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ORIGINAL ARTICLE

The waiting time for prostate cancer treatment in Italy: analysis from the PROS-IT CNR Study

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ABSTRACT

BACKGROUND: Prostate cancer (PCa) is the second most common neoplasm in male patients. To date, there's no certain indication about the maximum waiting time (WT) acceptable for treatment beginning and the impact on oncological and functional outcomes has not been well established.
METHODS: Data from the National Research Council PCa monitoring multicenter project in Italy (Pros-IT CNR) were prospectively collected and analyzed. WT was defined as the time from the bioptical diagnosis of PCa to the first treatment received. Patients were divided in two groups, using a time frame of 90 days. Quality of life was measured through the Italian version of the University of California Los Angeles-Prostate Cancer Index (UCLA-PCI) and of the Short-Form Health Survey (SF-12). The occurrence of upgrading, upstaging, presence of lymph node metastasis and positive surgical margins at the final histopathological diagnosis, and PSA at 12 months follow-up were evaluated.
RESULTS: The overall median WT was 93 days. The logistic multivariable model confirmed that age, being resident in Southern regions of Italy and T staging at diagnosis were significantly associated with a WT>90 days. At 6 months from

diagnosis the mean SF-12 score for the emotional-psychological component was significantly lower in WT≥90 days group (P=0.0428). Among patients treated with surgical approach, no significant differences in oncological outcomes were found in the two groups.
CONCLUSIONS: In our study age, clinical T stage and provenance from Southern regions of Italy are associated with a WT>90 days. WT might have no impact on functional and oncological outcome.

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KEY WORDS: Waiting lists; Prostatic neoplasms; Prostatectomy; Radiotherapy; Androgens.

Prostate cancer (PCa) is the second most common neoplasm in male patients. It represents the 15% of all cancers diagnosed worldwide, with low mortality rate, being the fifth cause of death (6.6%) from cancer in male.[1]

According to the International Society of Urological Pathology (ISUP) 2014 grades, PCa has a variable aggressiveness and biological behavior.[2] In this context, considering prostate specific antigen (PSA), ISUP grade and clinical TNM stage,[3] PCa is stratified according to European Association of Urology (EAU) classification, in three risk groups (low-risk, intermediate-risk and high-risk disease) for biochemical recurrence.[4] To date, different treatment modalities are available, such as active surveillance (AS), surgery (radical prostatectomy, RP), radiotherapy (RT) and androgen deprivation therapy (ADT).[4] For localized disease, no active treatment option has shown superiority,[4] although pathological outcomes in patients eligible for AS are sometimes different from what is expected.[5] Therefore, management decisions should be discussed in multidisciplinary team, considering both benefits and side effects of each type of treatment, according to patients needs and characteristics.[4] Moreover, to date, there's no certain indication about the maximum waiting time (WT) for treatment beginning. For these reasons, open questions still remain on, such us which is the best timeframe for such tumor to provide treatment and if different risk classes might have reserved different timing for treatment. Moreover, the impact of WT on oncological and functional outcomes has not been well evaluated.

In Italy health care is supported by regional protocols as well as institutional programs for PCa that aim to support and integrate international guidelines. Nevertheless, the awareness that cancer care WT might be too long, especially in some regions of the country, persists.

The present work focuses on the potential role of the WT (defined as the time between the diagnosis and the first treatment) in patients with PCa. In particular, aim of the study is to analyze the influence of individual and medical factors on WT, and its impact on quality of life (QoL) and oncological outcomes.

Materials and methods

The Pros-IT CNR study

The National Research Council PCa monitoring project in Italy (Pros-IT CNR) is an ongoing, multicenter and prospective study, aiming to monitor the QoL in a sample of patients diagnosed with biopsy-verified PCa, following them with follow-up at 6, 12, 24, 36, 48 and 60 months from the diagnosis.[6] Demographics and anamnestic data, pharmacological treatments, comorbidities, initial diagnosis, cancer clinical staging and QoL were evaluated at enrollment.[7] At each follow-up type, starting date of treatments received for PCa and QoL were evaluated.[8] WT was defined as the time from diagnosis to the first treatment received for PCa and was calculated in days. Considering the WT, patients were divided in two groups, using a time frame of 90 days.

