Lymph Nodes Invasion of Marcille's Fossa Associates with High Metastatic Load in Prostate Cancer Patients Undergoing Extended Pelvic Lymph Node Dissection: The Role of "Marcillectomy"

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Keywords

Marcille's fossa · Marcille's triangle · Prostate cancer ·
Extended pelvic lymph node dissection

Abstract

Introduction: To assess the incidence of malignancy involvement of lymph nodes (LNs) in Marcille's fossa in patients undergoing robot assisted radical prostatectomy (RARP) and extended pelvic lymph nodes dissection (ePLND) for prostate cancer (PCa). **Design, Setting, and Participants:** Between January 2014 and December 2017, details of patients who underwent RARP and ePLND were prospectively analysed. All the nodal packets were dissected separately, grouped into left and right nodes and submitted in separate packages to dedicated pathologist. **Results and Limitations:** Two hundred and twenty-one patients underwent ePLND and RARP in the study period. In aggregate, Marcille's LNs involvement was found in 5 (2.3%) of patients, 2 on the left side and 3 on the right side. Per cent of positive cores and Gleason at biopsy are clinical predictors of LNs invasion; moreover, in the surgical specimen, seminal vesicle invasion and high-grade cancer were factors related to loco-regional

metastases. **Conclusions:** Marcille's nodes involvement is associated to contemporarily multiple LN metastases in other template locations in high-risk PCa patients. The Marcille's lymphadenectomy would be recommended when planning an ePLND in high-risk PCa.

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Introduction

Prostate cancer (PCa) can disseminate through lymphatics, peri-neural spaces and venous routes. Obviously, this condition influences its natural history. Periprostatic lymphatic networks include ascending, lateral and posterior routes [1].

Nowadays, both conventional and functional imaging have poor accuracy in detecting preoperative nodal status, because of many early metastases of lymph nodes (LN) in PCa are micro or occult metastases [2]. Extended pelvic lymph nodes dissection (ePLND) results to be the most

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Fig. 1. Steps of the Marcillectomy during ePLND for PCa. The dotted-dash line area indicates the exposed Marcille's fossa (**a**) identification of the external iliac LN group which is dissected laterally to the genitofemoral nerve at the lateral edge of the internal iliac artery and vein. **b** With the Prograsp™ the external iliac vessels are pulled medially permitting lymphatic removal posterior to

these vessels. **c** This enables the visualization posteriorly to the obturator nerve, at the level of the pelvic floor, when the triangle of Marcille's and deep LN packets are removed. Steps of the Marcillectomy during ePLND for PCa. The dotted-dash line indicates the exposed Marcille's fossa.

accurate nodal staging procedure in PCa [3]. European Urology Association guidelines recommend performing extended ePLND in intermediate [4] and high-risk PCa patients [5]. Multiple statistical models predicting lymph node involvement in PCa exist to support clinical decision-making regarding extended pelvic ePLND [6].

However, there is still no agreement on the lymph nodal fields that should be removed and different ePLND templates have been proposed [7–9].

A progressive extension of the anatomical template by adding more nodal fields would further reduce the risk of missing positive LN; however, it may lead to longer operating times and a higher risk of complications [10].

The Marcille's triangle or fossa is a pelvic anatomical region, which is limited by the fifth lumbar vertebra medially, from the inner edge of the muscle large psoas laterally, from the upper edge of the wing of the sacrum below [11, 12]. LNS of this anatomical are related to the prostate lymphatic system [9]. However, the dissection of Marcille's LNs is a subject that has not been investigated in robotic surgery.

The aim of the present study is to assess both the prevalence and the incidence of malignancy involvement of nodes in Marcille's Triangle in patients undergoing robot assisted radical prostatectomy (RARP) and ePLND for PCa.

