

The Role of “Marcillectomy” in Extended Pelvic Lymph Node Dissection for High-Risk Prostate Cancer Patients

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Abstract

Extended pelvic lymph node dissection (ePLND) is currently the most accurate method for staging prostate cancer (PCa) lymph node (LN) and has been widely adopted, and according to the guidelines of the European Association of Urology, it is recommended for intermediate and high-risk PCa patients. As a landing point for pelvic lymphatic drainage, Marcille's LN is considered an important site for LN metastasis of PCa. By performing histopathologic and molecular analyses, significant lymphatic drainage can be detected in the triangular fossa of Marcille. The Marcille's lymphadenectomy, called “Marcillectomy”, is able to bring about potential oncology benefits in patients with small-volume lymph node metastases without increasing the rate of complications, which will revolutionize the traditional ePLND approach and recommend the use of Marcillectomy in all high-risk PCa patients.

Introduction

Prostate cancer is the most common malignant tumor in the male genitourinary system and the second most prevalent male malignant tumor worldwide [1]. According to the World Health Organization's International Agency for Research on Cancer (IARC), it is estimated that in 2020, the incidence rate of prostate cancer in China will reach 15.6 per 100,000 people, with more than 115,000 new cases and 51,000 deaths [1]. Clinically, lymphatic drainage characteristics play an important role in tumor progression in prostate cancer (pCA) and are crucial for surgical prognosis. Therefore, extended pelvic lymph node dissection (ePLND), which is currently the most accurate method for lymph node (LN) staging of prostate cancer [2], has been widely performed and is recommended for intermediate- and high-risk patients according to the guidelines of the European Urological Association [3]. Although there is no consensus on the LN fields that should be excised, most ePLND templates include at least the external iliac, obturator, and internal iliac regions [4,5], and the optimal LN dissection extent has not yet been determined [3,6].

Marcille's Fossa is an anatomical region of the pelvis. As the landing point for pelvic lymphatic drainage, Marcille's LNs is considered an important site for LN metastasis of prostate cancer [7,8]. In the early 20th century, Marcille et al [9] first proposed the concept of Marcille triangle, and in 2013, Osmonov et al [10] explicitly included Marcille

fossa as a separate component of the ePLND template for the first time. However, adding more LNs gradually expanding the anatomical template may lead to longer operative times and a higher risk of complications which are also not negligible in terms of prognosis [11,12]. Therefore, it is essential to investigate the morbidity of PLND, especially when the newly dissected area is expected to add little clinical information, before determining the optimal margin for LN dissection [8,13]. In addition, recent mapping studies and molecular analyses [14-16] have further confirmed that LN metastases can be detected in the Marcille's fossa of PCa patients, which may revolutionize the traditional ePLND approach and promote the use of MARCILLECTOMY in all high-risk PCa patients.

Anatomic extent of Marcillectomy in ePLND

The triangular fossa of Marcille (Figure 1) is located lateral to the common iliac vessels, medial to the inner edge of the lateral teres major muscle, above the proximal obturator nerve, and anterior to the sciatic nerve [9,17]. The process of clarifying the anatomical extent of the Marcille's fossa has been accompanied by the ongoing popularization of ePLND for PCa. In 2011, Osmonov et al [18] initiated the "step-by-step" extended LN dissection in patients undergoing radical prostatectomy. Analysis of LN samples from 105 patients who underwent radical prostatectomy yielded positive LNs in 15 patients, and found that one of them had LN metastases in a specific area above the sciatic nerve, medial to the common iliac artery and

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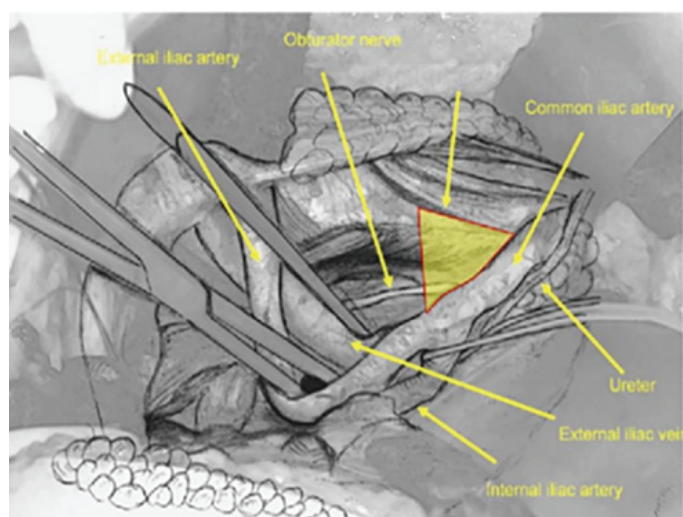


Figure 1. Schematic anatomy of the triangular fossa of Marcille (the yellow triangular region).

ureter, which the researchers termed the "presciatic area". In the subsequent study [10] in 2013, the researchers finally identified this as Marcille's fossa and included it as one of the six main components of the ePLND template for PCa patients.