Patients' QoL was measured with the Italian version of the University of California Los Angeles-Prostate Cancer Index (Italian UCLA-PCI)[9] and the Italian version of the Short-Form Heath Survey (SF-12 Standard v1 scale).[10] UCLA-PCI questionnaire assesses urinary function and bother (UF, UB), bowel function and bother (BF,

BB), sexual function and bother (SF, SB), with responses scored from 0 to 100 (or higher) indicating better conditions. SF-12 includes physical and mental component subscales (PCS and MCS, respectively), both ranging from 0 to 100, with 100 indicating best self-perceived health.

Oncological outcomes were assessed in patients undergone RP, evaluating the occurrence of upgrading, upstaging, presence of lymph node metastasis and positive surgical margins (defined as microscopic if lower than 2 mm, and macroscopic if higher than 2 mm) at the final histopathological diagnosis, and PSA at 12 months follow-up lower than 0.07 ng/mL.

Ethics

The Pros-IT CNR study protocol was approved by the Ethics Committee of the clinical coordinating center (Sant'Anna Hospital, Como, Italy; register number 45/2014) and by the Ethics Committees of each other participating center.

The study was carried out in accordance with the principles of the Declaration of Helsinki and all participants gave their informed consent.

Statistical analysis

Data were analyzed without imputation of missing values. Categorical variables are presented as numbers and percentages, while continuous variables are reported as means and standard deviations (SD) or medians and quartile 1 (Q1) and quartile 3 (Q3). Normal distributions of continuous variables were tested using the Shapiro-Wilk test.

WT from diagnosis to the first treatment received for PCa was calculated in days. Median WT values were computed stratifying the population according to patients' characteristics at diagnosis and compared using Kruskal-Wallis H test or Wilcoxon rank-sum test. Median WT, calculated according to treatment received for PCa, were compared using Generalized Linear Model on rank-transformed data, adjusting for age at diagnosis.

A multivariable logistic regression model was defined to identify characteristics at diagnosis associated with WT dichotomized according to the median of its overall distribution (≥90 *vs.* <90 days). Covariates included in the model were age, education (≥ high school diploma; ≤ lower secondary school diploma), geographical area of residence (Northern, Central or Southern regions of Italy), body mass index (BMI <25 kg/m^2, 25-29.9 kg/m^2, ≥30 kg/m^2), family history of PCa, number of comorbidities with moderate, severe or extremely sever impairment (according to Cumulative Illness Rating Scale, CIRS;[11]), having diabetes mellitus, Gleason Score (GS) at diagnosis (≤6, 3+4, 4+3, ≥8), T staging at diagnosis (T1, T2, T3 orT4)) and PSA at diagnosis (<10 ng/mL, 10-20 ng/mL, ≥20 ng/mL). Linearity of covariates and possible interactions were evaluated. Odds ratios (OR) were presented together with their 95% confidence intervals (CI). A further model was developed considering D'Amico risk classes as independent variables, instead of GS, T staging and PSA at diagnosis as single variables. Sensitivity analyses were also performed evaluating models with different cut-off for WT (quartile 1, 55 days), and excluding patients undergoing ADT or active surveillance (AS) as PCa treatments.

Mean QoL scores according to UCLA-PCI and SF-12 were calculated for the baseline, 6- and 12-months follow-ups, stratifying by dichotomized waiting time (≥90 *vs.* <90 days). Mixed-effects models (Proc Mixed) were used to study changes in QoL related to waiting time ≥90 days, adjusting for baseline score. Models were adjusted also for GS at diagnosis, T staging, PSA and treatment received for PCa (RP; RP and RT and/or ADT; exclusive RT; RT and ADT; only ADT; AS). Compound symmetry covariance structure and Tukey adjustment for multiple comparisons were applied.

A P value<0.05 was considered to be statistically significant. Analyses were performed using SAS v. 9.4 software.

