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# The Changing Face of cN0M0 Prostate Cancer Being Found With pN+ After Surgery in the Contemporary Era: Results of an International European Survey on Disease Management

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**Key Words:** Positive nodes, Prostate Cancer, Survey, Young Academic Urologists, Lymph node



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## Abstract

**Heterogeneity exists in positive nodes (pN+) preoperative negative conventional staging (cN0M0) prostate cancer (PCa) men management. We performed a survey to investigate the current opinion on this issue in the European urological community. An acceptable awareness of pN+ disease and management was found. pN+ PCa was considered as a multifaceted category needing a risk-adapted approach. Expectant compared to immediate upfront management and new imaging modalities are increasingly considered.**

**Introduction:** The urological community's opinion over the management of men being found with pathologically positive nodes (pN+) following radical prostatectomy (RP) performed with curative intent after preoperative negative conventional staging (cN0M0) has never been assessed. This remains crucial, especially considering the advent of novel imaging modalities. Our aim was to investigate the current opinion on management of pN+ cN0M0 prostate cancer (PCa) in the European urological community. **Methods:** Following validation, a 31-item survey, complying with the Cherries checklist, was distributed using a web link from December 2021 to April 2022 to 10 urological societies mailing list. Social media (Twitter, Facebook) were also used. **Results:** We received 253 replies. The majority were Urologists (96.8%), younger than 60 (90.5%); 5.2% did not have access to PET-scans; 78.9% believed pN+ is a multifaceted category; 10-years CSS was marked as 71 to 95% by 17.5%. Gold standard management was stated not being ADT by 80.8% and being RT±ADT by 52.3%. Early sRT±ADT was considered an option vs. aRT±ADT by 72.4%. In case of BCR 71% would perform and decide management based on PSMA-PET whilst 3.7% would not perform PSMA-PET. pN+ management is still unclear for 77.1%. On multivariate analysis PSMA-PET availability related to a lower and higher likelihood of considering aRT±ADT as standard and of considering early salvage versus aRT respectively ( $P < .05$ ). **Conclusions:** The Urological community has an acceptable awareness of pN+ disease and management, although it may overestimate disease aggressiveness. The majority consider pN+ PCa as a multifaceted category and rely on a risk-adapted approach. Expectant compared to immediate upfront management and new imaging modalities are increasingly considered.

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## Introduction

Radical prostatectomy (RP) is one of the most frequently performed treatment options for localized prostate cancer (PCa) with approximately 1330 RPs per million cases being performed yearly in the United States.<sup>1</sup> Five to 10% of cases undergoing surgery with lymphadenectomy are found with positive nodes, despite a preoperative conventional negative staging using axial imaging (abdominal CT scan or prostate mpMRI and bone scan; cN0cM0).<sup>2-5</sup>

The presence of PCa in the pelvic nodes (pN+) represents one of the most important prognostic factors for PCa recurrence and mortality, where pN1 patients have a worse prognosis if compared with their counterparts with node-negative disease.<sup>6,7</sup>

Nonetheless, optimal management for node-positive patients still remains unclear.

Despite the fact that all patients, according to the TNM classification, are categorized as pN1, regardless of the number and location of positive nodes, the long-term prognosis of this group is highly heterogeneous and varies significantly according to disease characteristics.

The sole randomized trial dates back to more than 2 decades ago, including men from the pre-PSA era, generally with a relatively high disease burden and number of positive nodes.<sup>8,9</sup>

Several retrospective studies published in the intervening years suggest pN+ PCa is a heterogeneous and multifaceted group, yielding survival benefits from different treatment approaches, depending on disease and on patient's features, rather than from the sole ADT as treatment paradigm.<sup>10</sup> To date, the optimal way to manage pN+ disease remains unknown and the level of evidence is still low.<sup>3</sup> Furthermore, new imaging modalities, namely PSMA- and Choline-PET are revolutionizing PCa diagnosis and staging both in a first-line and recurrence PCa setting. Nonetheless, their impact on disease management and, so far, on survival, remains to be quantified.

Since there are no recent studies identifying the trends in pN+ management therapeutic strategies, especially in Europe, and including novel imaging modalities, we thought this as the optimal time to perform an international survey, to investigate the Urological community's current perception and preferred management of PCa men being found with pathologically positive nodes (pN+) following RP with curative intent and preoperative negative conventional staging (cN0M0).

