (8.9%) patients who would have been misclassified by HE. Only 1 patient from the OLN + group had 2 LNs affected, the rest of them had tumor cells on a single node. The median size of the IHC-detected LN metastasis was 0.4 mm (range 0.02 − 1.2). The median size of the LN metastasis in the pN + group was 3.5 mm (range 0.2−25).

In contrast with the OLN - group, the majority of patients from the OLN+ and pN+ groups had locally advanced disease and positive surgical margins. These differences were statistically significant, $P < 0.01$ and $P = 0.02$, respectively. Table 1 summarizes the main clinicopathological characteristics of the overall cohort.

Noticeable, most patients from the pN+ group (70%) required secondary strategies, whereas 75% of patients from the OLN − group remained with undetectable PSA at the end of the follow-up. These differences are summarized in Table 2.

At the end of follow-up, 6 (2.6%) OLN -, 4 (17%) OLN + and 6 (22%) pN+ patients developed metastatic progression. Median time to metastatic progression was 48 (32 −66), 61 (45−66) and 58 (31−79) months for OLN -, OLN + and pN+ patients, respectively. This difference was not statistically significant ($P = 0.8$). In univariate analysis, LN status was the strongest predictor of BCR, whereas Gleason was the strongest predictor for metastasis development. In the multivariate analysis, OLN + patients were not proven to be at higher risk of biochemical recurrence HR 1.8 ($P = 0.09$) however, they were at higher risk of metastatic progression HR 12 (95% CI 2.4−56; $P = 0.002$) than OLN - patients. This data is summarized in Table 3.

As shown in Figs. 2 and 3, patients from the OLN + group had a biochemical and clinical trend more similar to the pN+ group than to the OLN- group. Only one death was registered in the overall cohort.

Table 1
Baseline characteristics

| | Group | | | |
|---|---|---|---|---|
| | OLN - | OLN + | pN + | *P*-value |
| n | 233 | 23 | 27 | |
| Age, median (IQR) | 64 (58−69) | 65 (58−68) | 64 (57−69) | 0.97 |
| PSA, median (IQR) | 6 (4.5−9) | 8 (6−12) | 7.1 (4.9−9.7) | 0.09 |
| Pathological stage, n (%) | | | | <0.001 |
| pT2 | 143 (61) | 4 (17) | 6 (22) | |
| pT3 | 90 (39) | 19 (83) | 20 (78) | |
| Gleason score, median (IQR) | | | | 0.13 |
| 6−7 | 211 (90) | 19 (83) | 24 (89) | |
| 8−10 | 22 (10) | 4 (17) | 3 (11) | |
| R1 status, n (%) | 81 (35) | 14 (61) | 14 (52) | 0.02 |
| LNs removed, median (IQR) | 18 (11-24) | 21 (14-28) | 20 (15-22) | 0.44 |

## 4. Discussion

Current evidence on the value of immunohistochemistry in assessing the LN status of CaP patients is scarce. In our experience, 8.9% of patients were additionally detected by IHC and they were at a higher risk of metastatic progression than OLN - patients.

Identifying the status of LNs in radical prostatectomy specimens has a significant impact in terms of prognosis

Table 2
Biochemical evolution and need for secondary treatments of the overall cohort

| | Group | | | |
|---|---|---|---|---|
| | OLN - | OLN + | pN + | *P*-value |
| **PSA persistency after surgery, n (%)** | 5 (2.2) | 1 (4.4) | 5 (19) | <0.001 |
| **Biochemical recurrence, n (%)** | 45 (19) | 10 (44) | 14 (52) | <0.001 |
| **Need for secondary treatments, n (%)** | 30 (13) | 8 (35) | 19 (70) | <0.001 |
| **Undetectable PSA, n (%)** | 174 (75) | 10 (44) | 6 (22) | <0.001 |