Results

Patients' and cancer characteristics

From September 2014 to September 2015, 1705 patients were enrolled in the Pros-IT CNR study by 97 centers, including 51 Urology, 39 Radiation Oncology and seven oncological facilities located throughout Italy. Overall, 32 patients had distant metastasis at diagnosis, 1537 participated to the first follow-up at 6 months from

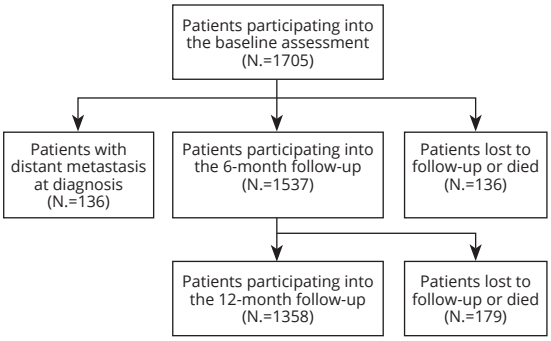

Figure 1.—Flow diagram of the analytic cohort considered.

the diagnosis and 1358 to the second follow-up at 12 months from the diagnosis (Figure 1). At PCa diagnosis, the mean age of patients was 68.9±7.4 years, the median PSA level was 7.2 ng/mL (interquartile range [IQR]: 2, 10.6) and the GS was ≤6 for 718 patients (42.8%), 3+4 for 381 (22.7%), 4+3 for 233 (13.9%) and ≥8 for 349 patients (20.8%).

Waiting times

Data on WT were available for 1466 participants. The overall median WT in the Pros-IT CNR sample was 93 days (IQR: 55, 140).

Figure 2 depicts median WT for different

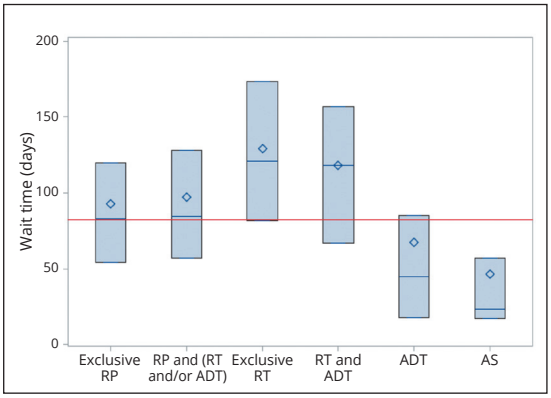

Figure 2.—Median, Q1, Q3 and mean WT according to different treatments for PCa. Each of the box describes the variable WT for a particular PCa type of treatment. The length of the box represents the interquartile range (Q1; Q3). The diamond symbol in the box interior represents the group mean, the horizontal line in the box interior represents the group median, the red horizontal line represents the overall median value.
ADT: androgen deprivation therapy; AS: active surveillance; RP: radical prostatectomy; RT: radiotherapy.

type of PCa treatment, including both unimodal and multimodal approach. In particular, median WT in patients undergone RP (37.2%) was 83 days (IQR: 54, 120), in patients undergone RT (23.1%) was 121 days (IQR: 82, 174) and in patients treated with ADT alone (5.7%) was 45 days (IQR: 18, 85).

Regarding multimodal approach, among patients undergone RP associated to RT and/or ADT (10.6%) median WT was 85 days (IQR: 57, 128), RT with ADT (17.9%) was 118 days (IQR: 67, 157) (P<0.0001, adjusted for age at diagnosis).

Table I shows median WT according to the different patients and tumors characteristics at diagnosis. Significantly higher median WT values were observed among older patients (P=0.002), participants living in Southern regions of Italy (P=0.03), with educational level lower than secondary school diploma (P=0.03), diabetes mellitus (P=0.01) and T2, T3 or T4 staging at diagnosis (P=0.0001). Statistically significant differences were detected, with a non-linear trend, also for PSA at diagnosis (P=0.01).

As shown in Table II, the logistic multivariable model substantially confirmed these results: characteristics at diagnosis significantly associated with a waiting time higher than 90 days were age (65-69 *vs.* 18-64 years, OR=1.74, 95% CI 1.27, 2.40; 70-74 *vs* 18-64 years, OR=1.75 95% CI 1.28, 2.40; 75+ *vs.* 18-64 years, OR=1.79, 95% CI 1.29-2.50), being resident in Southern regions of Italy compared to the Northern ones (OR=2.23, 95% CI 1.26-3.93), and having a T staging at diagnosis T2 vs T1 (OR=1.30, 95% CI 1.02-1.66) or T3, T4 *vs.* T1 (OR=2.08, 95% CI 1.38-3.16). Education, BMI, family history of PCa, number of comorbidities, PSA and GS at diagnosis were not associated with higher WT in the logistic model. A further logistic model developed including D'Amico risk classes among covariates instead of T staging, GS and PSA at diagnosis confirmed the role of age and being resident in Southern regions of Italy; the OR for intermediate and high D'Amico risk classes vs low were 1.08 (95% CI 0.81-1.42) and 1.39 (95% CI 1.03-1.86), respectively. In sensitivity analyses results were substantially confirmed.