## Materials and Methods

A 31 items web-based questionnaire was created by 2 authors (G.M; G.G) according to the checklist for Reporting Results for E-Survey (CHERRIES) checklist.<sup>11</sup>

The questionnaire (Supplementary Material 1) comprised 14 items concerning physicians' personal demographics (Part 1), 7 items addressing the current management preferences of pN+ disease (Part 2), 9 items addressing the future perspectives/opinions on pN+ disease (Part 3) and a table showing 6 clinical cases (Part 4).

The survey was shared, discussed, re-assessed and initially validated by 6 urologists with PCa experience - YAU EAU Prostate Cancer working group.

Subsequently, usability and technical functionality was tested through a second validation phase which included the questionnaire being sent by email to 20 urologists using the SurveyMonkey platform. Feedbacks were collected and changes were made.

The open survey was finally distributed to different specialists through the mailing list of 10 national European urological societies. Facebook and Twitter were also used to disseminate the survey. The aim was to reach as many Urologists and PCa physicians as possible, including residents, mainly within the European area, with no exclusion criteria.

Participation in the survey was on a voluntary basis without incentives. Overall dates of distribution and the mailing lists of the societies involved are reported in Table 1. Participants were told the average length of time to complete the survey (7 minutes, from the validation phase) and were made aware of the investigators (Young Academic Urologists Prostate Cancer Working Party).

The items were nonrandomized; respondents were free to change their answers until questionnaire submission. A minimum number of 200 respondents and a maximum time lapse of 4 months were a priori considered as requirements to accomplish the survey. From December 2021 to April 2022, 16 European urological societies from 16 countries and the European Association of Urology (EAU) were asked to distribute the questionnaire to their members. Ten societies agreed to participate (Table 1). All members in the mailing list of participating societies were offered to participate (no specialty, age or other restrictions).

All data were exported and analyzed using SPSS Statistical Software Version 28. Continuous variables were summarized using median (IQR); categorical variables were summarized as frequencies and percentages. Bivariate associations between baseline respondent's characteristics and replies were calculated using the Pearson's chi-square or T-test. Multivariate analyses were performed using binary logistic regression with 95% Confidence Intervals (CI). Statistical significance was set at  $P < .05$ .

## Results

### Respondents

We received 253 replies from 34 countries, with France and Italy being the 2 most represented countries. Complete surveys (n = 203 - 80.24%) were considered in the cumulative analysis. Response rate was not measured as number of responding members per society, double receivers and respondents through social media were not measurable.

Baseline features of respondents are shown in Table 2. The majority were Urologists (96.8%), younger than 60 (90.5%) and working as consultants (67.6%) in academic (47%) or major urban hospitals (28.1%). PCa was considered the main field of expertise by 54.4% and

**Table 1** List of Societies That Were Asked to Distribute the Survey to Their Members

LIST OF CONTACTED SOCIETIES	COUNTRY	Participation
<b>AEU- Spanish association of urology</b>	Spain	<b>Yes</b>
<b>AFU- French Association of Urology</b>	France	<b>Yes</b>
<b>BURST- British Urology Researchers in Surgical Training</b>	England	<b>Yes</b>
<b>CUS- Czech Urological Society</b>	Czech Republic	<b>Yes</b>
<b>DGU- German Urology Society</b>	Germany	<b>Yes</b>
<b>NUA- Norwegian Urological Association</b>	Norway	<b>Yes</b>
<b>NUF- Scandinavian Association of Urology</b>	Scandinavia	<b>Yes</b>
<b>NVU- Dutch Association of Urology</b>	Netherlands	<b>Yes</b>
<b>OGU-Austrian Society of Urology</b>	Austria	<b>Yes</b>
<b>YAU- Young academic urologists - European Association of Urology</b>	Europe	<b>Yes</b>
APU- Portuguese Association of Urology	Portugal	No
EOE- Hellenic Urological Association	Greece	No
ISU- Irish Society of Urology	Ireland	No
PTU- Polish Urological Association	Poland	No
SBU- Belgian Association of Urology	Belgium	No
SIU- Italian Society of Urology	Italy	No
TUA- Turkish Association of Urology	Turkey	No

Bold = agreed in participating.

45.5% stated to perform 1 to 30 RP per year. Only a minority never managed pN+ patients (7.9%) and 83.4% stated encountering 0 to 5 men with pN+ disease every 6 months. Access to Choline and/or PSMA-PET was relatively high with 46.2% having access at their center and 40.7% being able to use it as a staging imaging modality (before surgery). More than half (67.1%) discussed all new PCa cases at their institutional Multidisciplinary Meeting (MDM).