Table 3
Univariate and multivariate analysis of biochemical recurrence and metastasis progression

| | Univariate analysis | | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | Biochemical recurrence RR (95% CI) | *P* value | Metastasis progression RR (95% CI) | *P* value | Biochemical recurrence RR (95% CI) | *P* value | Metastasis progression RR (95% CI) | *P*-value |
| Lymph node status | | | | | | | | |
| OLN − | - | - | - | - | - | - | - | - |
| OLN + | 2.6 (1.3−5.1) | < 0.001 | 6.5 (1.8−23) | 0.004 | 1.8 (0.9−3.8) | 0.09 | 12 (2.4−56) | 0.002 |
| pN + | 3.8 (2.1−6.9) | 0.007 | 9.1 (2.9−28) | < 0.001 | 2.4 (1.3−4.7) | 0.006 | 16 (3.5−73) | < 0.001 |
| Gleason score | | | | | | | | |
| 6-7 | - | - | - | - | - | - | - | - |
| 8-10 | 3.6 (2.1−6.4) | < 0.001 | 14 (5−39) | < 0.001 | 2.7 (1.5−4.9) | 0.001 | 25 (6.2−97) | < 0.001 |
| pT status | | | | | | | | |
| pT1-pT2 | - | - | - | - | - | - | - | - |
| pT3-pT4 | 3.3 (1.9−5.5) | < 0.001 | 2.8 (0.96−8) | 0.06 | 2.3 (1.3−3.9) | 0.003 | 0.62 (0.17−2.3) | 0.5 |
| R1 status | | | | | | | | |
| R0 | - | - | - | - | - | - | - | - |
| R1 | 1.9 (1.2−3.2) | 0.01 | 2.1 (0.8−5.7) | 0.2 | 1.23 (0.72−2.11) | 0.4 | 0.4 (0.1−1.6) | 0.2 |

and management. Messing et al. [9] found that pN1 patients who underwent early androgen deprivation therapy (ADT) experienced a benefit in progression-free survival, cancer-specific survival (CSS) and OS in comparison with the observation cohort. However, it is of note that the prognosis of pN1 patients is highly heterogeneous. Patients with < 3 positive LNs can achieve a CSS of 70%−85% at 10 years; meanwhile, it diminishes to 30%−70% when ≥ 3 LNs are affected [1,2,9]. Since all of the OLN + patients in our cohort had < 3 metastatic LNs, we decided to exclude patients with ≥ 3 LNs in the pN+ group to make groups more comparable. In this sense, we found a similar prognosis in terms of BCR and MFS in the OLN + and pN + groups.

The detection of metastatic LNs varies according to the approach: macroscopic handling of histologic specimens, frozen-section examination, total inclusion of the tissue, serial sectioning, or the application of alternative techniques such as IHC or real-time reverse transcriptase

