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Impact of ^{68}Ga-PSMA-11 PET on the Management of recurrent Prostate Cancer in a Prospective Single-Arm Clinical Trial

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ABSTRACT

Introduction: Prostate-specific membrane antigen ligand positron emission tomography (PSMA PET) induces management changes in patients with prostate cancer. We aim to better characterize the impact of PSMA PET on management of recurrent prostate cancer in a large prospective cohort. Methods: We report management changes following PSMA PET, a secondary endpoint of a prospective multicenter trial in men with prostate cancer biochemical recurrence. Pre-PET (Q1), Post-PET (Q2) and Post-Treatment (Q3) questionnaires were sent to referring physicians recording site of recurrence, intended (Q1 to Q2 change) and implemented (Q3) therapeutic and diagnostic management. Results: Q1/Q2 response was collected for 382/635 (60%, intended cohort), Q1/Q2/Q3 for 206 patients (32%, implemented cohort). Intended management change (Q1/2) occurred in 260/382 (68%) patients. Intended change (Q1/2) was considered major in 176/382 (46%) patients. Major changes occurred most often for patients with PSA of 0.5 to <2.0 ng/mL (81/147, 55%). By analysis of stage-groups, management change was consistent with PET disease location, i.e. majority of major changes towards active surveillance (47%) for unknown disease site (103/382, 27%), towards local/focal therapy (56%) for locoregional disease (126/382, 33%), and towards systemic therapy (69% M1a; 43% M1b/c) for metastatic disease (153/382, 40%). According to Q3 responses, intended management was implemented in 160/206 (78%) patients. A total of 150 intended diagnostic tests, mostly CT (n=43, 29%) and bone Scans/NaF-PET (n=52, 35%), were prevented by PSMA PET; 73 tests, mostly biopsies (n=44, 60%) as requested by the study protocol, were triggered (Q1/2). Conclusions: According to referring physicians, sites of recurrence were clarified by PSMA PET and disease localization translated into

management changes in more than half of patients with biochemical recurrence of prostate cancer.

INTRODUCTION

Positron-Emission-Tomography (PET) using ^{68}Gallium-labeled ligands of the prostate-specific membrane antigen (PSMA) stages prostate cancer with high accuracy (*1,2*). Among other factors, disease location and extent critically guide management of recurrent prostate cancer (*3,4*).

The impact of ^{68}Ga-PSMA-11 PET (PSMA PET) on the management of biochemically recurrent prostate cancer has been assessed in several retrospective studies or smaller prospective cohorts (*5-8*). A recent meta-analysis investigating impact of PSMA PET on management at primary staging or biochemical recurrence reported management changes in approximately half of patients, but found considerable heterogeneity among trials depending on PSA level, PET positivity, and type of change definition (*9*). Overall, common management pathways and their association with PSA or PSMA PET stage have not been characterized in a large prospective patient cohort yet.

Our recent prospective multicenter trial confirmed high detection rates, positive predictive value, and inter-reader reproducibility along with favorable safety of PSMA PET in 635 patients with biochemically recurrent prostate cancer (*10-12*). Here we assess the impact of PSMA PET on the diagnostic and therapeutic management of biochemically recurrent prostate cancer, a secondary endpoint of this trial. To identify management pathways, intended and implemented management change was determined for different stage groups, defined by PSMA PET.

MATERIALS AND METHODS

Study Design

Patients were recruited at the University of California, Los Angeles (NCT02940262) and the University of California, San Francisco (NCT03353740) (*10*). In brief, patients with histopathologically confirmed prostate adenocarcinoma and biochemical recurrence were eligible. Biochemical recurrence was defined as a PSA of 0.2 ng/mL or higher measured more than six weeks after prostatectomy or a rise of PSA 2 ng/mL or higher above nadir following radiation therapy.

^{68}Ga-PSMA-11 PET

Imaging procedure was reported previously (*10*). In brief, all patients underwent ^{68}Ga-PSMA-11 PET/CT or PET/MRI in accordance with present imaging guidelines (*13*). Images were interpreted by local clinical read, and for study report additionally by three blinded readers using an image-based TNM-staging system (PROMISE) following regions for recurrence: prostate, prostate bed, and seminal vesicle remnants (Tr), pelvic lymph nodes (N1) (internal iliac, obturator, external iliac, perirectal, presacral, common iliac, other), extrapelvic lymph nodes (M1a) (retroperitoneal, inguinal, chest, other), bone (M1b), and visceral organs (M1c) (*14*).