### Knowledge of pN+ PCa

Replies concerning the knowledge of current pN+ evidence are summarized in Table 3. More than 3 on 4 (78.9%) believe pN+ is a multifaceted category with different subgroups and outcomes, more than half that pN+ is a curable disease (61.4%) and that its recommended treatment depends on patients and disease features (52%). Five year BCR-free survival in case of observation and 10-years CSS were marked as 20% by 30.5% and as 71 to 95% by 17.5% respectively.

The 3 most considered factors to guide management were Gleason Score at RP (87.9%), first postoperative PSA (83%) and number of positive nodes (81.2%). Similarly, the 3 deemed most important were Gleason Score at RP (68.2%), first postoperative PSA (62.8%) and number of positive nodes (61.0%). However, whilst the fourth most considered factor was positive margins (71.3%), the fourth deemed most important was PSMA-PET results performed in case of recurrence (45.7%) – (PSMA-PET considered important to guide management in case of recurrence by 66.4%). The 3 less considered factors were maximum positive node diameter (17.5%), preoperative mpMRI (20.2%) and nodes laterality (26.9%).

### Management pN+ PCa

Sixty-nine percent stated considering all options depending on the case; 11.7% never considered observation. The vast majority (80.8%) stated ADT is not the gold standard option for pN+ patients whilst RT ± ADT was thought to be the gold standard by 52.3%. Interestingly, early salvage RT ± ADT instead of immediate adjuvant RT ± ADT was considered an option by 72.4%.

Seventy-one percent would perform and decide management option based on PSMA-PET results in case of BCR after RP. Postoperative PSMA-PET in case of a pN+ report would be performed soon only in case of PSA persistence by the majority (60.7%) whilst 10.7% would perform it soon after RP in any pN+ case. Only 3.7% of respondents would not perform PSMA-PET in case of BCR (Table 4).

The majority of respondents believe management of pN+ disease is still not very clear and there is room for improvement (77.1).

### Clinical Cases

Clinical cases are available as Figure 1. Rate of initial observation decreased with increasing PSA, stage, positive margins and number of positive nodes, in favor of increasing rates of adjuvant RT ± ADT. Rates of immediate adjuvant ADT remained mostly low (highest in case of 3 positive nodes with 25.1%).

**Table 2** Baseline Features of the Survey Respondents

Demographics	%	n°	Demographics	%	n°
Answers	100.0	(253)	RP performed/year		
Country of practice			No	23.3	(59)
France	34.0	(86)	1-30	45.5	(115)
Italy	10.3	(26)	31-100	25.7	(65)
Poland	7.5	(19)	>100	5.5	(14)
Norway	7.1	(18)	RT performed/year		
Spain	5.5	(14)	No	68.4	(173)
UK	5.5	(14)	1-30	22.1	(56)
Portugal	5.5	(14)	31-100	6.7	(17)
Germany	3.2	(8)	>100	2.8	(7)
Turkey	2.4	(6)	MDM <sup>a</sup>		
Netherlands	2.0	(5)	No	4.0	(10)
USA	1.6	(4)	Only selected cases	28.9	(73)
Others	15.4	(39)	All cases	67.1	(160)
Age			pN+ managed/6 mo		
18-39	50.0	(127)	0-5	83.4	(211)
40-59	40.3	(102)	6-10	12.2	(31)
60-79	9.5	(24)	11-20	1.6	(4)
Speciality			>20	2.8	(7)
Urologist	96.8	(245)	PSMA/Choline PET Availability		
Oncologist	0.8	(2)	Centre	46.2	(117)
Radiotherapist	0.8	(2)	City	27.7	(70)
Other	1.6	(4)	Region	20.9	(53)
Position			No	5.2	(13)
Consultant	67.6	(171)	Staging PSMA/Choline PET		
Academic	15.8	(40)	Centre	40.7	(103)
Resident	14.2	(36)	City	21.4	(54)
Retired	0.8	(2)	Region	15.0	(38)
Other (please specify)	1.6	(4)	No	22.9	(58)
Institution					
Academic	47.0	(119)			
Major urban hospital	28.1	(71)			
Minor urban / Rural hospital	4.0	(10)			
Private practice	20.9	(53)			
Experience Abroad	39.1	(99)			
PCa Main Expertise	54.4	(138)			

Consultant= defined as after residency; Academic=Academic career; Resident=including academic residents; Working Institution=main place of practice. RT = radiotherapy session  
<sup>a</sup> MDM = multidisciplinary team meeting discussion discussing each new PCa diagnosis; Managed pN+ patients = ever managed a patient with pN+ disease; Staging PET = PET scan available to be performed also as a staging procedure (before treatment).