TABLE I.—*WT from diagnosis to the first PCa treatment according to patients' and tumor's characteristics.*

Characteristics	N. (%)	WT (days)		
		Median (Q1, Q3)	P value	*Post-hoc*
Age group, years			0.0029	1 *vs.* 2 0.0059
18-64	393 (26.2%)	81 (48-128)		1 *vs.* 3 0.0073
65-69	349 (23.3%)	94 (59-133)		1 *vs.* 4 0.0009
70-74	385 (25.7%)	95 (58-139)		2 *vs.* 3 0.9962
75+	373 (24.9%)	101 (55-152)		2 *vs.* 4 0.3861
BMI			0.2542	
<25 kg/m²	495 (33.8%)	87 (52-132)		
25-29.9 kg/m²	746 (50.9%)	94 (55-140)		
≥30 kg/m²	225 (15.4%)	95 (56-150)		
Level of education			0.0370	
≤ lower secondary school diploma	768 (51.8%)	95 (57-145)		
≥ high school diploma	714 (48.2%)	90 (51-132)		
Geographical area of patient's residence			0.0330	1 *vs.* 2 0.0635
Northern Italy	819 (56.3%)	89 (53-134)		1 *vs.* 3 0.0222
Center	375 (25.8%)	95 (55-152)		2 *vs.* 3 0.6130
Southern Italy	261 (17.9%)	101 (61-146)		
Geographical area of hospital			0.1742	
Northern Italy	890 (59.3%)	90 (54-134)		
Center	390 (26.0%)	93 (55-149)		
Southern Italy	220 (14.7%)	98 (56-147)		
Family history of PCa			0.8386	
No	1231 (82.8%)	91 (55-140)		
Yes	255 (17.2%)	93 (55-135)		
Diabetes mellitus			0.0106	
No	1264 (84.7%)	89 (53-138)		
Yes	228 (15.3%)	105 (65-148)		
N. comorbidities with moderate, severe or extremely severe impairment			0.5156	
0, 1, 2	1266 (84.6%)	91 (54-137)		
3+	230 (15.4%)	96. (55-151)		
GS at diagnosis			0.2899	
≤6	634 (42.9%)	93 (53-135)		
3+4	342 (23.1%)	88 (54-135)		
4+3	209 (14.1%)	104 (61-151)		
≥8	294 (19.9%)	92. (54-142)		
T staging at diagnosis			0.0001	1 *vs.* 2 0.0024
T1	690 (48.5%)	84 (49-127)		1 *vs.* 3 0.0002
T2	571 (40.2%)	93 (55-144)		2 *vs.* 3 0.0846
T3 or T4	161 (11.3%)	109 (61-157)		
PSA at diagnosis			0.0131	1 *vs.* 2 0.0088
<10 ng/mL	1055 (70.8%)	89 (55-135)		1 *vs.* 3 0.2507
10-20 ng/mL	298 (20.0%)	105 (62-149)		2 *vs.* 3 0.0273
≥20 ng/mL	137 (9.2%)	84 (39-151)		
D'Amico Risk class			0.0002	1 *vs.* 2 0.0051
Low	363 (24.7%)	83 (44-126)		1 *vs.* 3 <0.0001
Intermediate	581 (39.6%)	93 (56-141)		2 *vs.* 3 0.1027
High	523 (35.7%)	102 (61-150)		

BMI: Body Mass Index; GS: Gleason Score; PCa: Prostate Cancer; PSA: Prostate Specific Antigen; WT: waiting time.