In the study by Porcaro et al [11], 17% (5 out of 30) of the LN-positive patients developed metastases in this region. Moreover, by analyzing the baseline and pathological characteristics of these patients separately, the Marcille's lymphadenectomy, called "Marcillectomy" is recommended when ePLND is planned for patients with high-risk PCa.

Identification of Marcille's nodes involvement in PCa metastasis

Lymph node mapping studies

Currently, as early LN metastases in prostate cancer are mostly micrometastases or occult metastases, the accuracy of conventional and functional imaging in detecting preoperative LN status is comparatively poor [19,20]. When molecular techniques were used, micrometastases were found in up to 30% of patients with histologic classification of pN0 disease [21]. This improved only after Boni et al [22] pioneered the use of Indocyanine Green (ICG) for guiding sentinel LN detection in partial nephrectomy and radical prostatectomy (RP), which ultimately led to the confirmation of the role of the triangular fossa of Marcille in LN metastasis of prostate cancer.

Using ICG-guided PLND technique, Ram et al [15] analyzed a total of 1278 nodes resected in low- and intermediate-risk PCa patients who underwent RP, of which 19 were metastatic and 16 were considered ICG-stained nodes intraoperatively. The negative predictive value (NPV) of 99.6% had been achieved. Moreover, 9 (18.4%) positive LNs were obtained in the Marcille area at the overall level. In 2016, Nguyen et al [14] further determined the value of ICG fluorescence sentinel LN detection in intermediate- and high-risk PCa patients undergoing RP and PLND for LN metastasis. By performing sextant intraprostatic injection of ICG (base, midlevel, and apex on both sides) in 42 patients, the researchers found that the Marcille fossa had significant drainage and that up to 18% of the sentinel LNs could be detected in this area.

Maderthaner et al [7] illustrated Marcillectomy by assessing

451 patients and examining the locations and number of nodal metastasis. They concluded that a more extended template detects LN involvement in the common iliac region and the Triangle of Marcille with no increased complication rates. With the extension of the template to the ureteric crossings and the inclusion of Marcille's fossa, LN metastases can be identified in these new regions, both in the context of minimal LN disease (≤ 2 LN metastases) and in the context of merging with multiple LNs in other locations.

Lymph node molecular analyses

LN molecular analysis refers to a multiple of molecular and histological techniques targeting prostate-specific gene expression, including reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemical staining, for the detection of micrometastatic cancer cells in pelvic LNs surgically removed during RP for PCa. In previous studies, the decisive role of molecular analysis in detecting prostate cancer LN metastasis in Marcille fossa has been confirmed in the following three dimensions: (1) In traditional histopathologic analyses, small-volume metastases are at a quite high rate of missed diagnosis, due to sampling errors in LN sections and omission in microscopic examinations [23,24]; (2) The presence of molecular metastases is closely associated with tumor prognosis after radical prostatectomy [24,25]; (3) Recent studies [25-27] have demonstrated the accuracy of detecting metastasis by real-time detection and quantitative PCR-based assay of pathologically negative LNs from Lymphatic drainage landing sites.

In 2019, Bando et al [8] innovatively assessed the distribution of occult LN metastases in the Marcille fossa by quantitative RT-PCR. In 223 dissected Marcille's LNs of 52 patients with clinically localized high-risk prostate cancer, molecular analysis identified 7(3.1%) occult LN metastases in Marcille's fossa, compared to none(0%) of positive LNs in histopathological analysis detected ($P < 0.01$). Molecular analysis suggested the fossa of Marcille had a high probability of extensive metastasis in clinically localized high-risk prostate cancer.

Clinical outcomes of Marcillectomy in ePLND

Potential oncologic benefits

Numerous studies [28-31] have found that resection of more LNs in node-positive patients with ePLND relatively improved cancer-specific survival. Schumacher's study [32] showed that patients with 1, 2, and ≥ 3 positive LNs were able to achieve 10-year cancer-specific survival rates of 72%, 79%, and 33%, respectively. Whereas patients with ≥ 3 LN-positive RPs had a significantly higher risk of biochemical recurrence compared to patients with low-volume LNs, in the study by Touijer et al [33]. Therefore, for patients with low-volume nodal disease (with ≤ 2 LN metastases) or negative LN, oncologic benefit is most likely to be achieved by receiving ePLND [28]. In the contemporary cohort with Marcillectomy, Maderthaner et al [7] found that three patients with minimal LN disease had one or two metastases in the common iliac region or Marcille fossa, the researchers further proposed a hypothesis that ePLND with Marcillectomy is associated with a survival benefit, although more case-control studies are needed in the future.