### Uni- and Multivariate Analysis

Univariate analyses are available as Supplementary Material 2.

We considered the 5 risk factors selected as the most important in the pN+ decision making. No major associations were noted on multivariate analysis (Table 5). A higher likelihood of considering: postoperative PSA was related to performing less radical prostatectomies ( $P = .012$ ) and discussing all cases at MDMs ( $P = .021$ ) and a higher likelihood of not considering surgical margins ( $P = .004$ ) was related to having managed pN+ patients. No significant associations were highlighted for number of positive nodes, Gleason score at RP, PSMA PET results.

In the context of pN+ standard management, discussing all cases at MDM was associated with a decreased likelihood of considering ADT as the standard ( $P = .001$ ); availability of PSMA-PET either at the respondent's own center ( $P = .019$ ) or in the region ( $P = .039$ ) was related to a lower likelihood of considering adjuvant RT ± ADT as the standard. A younger age (<50 years old;  $P = .033$ ) and availability

**Table 3** Knowledge of cNOMO pN+ PCa

Knowledge	%	n°	Knowledge	%	n°
<b>pN+</b>			<b>Risk factors for pN+ management to be considered</b>		
Single category - poor outcomes	6.3	(14)	Gleason Score at radical prostatectomy	87.9	(196)
Single category - mainly poor outcomes	14.8	(33)	First post-operative PSA (6 weeks)	83.0	(185)
Multifaceted category - different subgroups and outcomes	78.9	(176)	Number of positive nodes	81.2	(181)
<b>5 years PCa-free - if observed</b>			Surgical margins	71.3	(159)
0-5%	17.9	(40)	PSMA PET results, performed in case of postoperative PSA rising	66.4	(148)
10%	24.3	(54)	Extra-nodal extension	51.6	(115)
20%	30.5	(68)	Node density*	46.6	(104)
30%	19.7	(44)	T-stage	44.4	(99)
≥40%	7.6	(17)	Pre-operative PSA	43.9	(98)
<b>Recommended treatment</b>			Number of retrieved nodes	39.5	(88)
Observation ± repeat imaging when indicated	12.6	(28)	Lympho-vascular invasion	35.0	(78)
ADT	6.3	(14)	Nodes laterality (unilateral vs bilateral)	26.9	(60)
aRT ± ADT	29.1	(65)	Pre-operative prostate mpMRI	20.2	(45)
Depends on patients & disease features	52.0	(116)	Maximum positive node diameter	17.5	(39)
<b>10 years-CSS</b>			<b>Most important^^</b>		
5-30%	11.2	(25)	Gleason Score at radical prostatectomy	68.2	(152)
31-50%	30.9	(69)	First post-operative PSA (6 weeks)	62.8	(140)
51-70%	40.4	(90)	Number of positive nodes	61.0	(136)
71-95%	17.5	(39)	PSMA PET results, performed in case of postoperative PSA rising	45.7	(102)
<b>pN+ curable</b>			Surgical margins	39.0	(87)
Yes	61.4	(137)	Node density	29.6	(66)
No	22.4	(50)	Extra-nodal extension	27.4	(61)
Do not know	16.2	(36)	T-stage	23.8	(53)
			Pre-operative PSA	19.7	(44)
			Number of retrieved nodes	17.5	(39)
			Lympho-vascular invasion	14.8	(33)
			Nodes laterality (unilateral vs bilateral)	13.0	(29)
			Maximum positive node diameter	8.1	(18)
			pre-operative prostate mpMRI*	7.2	(16)

of PSMA-PET in the region ( $P = .048$ ) were associated with an increased consideration of early salvage vs. adjuvant radiotherapy. Being an academic ( $P = .038$ ) related to an increased likelihood of observation vs. immediate treatment so as PSMA-PET availability in the region (0.037). No significant correlations with considering pN+ management unclear were highlighted.

### Discussion

To our knowledge, this is the first international survey investigating the knowledge and opinions of the European urological community on the pN+ PCa and its management. Overall, several findings are of interest.