Effect of WT on QoL

Tables III and IV summarize QoL mean scores at each time point considered in the present analyses (baseline, 6 and 12 months after diagnosis) and the score differences between the two groups (≥90 *vs.* <90 days) from mixed models. No significant differences between groups were observed in the mixed models at any time point in relation to UCLA-PCI scores. According to SF12 MCS, at 6 months from diagnosis the mean emotional and psychological

TABLE II.—*Logistic regression model with outcome WT dichotomized (≥90 vs. <90 days).*

Parameters	OR	95% CI	P value
Age at diagnosis, *vs.* 18-64 years			
65-69	1.74	1.27-2.40	0.0009
70-74	1.75	1.28-2.40	0.0008
75+	1.79	1.29-2.50	0.0011
BMI, *vs.* <25 kg/m^2			
25-29.9 kg/m^2	1.22	0.95-1.56	0.1210
≥30 kg/m^2	1.18	0.83-1.68	0.3548
Education, ≥ high school diploma *vs.* ≤ lower secondary school diploma	0.95	0.76-1.20	0.6813
Geographical area of patient's residence, *vs.* Northern Italy			
Center	1.06	0.64-1.75	0.8355
Southern Italy	2.23	1.26-3.93	0.0066
Family history of PCa	1.21	0.90-1.62	0.2043
Diabetes mellitus	1.18	0.86-1.63	0.3068
3+ comorbidities moderate, severe or extremely severe impairment, *vs.* 0, 1, 2	0.96	0.70-1.32	0.8138
GS at diagnosis, *vs.* ≤6			
3+4	0.76	0.57-1.02	0.0623
4+3	0.90	0.63-1.29	0.5625
≥8	0.74	0.53-1.06	0.0867
T staging at diagnosis, *vs.* T1			
T2	1.30	1.02-1.66	0.0374
T3 or T4	2.08	1.38-3.16	0.0001
PSA at diagnosis, *vs.* <10 ng/mL			
10-20 ng/mL	1.30	0.97-1.75	0.0813
≥20 ng/mL	0.92	0.60-1.42	0.7066

OR: odds ratio; CI: confidence interval.

TABLE III.—*UCLA-PCI score over time, by different WT.*

Timepoint	WT<90 days Mean (95% CI)	WT≥90 days Mean (95% CI)	P value §	WT≥90 *vs.* <90 days	
				Mean diff. (95% CI)	P value §
UCLA PCI UF			0.1159		
Baseline	96.1 (94.5, 97.7)	94.4 (92.7, 96.1)		1.72 (-1.29, 4.72)	0.5801
6 months	83.3 (81.7, 84.9)	84.1 (82.4, 85.8)		-0.84 (-3.89, 2.22)	0.9706
12 months	87.1 (85.4, 88.8)	87.5 (85.7, 89.3)		-0.41 (-3.62, 2.80)	0.9991
UCLA PCI UB			0.0610		
Baseline	90.5 (88.5, 92.5)	89.3 (87.2, 91.4)		1.14 (-2.64, 4.92)	0.9560
6 months	81.5 (79.5, 83.5)	78.5 (76.4, 80.7)		2.97 (-0.89, 6.82)	0.2410
12 months	84.3 (82.2, 86.5)	85.7 (83.4, 87.9)		-1.34 (-5.40, 2.72)	0.9364
UCLA PCI BF			0.1988		
Baseline	93.7 (92.7, 94.8)	94.0 (92.9, 95.1)		-0.32 (-2.34, 1.69)	0.9974
6 months	92.9 (91.8, 94.0)	91.9 (90.8, 93.1)		0.97 (-1.08, 3.02)	0.7563
12 months	85.5 (84.4, 86.6)	84.2 (83.1, 85.4)		1.27 (-0.88, 3.43)	0.5424
UCLA PCI BB			0.0657		
Baseline	92.9 (91.5, 94.4)	93.6 (92.1, 95.1)		-0.67 (-3.39, 2.05)	0.9817
6 months	90.9 (89.5, 92.4)	90.9 (89.3, 92.4)		0.06 (-2.72, 2.85)	1.0000
12 months	92.4 (90.9, 93.9)	90.1 (88.5, 91.7)		2.30 (-0.62, 5.21)	0.2620
UCLA PCI SF*			0.6063		
Baseline	60.3 (57.6, 63.0)	59.9 (56.9, 63.0)		0.37 (-4.57, 5.31)	0.9999
6 months	26.4 (23.7, 29.2)	28.3 (25.1, 31.4)		-1.85 (-6.96, 3.25)	0.9052
12 months	33.9 (31.0, 36.7)	33.8 (30.5, 37.2)		0.01 (-5.38, 5.39)	1.0000
UCLA PCI SB*			0.4053		
Baseline	67.4 (63.7, 71.1)	68.6 (64.5, 72.8)		-1.21 (-8.01, 5.59)	0.9959
6 months	45.9 (42.2, 49.7)	43.1 (38.8, 47.4)		2.80 (-4.23, 9.82)	0.8660
12 months	51.0 (47.2, 54.9)	52.0 (47.4, 56.6)		-0.96 (-8.37, 6.45)	0.9991