Methods

Between January 2014 and December 2017, details of all consecutive patients who underwent RARP and ePLND with intent to cure locally advanced PCa performed by 2 expert surgeons (W.A. and V.D.M.) were identified from our prospectively collected in an

Institutional database. All the procedures were recorded, and video-tapes were examined at any convenience. Patients who underwent androgen deprivation therapy before the surgery were excluded from the analysis. Pre-operative data collected included age (years), body mass index (kg/m²), baseline total prostate specific antigen (ng/mL) serum levels, percentage of biopsy positive cores (%), total prostate volume (mL), tumour and nodal clinical stage and Gleason Grading Group in biopsy cores. Postoperative complication rates, classified according to Clavien-Dindo classification, were also assessed [13]. Patients were classified using the D'Amico clinical class risk categories [14] and staged according to the 2010 American Joint Committee on Cancer staging system for PCa.

The decision to perform an extended LN dissection was mainly based on pre-operative nomograms showing a risk of LN invasion greater than 5% [15]. In low-risk patients, the decision to perform an ePLND was based on clinical factors indicating an increased risk of tumour upgrading in the surgical specimen [16–19]. Dissected pelvic LNs were sampled according to a standardized anatomical template as follows: external iliac, Cloquet's, Obturator, Marcille's, and internal iliac nodes.

The Marcille's fossa or Marcille's Triangle is an anatomical region located in the vicinity of the lateral part of the fifth lumbar vertebra, the medial border of the psoas muscle laterally and the cephalad surface of the ala of the sacrum [11]. Figure 1 shows the surgical steps of the LNs dissection located in the Marcille's fossa: the vas deferens is transected along its course. The external iliac LN group is dissected laterally to the genitofemoral nerve at the lateral edge of the internal iliac artery and vein from the node of Cloquet to the ureteric crossing of the internal iliac artery. With the Prograsp™ at the 4th arm, the external iliac vessels are pulled medially permitting lymphatic removal posterior to these vessels. This enables the visualization posteriorly to the obturator nerve, at the level of the pelvic floor, when the triangle of Marcille's and deep LN packets are removed.

All the nodal packets were dissected sequentially and separately and then taken out through the 12-mm trocar. Surgical specimens were evaluated by the dedicated pathologist. Nodal packets

were grouped into left and right nodes, tagged and submitted in separate packages according to the Stanford protocol [5, 20]. Dissected LNs were counted and evaluated for cancer involvement, which was classified as absent, <5 or ≥ 5 nodes. All specimens were processed separately. Tumours were classified according to the Gleason Grading Group system [21].

The removed LNs were assessed for histopathological analysis. Pathologic work-up to detect LNs in the specimens comprised direct visualization, palpation and standard hematoxylin-eosin staining. Immunohistochemical staining was performed when appropriate. In each case, the numbers of removed and metastatic nodes were assessed. Prostate and nodal specimens were then staged according to the 2010 American Joint Committee on Cancer staging system for PCa.

Statistical Analysis

The patient's population was grouped according to LNs invasion (present or absent). Metastatic cases were classified according to the presence or absence of involvement or Marcille's fossa.

A descriptive analysis was performed reporting continuous and categorical variables as median, interquartile range (IQR) and frequencies, percentages (%). In the univariate analysis Kruskal-Wallis, chi-square and Fisher exact tests were used to compare continuous and categorical variables as appropriate.

A 2-tailed test with $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Between January 2013 and March 2017, a total of 221 patients underwent RARP and ePLND in our Institution including Marcille's fossa dissection bilaterally. Demographical and pathological data of the study populations are displayed in Table 1. Of the 221 investigated subjects, 30 (13.5%) had ASA score I, 175 (79.2%) ASA score II, and 15 (7.2%) ASA score III. The overall median (and IQR) baseline age, body mass index, prostate volume, proportion of positive cores, number of dissected LN, operating time, blood loss, and length of hospital stay are reported. Of the 221 patients included in the study, 26 (11.8%) were low risk, 129 (58.4%) intermediate risk, and 66 (29.9%) high risk. A total of 13 (5.9%) cases had clinical extraprostatic extension of the tumour. Suspected clinical LN invasion (enlarged nodes) was observed in 10 (4.5%) patients. A total of 43 (19.4%) patients presented with a Gleason Grading Group ≥ 4 at biopsy. In the surgical specimen, Gleason Grading Group score ≥ 4 was detected in 71 (32.2%) cases. Extraprostatic extension of cancer was observed in 68 (30.7%) patients of whom 29 (13.1%) had extracapsular extension and 39 (17.6%) seminal vesicle invasion. A total of 62 (28.1%) subjects had surgical margins invaded by cancer. No port-site recur-

rence on the abdominal wall was reported. Symptomatic lymphocele was observed in 5 (1.9%) subjects of whom 2 underwent percutaneous drainage and surgical drainage.