First, overall knowledge of pN+ disease was generally in line with most recent findings and evidence published in the last decade. The majority agreed pN+ disease is a multifaceted category with different subgroups which may benefit from a patient and risk-adapted strategy rather than a single approach, considering Gleason Score, postoperative PSA and number of positive nodes as the most important factors guiding management. Interestingly, replies showed a tendency towards an overestimation of overall pN+ disease aggressiveness compared to the available evidence; 73% stated 5 years BCR-free survival in case of observation being 20% or lower whilst data suggest rates ranging from 43% at 4 years to 28% at 10 years.<sup>10</sup> Similarly, also CSS was underestimated as most recent reports described a 10 years-CSS of generally 80% to more than 90%<sup>10</sup> with only 1 report detailing survival lower than 70% (69% CSS at 8 years when managing pN+ disease with adjuvant ADT).<sup>12</sup>

Eighty-two percent of respondents stated estimated 10-years CSS as lower than 70%. This comes as a surprise also considering the advent of new second-line treatments, which are likely to further prolong survival, in case of progression. Finally, whilst pN+ disease was considered curable by more than half, still as many as 22.4% believe it cannot be cured.

Second, no clear gold standard options were defined for pN+ management. However, a shift from aggressive upfront management towards a more expectant strategy was highlighted. This may reflect the rapidly evolving major shifts in pN+ PCa diagnosis and treatment rather than current evidence gaps.

**Table 4** Replies Concerning Management Options/Possibilities of pN+cNOMO PCa

Management	%	n°
Treatment option never considered		
Observation (monitor PSA ± salvage RT)	19.2	(41)
Adjuvant ADT	6.5	(14)
Adjuvant RT ± ADT	3.3	(7)
Salvage RT ± ADT	2.3	(5)
Consider all options depending on patients and PCa	68.7	(147)
Observation suitability		
Yes	42.5	(91)
Rarely	45.8	(98)
Never	11.7	(25)
ADT is the gold standard	19.2	(41)
RT ± ADT is the gold standard	52.3	(112)
Is early sRT ± ADT an option (vs. RT +/- ADT)?	72.4	(155)
If BCR		
Always treat (ADT and/or RT) all the cases	17.3	(37)
Allow observation	11.7	(25)
Perform PSMA PET & decision based on results	71.0	(152)
PSMA-PET soon after RP?		
Yes	10.7	(23)
Yes (only PSA persistence)	60.7	(130)
No	22.4	(48)
Do not know	6.2	(13)
PSMA-PET if BCR		
Yes, in all patients	65.4	(140)
Yes, some patients	29.0	(62)
No	3.7	(8)
Do not know	1.9	(4)
Management		
Clear & high level of evidence	3.3	(7)
Clear in the majority but > evidence needed	19.6	(42)
Still not very clear & room for improvement	77.1	(165)

Thirty-nine respondents (18.2%) did not complete this section.

ADT = Androgen deprivation therapy; aRT = adjuvant radiotherapy; BCR = Biochemical recurrence; sRT = salvage radiotherapy.

The only RCT specifically involving pN+ PCa found adjuvant ADT was associated with prolonged survival. Nonetheless, results are now hardly applicable to the majority of contemporary pN+ patients, as the trial dates as far back as the pre-PSA era. Furthermore, the trial focused on the role of immediate vs. ADT deferred at the time of visible distant metastasis, rather than deferred at the time of PSA recurrence or positivity of novel imaging techniques, which were not available to that time.<sup>8,9</sup> Not surprisingly, 81% of respondents stated ADT not being the current standard for pN+ disease. Interestingly, 52.3% stated RT with/without ADT as the reference management. This likely relies on multicenter retrospective series<sup>13</sup> highlighting potential survival benefits of adjuvant radiation and ADT in selected subgroups.