UCLA PCI: University of California Los Angeles-Prostate Cancer Index; BB: bowel bother; BF: bowel function; SB: sexual bother; SF: sexual function; UB: urinary bother, UF: urinary function; WT: waiting time.
§ P value from mixed-model repeated measures analyses, wait-time*time interaction, adjusted for baseline score; *models adjusted also for nerve-sparing.

TABLE IV.—*SF-12 score over time, by different wait-time.*

Timepoint	WT<90 days Mean score (95% CI)	WT≥90 days Mean score (95% CI)	P value §	WT≥90 *vs.* <90 days	
				Mean diff. (95% CI)	P value#
SF-12 PCS			0.8623		
Baseline	51.1 (50.5, 51.7)	51.0 (50.4, 51.5)		0.15 (-0.85, 1.16)	0.9983
6 months	49.8 (49.2, 50.3)	49.3 (48.7, 49.9)		0.42 (-0.60, 1.45)	0.8503
12 months	49.7 (49.1, 50.3)	49.3 (48.7, 50.0)		0.40 (-0.69, 1.48)	0.9036
SF-12 MCS			0.0076		
Baseline	48.7 (48.1, 49.3)	49.1 (48.5, 49.7)		-0.38 (-1.45, 0.68)	0.9110
6 months	50.8 (50.2, 51.4)	49.8 (49.2, 50.4)		1.02 (0.07, 2.12)	0.0428
12 months	53.7 (53.1, 54.3)	53.1 (52.5, 53.8)		0.56 (-0.60, 1.72)	0.7356

SF-12: Short-Form Heath Survey; MCS: mental component subscales; PCS: physical component subscales; WT: waiting time.
§P value from mixed-model repeated measures analyses, wait-time*time interaction, adjusted for baseline score; #*post-hoc* P value from mixed-model repeated measures analyses, with Tukey adjustment. Models were also adjusted for age at diagnosis, Gleason Score at diagnosis, T staging, PSA at diagnosis and treatment received for prostate cancer.

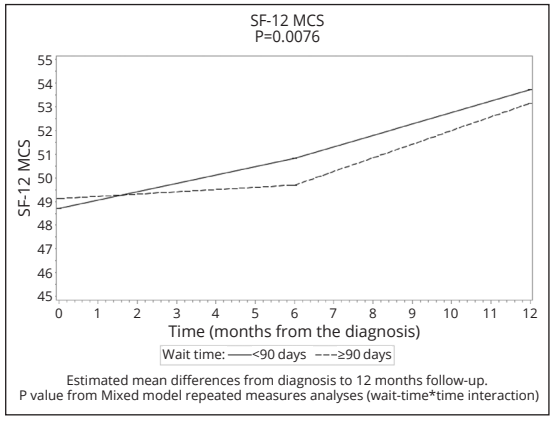

Figure 3.—Mean QoL scores from mixed models, by treatment over time, for SF-12 MCS.
MCS: mental component subscales; SF-12: Short-Form Heath Survey.

score of patients with a WT ≥90 days was significantly lower than that of patients with a WT lower than 90 days (49.8, 95% CI 49.2, 50.4 *vs.* 50.8 95% CI 50.2, 51.4; P=0.0428). The difference was not still significant at 12-months follow-up. Figure 3 shows mean QoL scores for SF-12 MCS from mixed models, by treatment over time.