All the specimens were examined by dedicated pathologist for evaluation. A median (IQR) of 28 (22–35) LNs were yielded. Globally 30 (13.5%) patients presented with an LNs invasion.

Figure 2 depicts the distribution of nodes removed from Marcille's fossa. No LN was found in 28.5 and 19.9% of cases in right and left triangle; In the 68.8 and 75.9% of cases a Marcille's count <5 nodes was found on the left and right side, while ≥ 5 nodes was found in 2.7 and 4.2% in the left and right Marcille's Triangle respectively. In aggregate, Marcille's LNs involvement was found in 5 (2.3%) of patients, 2 on the left side and 3 on the right side. No patient presented with the bilateral involvement of Marcille's fossa.

Table 2 depicts demographic, surgical and pathological data of the population with positive nodes. No differences were found when comparing patients with positive vs. negative Marcille's nodes except for the total number (median, IQR) of LNs with metastatic involvement that was found higher in patients with Marcille's node PCa metastasis (1 vs. 7; OR 2.871, 95% CI 1,158–7,119; $p = 0.023$).

Table 3 depicts clinical and pathological data of patients with Marcille's node involvement. Four out of 5 patients reported familiarity for PCa and were classified as "high risk" according to D'Amico's classification and presented an extracapsular extension. In all cases, the Marcille's nodes involvement was associated with a metastatic spread in the other lymphatic landing site.

Discussion

In order to reach the primary goal of oncologic surgery (i.e., complete resection) in pelvic malignancy, LN dissection templates proposed so far were increasingly extended [22]. We have previously demonstrated the role of Cloquet's nodes dissection during RARP and ePNLD [23]. Moreover, the interest on Marcille's region is not exclusive of academic purpose, but it is also important to understand a complex anatomical area in order to perform a lateral pelvic surgery [11]. Seventy-five per cent of all anatomical landing sites were included in the standard extended PLND [24]. Extending the anatomical template by adding more nodal areas could increase LNs removed [25], the chance to detect LN invasion [26] improved survival in patients pN0 [27] (virtually due to the occult micro-metastases removal).

Table 1. Clinical and pathological factors associated with lymph node invasion in the patient population