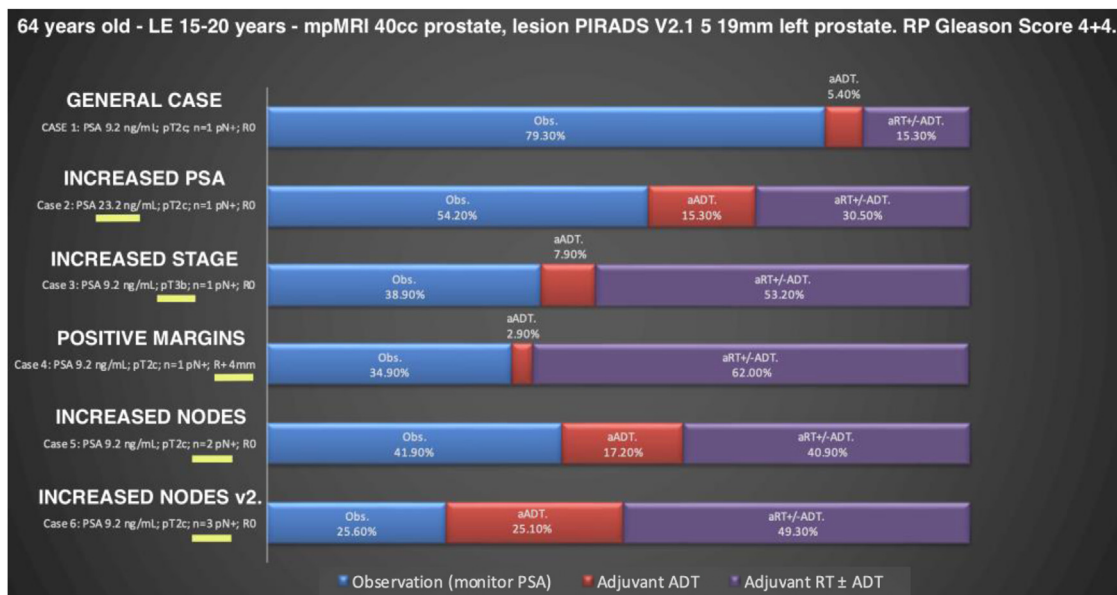
However, 71% favored the option of early salvage compared to adjuvant radiation. On the one hand, we should remain cautious. Results from the ARTISTIC meta-analysis recently proved early salvage RT may spare radiotherapy and its side-effects in men with localized-to-locally advanced PCa compared to adjuvant RT, whilst providing noninferior oncological outcomes.<sup>14</sup> However, adjuvant treatment may maintain relevant survival benefits in the context of pN+ disease, as proven by a recent large retrospective analysis.<sup>15</sup>

On the other hand, initial observation proved a reasonable option in several series. Even at a relatively long follow-up a non-negligible proportion of men is free from recurrence. Furthermore, we are increasing our ability to precisely diagnose and locate recurrence at an early stage, which allows an imaging-based rather than blind treatment of recurrence and takes us to the next point.

**Table 5** Multivariate Analysis of Possible Factors Influencing pN+ Management and Most Important Risk Factors. The Following Factors Were Not Considered in Multivariate Analysis Due to the Lack of Significant Associations on Univariate Analysis: Gleason Score at Radical Prostatectomy, PSMA PET Results in Case of Postop PSA Rising.