Effect of waiting time on oncological outcome in patient underwent RP

As shown in Table V, in patients undergone RP, no significant differences were found in the two groups (≥90 *vs.* <90 days) in terms of upgrading and upstaging. Moreover, no significant differences were observed in terms

TABLE V.—*Oncological outcomes for patients undergoing exclusive RP, by different WT.*

Parameter	Overall (N.=526)	WT<90 days (N.=287)	WT≥90 days (N.=239)	P value
Upgrading				
≤6 → 3+4, 4+3, ≥8	120 (46.3%)	63 (47.3%)	57 (45.2%)	0.7311
3+4 → 4+3, ≥8	43 (36.1%)	23 (30.3%)	20 (46.5%)	0.1114
4+3 → ≥8	10 (23.8%)	3 (16.7%)	7 (29.2%)	0.4726
Upstaging				
cT1 → pT2, pT3	293 (98.0%)	152 (98.0%)	141 (97.9%)	1.0000
cT2 → pT3	64 (35.8%)	44 (38.6%)	20 (30.8%)	0.2934
Positive lymph nodes §	7 (3.4%)	2 (1.7%)	5 (5.4%)	0.2457
Positive surgical margins				0.7790
No positive surgical margin	369 (73.1%)	200 (72.5%)	169 (73.8%)	
Microscopic positive surgical margin	112 (22.2%)	64 (23.2%)	48 (21.0%)	
Macroscopic positive surgical margin	24 (4.8%)	12 (4.4%)	12 (5.2%)	
PSA at the 12-month follow-up <0.07 ng/mL	360 (84.3%)	206 (85.1%)	154 (83.2%)	0.5965
PSA <0.07 ng/mL, UCLA-PCI UF ≥70, UCLA-PCI SF≥30 at the 12-month follow-up#	131 (43.5%)	77 (46.7%)	54 (39.7%)	0.2254

§ Only for patients undergoing lymphadenectomy; #only for patients undergoing nerve sparing,
PSA: prostate-specific antigen; UCLA PCI: University of California Los Angeles-Prostate Cancer Index; WT: waiting time.

of lymph node involvement, positive surgical margins and PSA lower than 0.07 ng/mL at 12 months follow-up.

Discussion

Despite the different incidence among geographical regions, PCa is the second most commonly diagnosed tumor in men.[1]

Considering the aggressiveness variability of PCa and the wide range of available treatments, European guidelines recommends different treatment options according to prognostic risk stratification. Active surveillance or active treatments can be offered for low-risk diseases; active treatments for those patients with intermediate-risk tumor and, where appropriate, a multimodal approach for high-risk PCa.[4]

Although international guidelines provide detailed information for the management of PCa, nowadays there's no consensus about the certain time frame for its treatment. The impact of WT on oncological and functional outcomes in patients affected by PCa is still debated and information in this regard are lacking. Moreover, in Italy, as part of the national health-care system, the single regions regulate and organize services destinated to citizens health care. Consequently, a great variability about the timing of PCa management persists between different countries and even between different areas of the same country.

The most important key finding of our study is that a WT higher than 90 days does not substantially impact on patient's health. Nevertheless, data on this aspect are fragmentary and conflicting.

Regarding oncological outcome, Gupta *et al*., in line with our results, found no significant differences in positive surgical margins, extra-prostate extension of the tumor, seminal vesicles and lymph node involvement between men underwent RP before and after 3 months after diagnosis.[12] Similarly, Zanaty *et al*. demonstrated that WT from prostate biopsy to surgery was not associated to unfavorable pathologic outcomes for any risk group.[13] Conversely, the systematic review conducted by Mhaskar *et al*. showed a survival benefit in patients treated early, but without difference in response rate, even if the definition of "late treatment" is very variable.[14]

Regarding to functional outcomes, in our study, no significant differences were observed at UCLA-PCI scores. Interestingly, at 6 months from diagnosis the mean emotional and psychological score (SF-12) was significantly lower in WT $\geq$ 90 days cohort. Nevertheless, this difference between the two cohorts was not still significant at 12-months follow-up. Therefore, in the PROSIT-CNR study, an early treatment allows to achieve an early emotional well-being, related to the immediate tumor control (probably related to the decrease of PSA value). On the contrary, evaluating the impact of time from biopsy to surgery, Westerman *et al*. found that, after 12 months, patients undergone RP$\leq$3 weeks after biopsy had significantly more incontinence and worse potency rates than those undergone RP in more than 12 weeks after biopsy.[15]