	Population	Lymph node invasion		<i>p</i> value
		absent	present	
<i>n</i> (%)	221	191 (86.4)	30 (13.6)	
Age, years, median (IQR)	66 (65–70)	65 (61–70)	67 (62.7–70.2)	0.189
BMI, kg/m ² , median (IQR)	25.3 (23.7–27.8)	25.6 (23.5–27.8)	25 (24.3–27.5)	0.565
PSA, ng/mL, median (IQR)	6.8 (5.1–8.9)	6.8 (5.2–8.7)	7.1 (4.9–10.1)	0.637
TPV, mL, median (IQR)	40 (30–51.5)	40 (30–51)	42 (29–58.2)	0.710
BPC, median (IQR)	41 (25–59)	36 (22–57)	50 (38–71)	0.004
PW, g, median (IQR)	52 (41.5–65)	52 (40–65)	55.5 (43–68.5)	0.276
LNR, <i>n</i> (%), median (IQR)	28 (22–34)	28 (22–33)	28 (23–36.5)	0.628
OT, min, median (IQR)	225 (200–255)	223 (200–253)	242.5 (200–270.5)	0.255
BL, mL, median (IQR)	250 (150–400)	250 (150–400)	250 (200–462.5)	0.460
DD, days, median (IQR)	4 (4–5)	4 (4–5)	4 (4–4.2)	0.366
cT1c, <i>n</i> (%)	127 (57.5)	113 (59.2)	14 (46.7)	0.345
cT2, <i>n</i> (%)	81 (26.7)	68 (35.6)	13 (43.3)	
cT3, <i>n</i> (%)	13 (5.9)	10 (5.2)	3 (10)	
cN0, <i>n</i> (%)	211 (95.5)	183 (95.8)	28 (93.3)	0.544
cN1, <i>n</i> (%)	10 (4.5)	8 (4.2)	2 (6.7)	
BGG 1, <i>n</i> (%)	46 (20.8)	42 (22)	4 (13.3)	0.002
BGG 2–3, <i>n</i> (%)	131 (59.8)	119 (62.3)	13 (43.3)	
BGG 4–5, <i>n</i> (%)	43 (19.4)	28 (15.7)	13 (43.3)	
Low-risk class, <i>n</i> (%)	26 (11.8)	24 (12.6)	2 (6.7)	0.088
Intermediate-risk class, <i>n</i> (%)	129 (58.4)	115 (60.2)	14 (46.7)	
High-risk class, <i>n</i> (%)	66 (29.9)	52 (27.2)	14 (46.7)	
pT2, <i>n</i> (%)	153 (69.2)	144 (75.4)	9 (8.30)	<0.0001
pT3a, <i>n</i> (%)	29 (13.1)	27 (14.1)	2 (6.7)	
pT3b, <i>n</i> (%)	39 (17.6)	20 (810.5)	19 (63.3)	
NSM, <i>n</i> (%)	159 (71.9)	142 (74.3)	17 (56.7)	0.045
PSM, <i>n</i> (%)	62 (28.1)	49 (25.7)	13 (43.3)	
PGG 1, <i>n</i> (%)	16 (7.2)	16 (9.4)	0 (0.0)	<0.0001
PGG 2–3, <i>n</i> (%)	134 (60.6)	125 (65.4)	9 (30)	
PGG 4–5, <i>n</i> (%)	71 (32.2)	50 (26.2)	21 (70)	
ASA 1, <i>n</i> (%)	30 (13.5)	26 (13.6)	4 (13.3)	0.821
ASA 2, <i>n</i> (%)	175 (79.2)	152 (79.6)	23 (76.7)	
ASA 3, <i>n</i> (%)	16 (7.2)	13 (6.8)	3 (10)	
CDS 0–2, <i>n</i> (%)	213 (96.4)	185 (96.8)	28 (93.3)	0.337
CDS 3a–3b, <i>n</i> (%)	8 (3.6)	6 (3.2)	2 (6.7)	
No RAD, <i>n</i> (%)	213 (96.4)	184 (96.3)	29 (96.7)	0.928
RAD, <i>n</i> (%)	8 (3.6)	7 (3.7)	1 (3.3)	

IQR, interquartile range; BMI, body mass index; PSA, prostate specific antigen; TPV, total prostate volume; BPC, biopsy positive cores; PW, prostate weight; LNR, lymph nodes removed; OT, operating time; DD, discharge day; cT, tumour clinical stage; cN, nodal; BGG, biopsy grade group; pT, tumour pathological stage; NSM, negative surgical margin; PSM, positive surgical margin; PGG, pathological tumour grade group; ASA, American Society of anaesthesiology score system; CDS, Clavien-Dindo score system; RAD, hospital re-admission.

Although the Marcille's Triangle was reported for the first time at the beginning of XIX century [12], fewer and sparse publications described its role in terms of pathological staging and oncological adequacy. A systematic review of the literature was performed in June 2018 by our group using the Medline, Scopus, and Web

of Science databases, searching for the terms “*Marcille's fossa*” or “*Marcille's Triangle*” in all fields of the records. The systematic search identified 8 studies: 1 anatomical study on cadavers [11], 4 in PCa [9, 28–30], 3 in bladder cancer [31–33]. Only one paper takes into account the “Marcillectomy” as an integral part of the ePLND in

Fig. 2. Distribution of removed and positive LN in Marcille's Triangle. LNs, lymph nodes.