	Most important Risk Factor									Management gold standard															
	First post-operative PSA (6 weeks)			Number of positive nodes			Surgical Margins			ADT			RT ± ADT			early RT ± ADT vs adjuvant			if BCR always treat vs others (observation or PSMA PET)			Level of evidence (clear vs not)			
	Multivariate			Multivariate			Multivariate			Multivariate			Multivariate			Multivariate			Multivariate						
	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	
Age			0.645									0.722 (0.4-1.4)	0.335	<b>0.46</b> ( <b>0.2-0.9</b> )	<b>0.033</b>									0.58	
<50 years old	1.0																							1.0	
≥50 years old	1.175	(0.59-2.34)																						1.234 (0.585-2.603)	
Position																									
Others	1.0											1.0												1.0	
Academic	0.588	(0.19-1.8)	0.348									0.881 (0.4-2.2)	0.784											<b>0.346 (0.1-0.9)</b>	<b>0.038</b>
Consultant	0.883	(0.36-2.2)	0.787									1.875 (0.6-5.9)	0.28											<b>0.252 (0.1-1.0)</b>	<b>0.055</b>
Country of practice	<b>0.458</b>	<b>(0.21-1.0)</b>	<b>0.052</b>																						
Europe																									
Others																									
Institution						0.315																			
Academic/Major urban hospital				1.397	(0.73-2.7)																				
Others				1.0																					
Experience Abroad																								0.777	
No																								1.0	
Yes														1.425	(0.7-2.7)									1.1 (0.568-2.133)	
PCa Main Expertise			0.681			0.875		0.628			0.441		0.558											0.599	
No	1.0			0.955	(0.54-2.7)		1.0		1.0		1.0		1.0										1.0		
Yes	1.146	(0.60-2.2)		1.0		0.83	(0.4-1.8)		0.732	(0.3-1.6)		0.825	(0.4-1.6)		1.652	(0.9-3.2)		1.341	(0.6-3.0)				0.836	(0.429-1.630)	
RP performed/year																									
No	1.0																								
1-30	<b>2.774</b>	<b>(1.3-6.1)</b>	<b>0.012</b>				1.022 (0.4-2.5)	0.961	<b>1.953</b>	<b>(0.7-5.2)</b>	<b>0.094</b>	0.814 (0.4-1.8)	0.615												
31-100	1.698	(0.7-4.2)	0.251				0.702 (0.2-2.0)	0.517	0.569	(0.2-2.1)	0.178	0.589 (0.2-1.5)	0.26												
>100	1.592	(0.4-6.1)	0.496				0.274 (0.3-2.7)	0.265	1.86	(0.4-9.7)	0.392	<b>0.255</b>	<b>(0.1-1.1)</b>	<b>0.071</b>											
RT performed/year																									
No RT				1.0			1.0																	1.0	
1-30/year				<b>1.985</b>	<b>(1.0-4.1)</b>	<b>0.06</b>	<b>0.371</b>	<b>(0.1-1.0)</b>	<b>0.057</b>															1.29 (0.587-2.827)	0.527
>30				<b>2.392</b>	<b>(0.9-6.4)</b>	<b>0.083</b>	0.996 (0.3-3.4)	0.995															1.1 (0.394-3.202)	0.828	
MDM*																									
No	1.0																							1.0	
Only selected cases	6.936	(0.76-63.0)	0.085							1.0														0.7 (0.119-4.079)	0.689
All cases	<b>12.936</b>	<b>(1.5-113.4)</b>	<b>0.021</b>							<b>0.196</b>	<b>(0.0-1.1)</b>	<b>0.06</b>												0.988 (0.186-5.238)	0.989
Managed pN+ patients								<b>0.004</b>																	
No							1.0																		
Yes							0.204 (0.1-0.6)																		
pN+ managed/6 mo																									
0-5				1.0																				1.0	
6-10				1.173	(0.5-2.8)	0.718																		0.417 (0.1-2.0)	0.277
>10				0.43	(0.1-1.9)	0.262																		<b>3.251 (0.8-13.2)</b>	<b>0.099</b>
PSMA/Choline PET Availability																									
No				1.0			1.0					1.0		1.0										1.0	
Centre				<b>3.624</b>	<b>(0.9-14.4)</b>	<b>0.067</b>	0.352 (0.1-1.3)	0.123				<b>0.814</b>	<b>(0.4-1.8)</b>	<b>0.019</b>	<b>3.246</b>	<b>(0.9-11.9)</b>	<b>0.076</b>	<b>0.276</b>	<b>(0.1-1.0)</b>	<b>0.06</b>				0.764 (0.177-3.294)	0.718
City				3.084	(0.7-13.1)	0.126	0.389 (0.1-1.6)	0.185				<b>0.589</b>	<b>(0.2-1.5)</b>	<b>0.083</b>	<b>4.076</b>	<b>(1.0-16.4)</b>	<b>0.048</b>	0.36 (0.1-1.5)	0.162						
Region				3.206	(0.7-14.1)	0.123	0.38 (0.1-1.6)	0.189				<b>0.255</b>	<b>(0.1-1.1)</b>	<b>0.039</b>	2.29 (0.6-9.1)	0.24		<b>0.183</b>	<b>(0.0-0.9)</b>	<b>0.037</b>					
pN+																									
single category - poor outcomes				1.0																				1.0	
single category - mainly poor outcomes				0.21	(0.1-0.9)	0.032																		0.549 (0.1-2.4)	0.432
multifaceted category				0.885	(0.3-3.0)	0.841																		0.348 (0.1-1.2)	0.103

**Figure 1** Clinical cases for which respondents had to state which of the 3 management options they would choose. Fifty respondents (19.7%) did not complete this section. \*Abbreviations: Adjuvant ADT = postoperative androgen deprivation therapy; Adjuvant RT ± ADT = postoperative radiation therapy performed with/without androgen deprivation therapy; mpMRI = multiparametric magnetic resonance; PIRADS: prostate imaging reporting & data system; RP = radical prostatectomy; PSA = prostate specific antigen.



Third, PSMA-PET has now a key role in the context of contemporary pN+ disease management after surgery. It is considered amongst the most important clinical factors and only 1 on 20 would not perform it in case of BCR. PSMA-PET availability also favors the use of RT in an early salvage rather than in an upfront adjuvant milieu. Another key finding relies in its accessibility as only after a few years from its introduction in clinical practice 95% had access to PET scans and 77% can use it as a first-line staging modality. This is in line with the vast literature highlighting the role of PSMA-PET in a recurrent setting,<sup>16</sup> with recent results of RCT proving its superiority compared to conventional imaging for first-line disease staging<sup>17</sup> and as a triage PCa exam together with mpMRI.<sup>18</sup>

Importantly, as highlighted by others, PSMA-PET prognostic value and its impact on disease progression and survival has yet to be understood.<sup>19</sup>

From a urological community perspective our work indicates pN+ disease awareness is good but outcomes for pN+ PCa are generally perceived as worse compared to what reported. Efforts need to be made by scientific societies to further improve current knowledge through lectures and scientific dissemination as pN+ prognosis is acceptable and likely to improve in the contemporary era due to novel available treatments. Furthermore, all urologists must be aware that a non-negligible proportion of pN+ men can be cured.