In our study, multivariable analysis suggests that age, clinical T stage higher than T1 and provenance from Southern regions of Italy are factors associated with a WT higher than 90 days. A longer WT for older patients and clinical T stage higher than T1 might be due to the complex evaluation before treatment. Considering the growth of population aged $\geq$65 years in the Europe and the correlation between PCa incidence and patients age, nowadays the evaluation of the elderly affected by prostate tumor has become more complex than in the past.[16, 17] In fact, considering the adverse effects related to each type of treatment, a careful assessment of risk factors and comorbidities in older patients should be done before planning surgery, RT or ADT.[18] In fact, as reported by Houterman *et al*., both age and comorbidity are strong independent prognostic factors in patients with PCa. In particular, the risk of death is three and two times higher in patient $\geq$80 years, in case of RT and ADT, respectively.[19] However, there's no consensus in literature about the factors related to high WT. In fact, Westerman *et al*., considering time between prostate biopsy and surgical treatment of PCa, found that patients undergone RP within 3 weeks of biopsy were older, with high preoperative PSA and clinically higher risk disease than those patients who waited 13-26 weeks.[15]

The potential role of provenance might be explained by two factors. First, it might be due to

the mobility of patients to choose the hospital for specialist consult. In England, Aggarwal *et al.* found that the 33.5% of men with PCa do not choose the nearest PCa surgical center. In fact, the choice appeared to be guided by the availability of robotic surgery and the reputation of individual clinicians.[20] Similarly, the 20.7% of patients bypass the nearest radiation therapy center to choose high-volume RT units or hospitals that offered hypofractionated or intensity modulated prostate radiation.[21]

Secondly, in some regions of the country, hospitals are spread on a wide area and the access for patients to specialistic centers could be difficult and time-consuming. Similarly, in Sweden and Denmark, despite national clinical pathways for cancer treatment have been assessed, a huge variability in WT have been described.[22, 23] In particular, Robertson *et al.* reported that the median WT from the specialist referral to the treatment ranged from 117 to 280 days among 21 counties.[22]

In many countries, national guidelines aim to respond to the lack of clear guidelines about the best timing for the treatment of oncological diseases, by identifying a specific time frame. In this regard, in UK, the Government White Paper entitled The New National Health Service (NHS) — Modern, Dependable specifies that every patient with suspicion of cancer would be able to see a specialist within 2 weeks from their general practitioner (GP) evaluation, according to urgency judgment.[24] However, as reported by Subramonian *et al*., only 34% of patients achieved a hospital specialist consultation in this time frame.[25] In the series reported by the Authors, the median WT from GP consultation to RP was 244 days for PCa and, as for bladder and renal cancers, the principal element of delay was the time from the diagnosis to the surgery (76 days).[25]

Nevertheless, it should be noted that the application of non-flexible rules for all type of tumors could not reflect the variability of biological features. In fact, PCa is often considered as a poorly aggressive or indolent cancer and this may be reflected in priorities.

Moreover, we have to consider that a huge amount of active strategies for therapeutic options for PCa exists. In this regard, giving the opportunity to have multiple consultations might result in wasting time and prolong the time to treatment.[12]

Limitations of the study

Our study is not devoid of limitations. First, this is an observational prospective study. Secondly, there's a lack of information about the availability of different treatment modalities in each center participating to the study. Third, in our analysis patients are not stratified on PCa risk classes and there's a lack of information about patients and tumor characteristics. In fact, these factors could be related to a complex decision making and, where applicable, to the necessity of imaging for staging purpose, a process that could be time consuming. Moreover, our study included 97 center which differ for volume and experience of surgeons and physicians. These factors might affect the outcome of the treatment modality and QoL of patients.

Despite these limitations, to the best of our knowledge, this is the first Italian multicenter study evaluating factors related to WT from diagnosis to treatment and also the functional and oncological impact of WT in patients with PCa.

Conclusions

In our study, age, clinical T stage and provenance from Southern regions of Italy are factors associated with a WT higher than 90 days. WT might have no impact on functional and oncological outcome. Our results provide suggestion for further studies evaluating if different geographical areas or different patients and tumors characteristics could be related to higher WT. Further high-quality studies are needed to assess the impact of WT on functional and oncological outcome at mid and long-term follow-up.

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