Table 2. Factors associated with involvement of Marcille's Triangle in patients with lymph node metastases

	Lymph node invasion with Marcille's Triangle involvement		p value
	absent	present	
n (%)	25 (83.3)	5 (16.7)	
Age, years, median (IQR)	67 (62.5–71.5)	68 (64–69.5)	1.000
BMI, kg/m ² , median (IQR)	25 (24.4–27.4)	24.8 (22.9–32)	0.957
PSA, ng/mL, median (IQR)	7.1 (4.9–9.8)	8 (5.7–16.4)	0.330
TPV, mL, median (IQR)	41 (28.5–55)	48 (35.5–64)	0.388
BPC, n (%), median (IQR)	50 (38–71)	67 (43.5–76.5)	0.435
PW, g, median (IQR)	54 (42–66)	61 (51–74)	0.435
LNR, median (IQR)	28 (22.5–35.5)	33 (25.5–43.5)	0.253
LNP, median (IQR)	1 (1–2)	7 (3.5–15.5)	0.001*
OT, min, median (IQR)	234 (200–264.5)	257 (185–282.5)	0.656
BL, mL, median (IQR)	300 (200–475)	200 (125–675)	0.431
DD, days, median (IQR)	4 (4–4.5)	4 (4–9)	0.915
cT1c, n (%)	12 (48)	2 (40)	0.714
cT2, n (%)	11 (44)	2 (40)	
cT3, n (%)	2 (8)	1 (20)	
BGG 1–3, n (%)	16 (64)	1 (20)	0.138
BGG 4–5, n (%)	9 (36)	4 (80)	
D'Amico 1–2, n (%)	15 (60)	1 (20)	0.157
D'Amico 3, n (%)	10 (40)	4 (80)	
pT 2 – 3a, n (%)	10 (40)	1 (20)	0.626
pT3b, n (%)	15 (60)	4 (80)	
NSM, n (%)	15 (60)	2 (40)	0.628
PSM, n (%)	5 (40)	3 (60)	
PGG 1–3, n (%)	8 (32)	1 (20)	1.000
PGG 4–5, n (%)	17 (68)	4 (80)	
ASA 1–2, n (%)	23 (92)	4 (80)	0.473
ASA 3, n (%)	2 (8)	1 (20)	
CDS 0–2, n (%)	24 (96)	4 (80)	0.310
CDS 3a – 3b, n (%)	1 (4)	1 (20)	
No RAD, n (%)	24 (96)	5 (100)	1.000
RAD, n (%)	1 (4)	0 (0.0)	

See also Table 1; LNP, number of positive nodes; (*), OR 2.871 (95% CI 1,158–7,119; $p = 0.023$) and area under the curve (AUC) = 0.948 (95% CI 0.851–1,000; $p = 0.002$).

PCa patients undergoing open radical prostatectomy [9].

According to these considerations, Maderthaner et al. [9] have evaluated the effect of a new extended PLND template including the common iliac vessels and the Marcille's fossa compared to their previous template. In their study, patients with pN+ disease had positive common iliac and Marcille's fossa LNs 17 and 7%, respectively, without significantly increasing the risk of complications. Moreover, Marcille's node involvement was associated with metastases in other template location. Although the Authors performed multivariable logistic regression analysis of variables associated with LN metastases, no data were presented in order to evaluate risk factors associated with Marcille's nodal involvement [9].

In our study, 17% (5 out of 30) of pN+ patients showed metastases on this area. Furthermore, analysing separately baseline and pathologic characteristics of those patients, it was found that high risk disease, familiarity, and contemporarily multiple LN metastases involvement in other template location were common characteristics. Considering the small sample on patients presenting lymph node involvement in Marcille's fossa, to perform a multivariable analysis was not possible. Moreover, we previously reported our analysis on the clinical predictors of LN invasion in low-, intermediate- and high-risk PCa patients who underwent ePLND [17, 34].