From a research perspective, we confirmed current gaps are also shared within the daily clinical practice with the majority stating pN+ management pathway remains unclear and requires implementation. Recent results from PCa management and imaging trials should be implemented in the context of pN+ disease to improve its understanding and, possibly, its prognosis. In particular, the role of observation and early salvage RT along with novel imaging modalities must be urgently assessed. Multicenter collaborations within our group are ongoing with the aim of providing a timely answer to these clinical questions.

Some limitations need to be acknowledged. The survey was open, on a voluntary basis and distributed with no exclusion criteria. Nonetheless, there is room for selection bias and the sampled population likely does not fully reflect the majority of practicing European Urologists. By using an electronic survey a relatively high proportion of respondents were young urologists stating PCa as main field of expertise, working in academic/tertiary referral centers and performing RP; Nationalities were also unbalanced. A language-related bias also needs to be kept in mind. Nonetheless, uni- and multivariate analysis did not highlight any major baseline difference significantly influencing survey results. Also, we did not measure a clear denominator due to unavailability to exclude double respondents and number of mailing list members not being disclosed by the different societies. We had to limit questionnaire length to obtain a sufficient number of replies. Hence, amongst clinical cases, observation and PSMA-PET imaging performance in case of PSA rise to guide subsequent treatment and/or early salvage radiother-



apy were not included as separate management possibilities. Nonetheless, these options remain appropriately comprised in the observation arm. However, the response rate can be assumed as low and remains in line with previous electronic surveys performed by our and other groups.<sup>20,21</sup> Whilst the absence of incentives and the voluntary base for undertaking the survey may have reduced the absolute number of respondents, we believe this represents a strength as no major conflict of interests is present, or any influence from major industries involved in PCa treatment.

## Conclusions

The Urological community has an overall acceptable awareness of pN+ disease and its management, although it may overestimate disease aggressiveness. The majority considers pN+ disease as a multifaceted category not identifying a gold standard option but rather relying on a risk-adapted approach. In this context, expectant compared to immediate upfront management is increasingly considered together with the use of novel imaging modalities. Future research should implement results of recent PCa management and imaging trials in the context of pN+.

### Clinical Practice Points

- Patients with cN0 M0 Prostate Cancer at preoperative conventional staging that are found with positive nodes at radical prostatectomy (RP) represent the 5 to 10 %. pN+ category is one of the most important prognostic factor for PCa recurrence and mortality. Several retrospective studies suggest that pN+ PCa represents a heterogeneous group that can be treated with different approaches, according to disease and patient characteristics, rather than with ormonotherapy only. Introduction of new imaging modalities as prostate-specific membrane antigen PSMA- and Choline- positron emission tomography (PET) is conditioning patients management.
- Our survey investigated the Urological community perception and opinion on treatment of cN0 M0 pN+ disease after RP. It highlighted that the majority considers pN+ disease as a multifaceted category with different subgroups which may benefit from a risk-adapted strategy; an overestimation of the overall pN+ disease aggressiveness compared to the available evidence was underlined; no clear gold standard pN+ management was identified, but a shift from aggressive upfront treatment to a more expectant management was highlighted; PSMA-PET is considered amongst the most important clinical factors in the context of contemporary pN+ management. The majority of respondent at our survey stated the management of pN+ still not very clear and needed of further evidence.
- Future research should implement results of recent pN+ PCa management. Observation and early salvage radiotherapy, along with the new imaging modalities, must be urgently assessed.

## Author contributions

Giancarlo Marra and Matteo Sacco had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Marra, Gandaglia. Acquisition of data: Sacco, Marra. Analysis and interpretation of data: Sacco, Marra. Drafting of the manuscript: Sacco, Marra, Gandaglia. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Sacco. Obtaining funding: None. Administrative, technical, or material support: None. Supervision: Marra. Other: None.

## Disclosure

The authors have stated that they have no conflicts of interest.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.11.012.

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