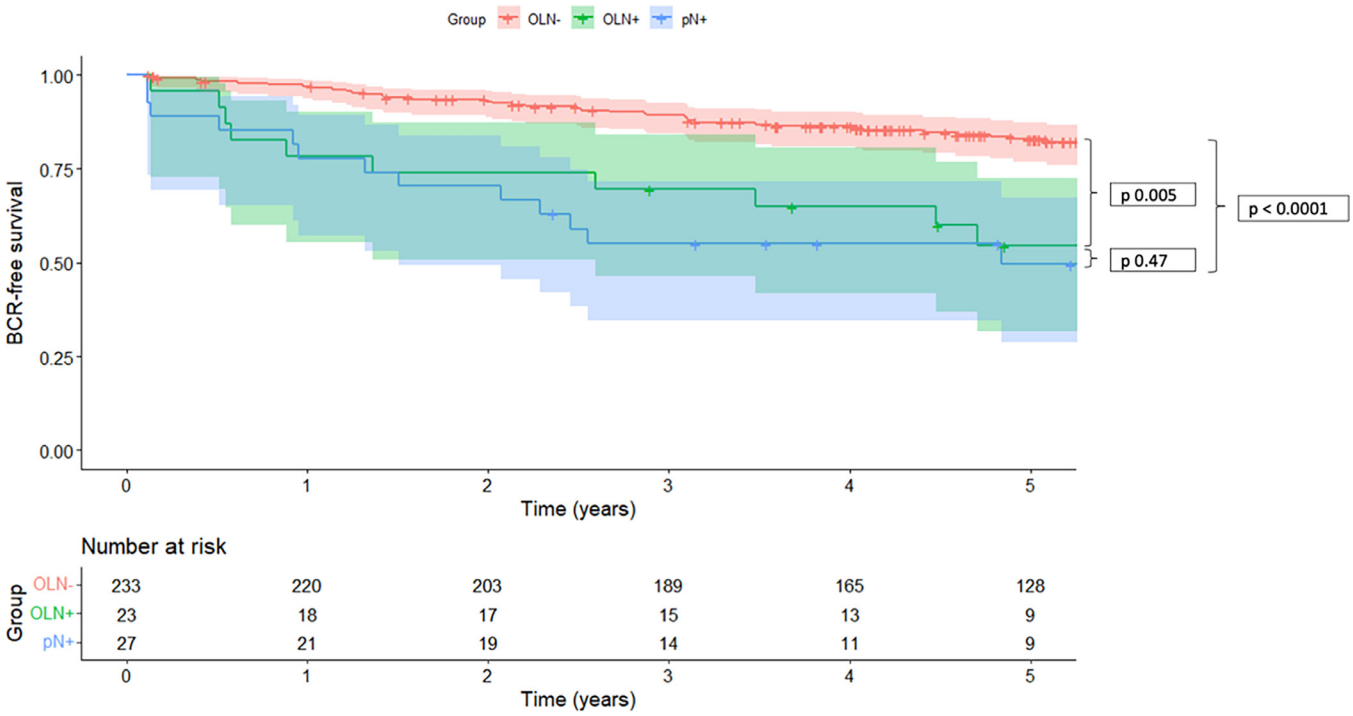


Fig. 2. Biochemical recurrence-free survival.

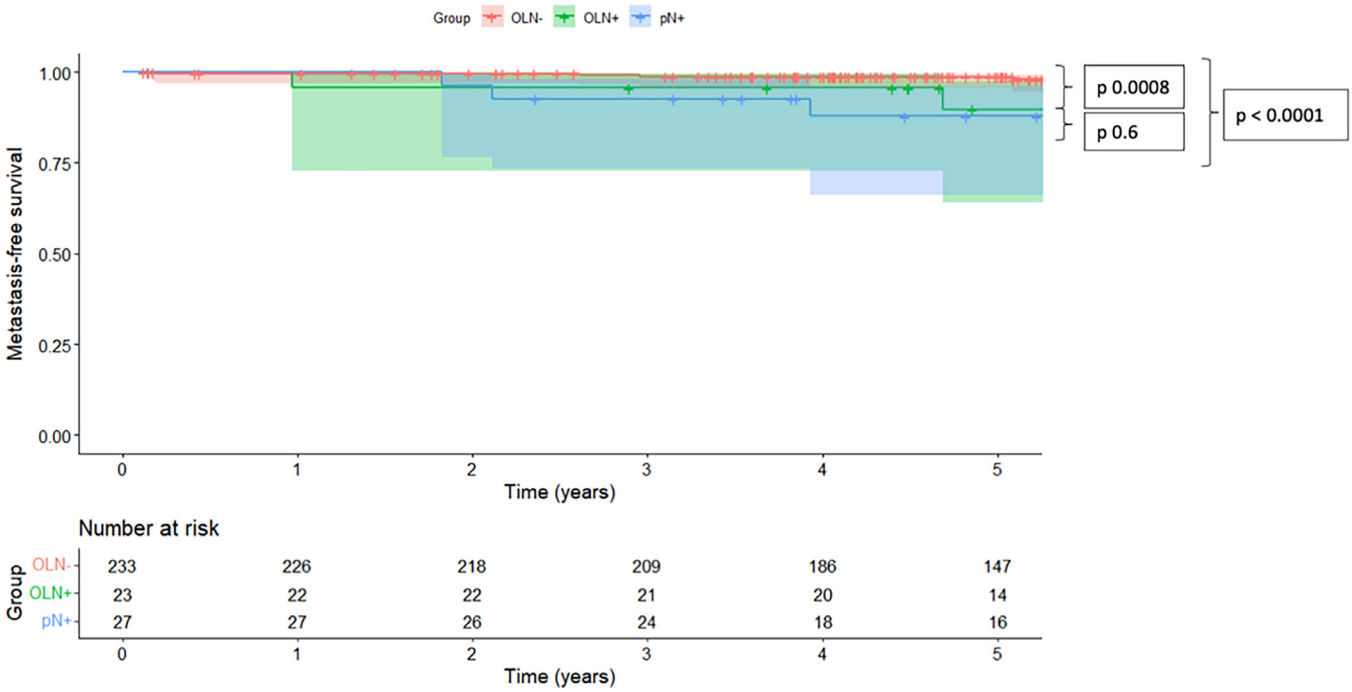


Fig. 3. Metastasis-free survival.

polymerase chain reaction (RT-PCR). An ISUP conference in 2010 highlighted the slight evidence of the use of IHC in the CaP setting and the unknown importance of detecting micrometastasis since the prognosis significance of this situation needed to be clarified [10]. Implementing IHC in clinical practice significantly increases expenses and labour time [11], which can explain why only a few scientific reports have been published since then.