Table 3. Clinical and pathological characteristics of patients presenting with Marcille's nodes involvement

	Patient 1	Patient 2	Patient 3	Patient 4	Patients 5
Age, year	68	66	62	69	70
BMI, Kg/m ²	23.5	33.1	24.8	30.9	22.4
Prostate volume, mL	38	70	48.6	33.1	58
PSA	4.7	8.0	6.8	12.4	20.5
Familiarity	Yes	Yes	No	Yes	Yes
Biopsy % core involvement	56	70	83	67	31
Bioptic gleaso grouping, <i>n</i> (%)	4	1	4	5	4
cT	2	1	3	2	1
cN	0	0	0	0	1
cM	0	0	0	0	0
D' amico classification	High	Low	High	High	High
Pathological gleason grouping, <i>n</i> (%)	5	2	4	4	5
pT	3b	2c	3b	3b	3b
Positve surgical margins					
positive, <1 mm	0	0	1	0	0
positive, ≥1 mm	0	1	0	0	1
pN	1	1	1	1	1
Lymph node yielded, total	33	27	41	45	30
Lymphnode yielded, right					
External iliac	13	7	9	9	7
Obturator	6	2	6	8	6
Cloquet	1	1	1	1	1
Marcille	2	2	2	5	2
Lymphnode yielded, left	11	15	23	22	11
External iliac	6	3	8	7	4
Obturator	5	7	9	12	2
Cloquet	0	1	1	1	2
Marcille	0	2	6	2	2
Lymph nodes involved, total	11	2	7	20	5
Lymph nodes involved, right	9	2	1	1	2
External iliac	5	0	1	1	1
Obturator	2	1	0	0	1
Cloquet	0	0	0	0	0
Marcille	2	1	0	0	0
Lymph nodes involved, left	2	0	6	19	3
External iliac	2	0	2	7	0
Obturator	0	0	1	9	1
Cloquet	0	0	0	1	0
Marcille	0	0	3	2	2
90 days complications	0	1	3b	0	0

IQR, interquartile range; BMI, body mass index; PSA, prostate specific antigen; TPV, total prostate volume; BPC, biopsy positive cores; PW, prostate weight; LNR, lymph nodes removed; OT, operating time; DD, discharge day; cT, tumour clinical stage; cN, nodal; BGG, biopsy grade group; pT, tumour pathological stage; NSM, negative surgical margin; PSM, positive surgical margin; PGG, pathological tumour grade group; ASA, American society of Anesthesiology score system; CDS, Clavien-Dindo score system; RAD, hospital re-admission.

Aggressiveness of tumour biology associates with multiple LN metastases. In our study, we have shown that Marcille's fossa are connected with the prostatic lymphatic system and their involvement associated with high metastatic load, which is supported by cancer biology. In

this context, LNs of Marcille's fossa could represent a critical lymphatic landing sites connecting the pelvic and extra pelvic lymphatic system of the prostate.

To the best of our knowledge, this is the first study that analyses specifically the quantitative prevalence of Mar-

cille's nodes and the incidence of malignancy involvement in a cohort of patients undergoing RARP and ePLND for PCa. Strengths of the paper are the prospective fashion; all the nodes packages were sent separately according to the most updated guidelines and were analysed and reviewed by a dedicated pathologist. However, the study is not without limitations, which include mainly different sets of patients collecting all risks group and the small number of patients with Marcille's node metastatic involvement. Wider multicentre series are needed in order to evaluate predictive factors of Marcille's nodes involvement in patients undergoing RARP and ePLND for PCa.

Conclusion

Marcille's nodes involvement is associated to contemporarily multiple LN metastases in other template locations in high-risk PCa patients. Wider series are required to comprehend predictor factors of Marcille's nodes involvement. Until then, the Marcille's lymphadenectomy, called "Marcillectomy", would be recommended when planning an ePLND in high-risk PCa patients and it should not be considered an option.

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Statement of Ethics

We declare that all subjects have given their written informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

Funding Source

No funding source was associated with this study.

Authors Contributions

A.B.P., G.E.C., M.S. and A.T. were responsible for analysis, and manuscript writing. W.A., A.B.C., G.E.C., M.S., A.T., V.D.M., F.M., and M.B. contributed to project development. A.B.P., G.E.C., and W.A. were responsible for manuscript editing. R.R., P.C., T.P., M.P., A.T., N.D.L., N.A., and D.I. collected all the required data.

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