Risk of complications

PLND and its extension have been reported to have higher complication rates, longer operative times, and longer hospital stays compared to traditional LN dissection templates (obturator fossa, and external and internal iliac nodes) [2]. Although

ePLND is generally a safe procedure, complication rates in the literature including Lymphoceles, pulmonary embolism, and vascular and ureteral injuries vary widely, from 2% to 51% [34,35]. Postoperative complication rates were therefore assessed by Clavein-Dindo (C-D) classification [36], and recent clinical studies have provided more insight into the application of Marcillectomy. Porcaro et al [11] observed that among 221 patients who underwent RP with Marcillectomy, 8 (3.6%) had complications of C-D classification grade 3 or higher. In the study by Bando et al [8], researchers found none patients of C-D classification grade ≥ 3 , whereas seven patients were found to have postoperative lymphoceles. Overall, the severe complication rate for Marcillectomy in ePLND did not change significantly and was at a low level.

Discussion

Studies prior to the 20th century [37] suggested that lymphatic drainage of the prostate roughly followed the echelon theory, i.e., as long as there was no tumor in the first echelon (areas caudal to the common iliac bifurcation), metastasis would not occur in the second echelon (common iliac vessels) or the third echelon (paraaortal/paracaval). However, Maderthaner et al [38] in 2008 found that only 63% of lymphatic landing sites were within the PLND bounded by the bifurcation of the common iliac artery, while approximately 75% of potential metastases were removed by LN dissection extending along the common iliac vessels to the ureteric crossing point, including the Marcille's triangular fossa. The above research and recent lymphatic scintigraphy studies [7,14] further confirm that lymph from almost all parts of the prostate drains bilaterally to different regions of the pelvis including Marcille fossa.

Generally, expanding the anatomical template by adding Marcille fossa increases the number of resected LNs and linearly increases the probability of detecting LN invasion, which in

turn improves pN0 patient survival by removing molecular micrometastases not detected by conventional pathologic management of LN [39,40]. However the higher complication rate associated with a larger anatomical template is also an important factor to consider. By statistically organizing all of the current clinical studies involving the Marcille triangle fossa as a separate component (Table 1), we obtained information on the recommendations for actively performing Marcillectomy for high-risk PCa patients, and it's encouraging to note that there was no higher severe complication incidence, but a large number of well-designed and long-term follow-up controlled studies are still required. In addition, the professionalism and meticulousness of the surgeon's operation is also a considerable element that should not be ignored.

Conclusion

In conclusion, both histopathologic and molecular analyses confirmed that significant lymphatic drainage could be observed in the triangular fossa of the Marcille. As the ability to provide potential oncologic benefit without a significant increase in complication rates, Marcillectomy is recommended in patients with high-risk prostate cancer until a more accurate LN dissection template can be determined.

Author contributions

ZW, XG, LZ: conceptualization. ZW, LG: writing—original draft preparation. XG, LZ: writing—review and editing. All authors have read and agreed to the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Table 1. Summary of Marcillectomy studies determining oncologic outcomes

Year published	Authors	Retrospective/prospective	Study design	n	Outcome measure
2018	Maderthaner et al [7]	retrospective	ePLND + Marcillectomy vs. ePLND	753	ePLND + Marcillectomy: Higher detection rate of LN metastasis and no higher risk of complications.
2020	Bando et al [8]	prospective	ePLND + Marcillectomy: histopathological vs. molecular analyses	52	Molecular analyses: High probability of extensive metastasis in Marcille's fossa
2013	Osmonov et al [10]	prospective	ePLND + Marcillectomy: intermediate-risk vs. high-risk PCa	174	Intermediate - and high-risk PCa: High probability of extensive metastasis in Marcille's fossa
2019	Porcaro et al [11]	prospective	ePLND + Marcillectomy	221	High-risk PCa: Higher detection rate of LN metastasis and no higher risk of complications
2016	Nguyen et al [14]	prospective	ePLND + Marcillectomy: ICG injections	42	Marcille's fossa receives significant lymph drainage
2016	Ramírez-Backhaus et al [15]	prospective	ePLND + Marcillectomy: ICG injections	84	ICG-guided ePLND: High probability of extensive metastasis in Marcille's fossa
2011	Osmonov et al [18]	prospective	ePLND (involving presciatic area)	106	ePLND: High probability of extensive metastasis in presciatic area

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