In our experience, IHC detected an additional 8.9% of patients, which aligns with the 7-28% detection rate reported in the literature [5,6,7,12]. We found OLN + patients to have a 1.8 higher risk of developing BCR in comparison with OLN − patients however, this was not statistically significant ($P = 0.09$). Others have found a similar risk (HR 1.7; HR 3.3) in this cohort of patients [7,13]. Long-term oncological data is even more limited. Maxeiner et al. [7] revealed a recurrence-free survival (RFS) of 23 and 59 months in 176 OLN - patients and 17 OLN + patients, respectively ($P < 0.001$). In our experience, the median MFS was 48 and 61 months in OLN − and OLN + patients. Of note is that the RFS definition is not reported in the Maxeiner study.

Interestingly, when pN + patients, detected by conventional HE, are compared to the aforementioned groups, we can elucidate a more similar oncological behaviour to the OLN + group than to OLN - patients. This idea was already presumed in 2014 by Schiavina et al. [6]. Our data shows no statistically significant differences in BCR and MFS in OLN + and pN + groups. Pagliarulo et al. [5] analyzed a cohort of pT3 patients who underwent prostatectomy and PLND with HE and complementary IHC analysis. By 10 years, the probability of recurrence (PSA or clinical) was 36%, 61%, and 69%; and the probability of dying from any cause was 20%, 44% and 31% for OLN -, OLN + and pN + patients, respectively. They hypothesized that patients from the pN + group had a longer OS than the OLN + group because they probably received early ADT, which might have impacted the patient's prognosis. In any case, it supports the idea that patients with micrometastasis LN disease have a biological prognosis similar to patients with evident LN involvement.

Current efforts are ongoing to detect CaP patients at high risk for metastasis development. As such, EAU guidelines recommend stratifying patients in the BCR setting according to the PSA doubling time and Gleason score [14]. Recently, conventional ADT plus enzalutamide for nine months has proven to delay metastatic progression in a cohort of high-risk patients [15]. The scenario of pN1 disease is controversial. Based on the number of LN affected, recommendations are given, and ADT +/- radiotherapy remains the standard treatment. We have found that around 20% of patients in the OLN + and the pN + group develop metastasis in a 5−6-year period. Hypothetically, both cohorts could benefit from an intensified treatment with the use of new-generation androgen receptor-targeted agents.

Importantly, IHC is an expensive and time-consuming procedure [6,11]. More recent molecular techniques, such as RT-PCR, can offer immediate LN analysis with promising results in breast and prostate cancer [16,17].

The main limitation of the study is its retrospective nature. OLN patients had less advanced disease and a lower rate of positive surgical margins than pN+ and OLN+ patients, which may have influenced oncological outcomes. Another concern is that the lymphatic specimen from the extended PLND did not undergo additional IHC. In this sense, we cannot know the added value of the IHC in a less

selective lymphadenectomy. A higher detection of OLN + patients can be hypothesized, but it should be balanced with the additional costs.

Additionally, RT-PCR seems a plausible alternative to IHC in detecting micrometastasis, and it could have been interesting to compare them face-to-face. Since the OLN + population has yet to be studied, the long-term results obtained in this report are of concern.

The similar oncological prognosis between the OLN + and the pN + group highlights the importance of adequately improving the anatomopathological analysis of the LN sample to stage patients with LN involvement. Extended PLND is a non-innocuous procedure with noteworthy costs [18]. The same efforts destined for ePLND should be equally directed to the optimal processing of lymphatic specimens.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Pedro de Pablos-Rodríguez:** Writing – original draft, Methodology, Conceptualization. **Francesco Claps:** Writing – review & editing. **Ana Aldaz Acín:** Investigation, Formal analysis. **Álvaro Gómez-Ferrer:** Writing – original draft, Investigation, Conceptualization. **Augusto Wong:** Writing – original draft. **Juan Boronat Catalá:** Methodology, Conceptualization. **Ana Calatrava Fons:** Writing – review & editing, Investigation. **Antonio Coy García:** Formal analysis. **Juan Casanova-Ramón Borja:** Writing – review & editing. **Miguel Ramírez Backhaus:** Writing – review & editing, Conceptualization.

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