Management

Figure 1 illustrates patient flow and physician surveys. To assess change in intended management after PSMA PET, referring physicians received a Pre-PET Questionnaire (Q1, Supplemental Figure 1) upon scheduling of the patient and a Post-PET Questionnaire (Q2, Supplemental Figure 2) along with the written PSMA PET report and a DVD with PET/CT or PET/MRI images. In Q1, referrers were asked to indicate their pre-PET site of recurrence, which diagnostic tests they would order and their currently

intended management if PSMA PET was not available. In Q2, referrers were asked again to indicate post-PET site of recurrence and their intended management based on current clinical work-up, including PSMA PET/CT or PET/MRI. Additionally, they were asked whether PSMA PET enabled them to avoid or trigger any test or procedure. As part of follow-up, referring physicians received a 3 to 6-month follow-up questionnaire (Q3, Supplemental Figure 3) asking the referrers whether the intended management noted on Q2 was implemented.

Inter-modality changes were considered major changes, with the exception of adjuvant androgen deprivation therapy (ADT) added to or removed from local therapy, which was considered a minor change. Furthermore, we considered a switch of systemic treatment (i.e. modality Abiraterone/Enzalutamide to chemotherapy) as major change. Otherwise intramodality changes were regarded as minor changes. A detailed description of change categories can be found in Supplemental Table 1.

This study was approved by local institutional review boards at UCSF and UCLA, and written informed consent was obtained from all patients. Trial data were collected in a central REDcap database. Descriptive statistics were used to analyze and present data. All analyses were performed using R-statistics (R version 3.4.0).

RESULTS

Baseline Characteristics

382 of 635 (60%) patients had complete Q1 and Q2 surveys (intended management cohort). Complete Q1, Q2 and Q3 surveys were available for 206 patients (32%, implemented management cohort).

Baseline characteristics of the intended management cohort are summarized in Table 1. Before PSMA PET, referring physicians responded that the location of disease was unknown in 262 of 382 patients (68%); 64 of 382 (17%) patients had locoregional disease, and 56 of 382 (15%) patients had metastatic disease.

Site of Recurrence and intended Management Change

Figure 2 illustrates survey-based site of recurrence and intended management changes (Q1/2) stratified by PSMA PET disease stage groups.

In the subgroup with no lesion localization by PSMA PET (n=103 of 382, 27%), referring physicians reported unknown disease location for 63 of 103 (61%; -19% change from baseline) patients according to the post-PET survey. Major change was recorded for 38 of 103 (37%) patients with the largest subgroup (18 of 38, 47%) changing to intended active surveillance.

In the subgroup with locoregional disease by PSMA PET (n=126 of 382, 33%), referring physicians reported suspicion of locoregional disease in 91 of 126 (72%; +51% change from baseline) patients according to the post-PET survey. Major change was recorded in 61 of 126 (48%) patients with the largest subgroup being intended for local treatment options (34 of 61, 56%).

In the subgroup with extra-pelvic nodal metastatic disease (M1a) according to PSMA PET (n=64 of 382, 17%), referring physicians reported suspicion of metastatic disease in 37 of

64 (58%; +41% change from baseline) cases after PET. Major change was recorded in 31 of 64 (48%) patients with largest group shifting towards systemic therapy (20 of 31, 65%) post-PET.

In the subgroup with osseous (n=85, M1b) or visceral metastatic (n=4, M1c) disease by PSMA PET, referring physicians reported suspicion of metastatic disease in 65 of 89 (73%; +37% change from baseline) patients after PET. Major change in intended management occurred in 46 of 89 (52%) patients, with the largest groups being intended for either focal (15 of 46, 33%) or systemic therapy (20 of 46, 43%) post-PET.

Rate of major change was different for the pre-defined PSA ranges: 39% for <0.5 ng/ml (n=85), 58% for 0.5 to <1.0 ng/ml (n=57), 53% for 1.0 to <2.0 ng/ml (n=90), 45% for 2.0 to <5.0 ng/ml (n=96), and 35% for ≥5.0 ng/ml (n=54) as demonstrated in Supplemental Figure 4.

Rate of major change was different among patients with previous prostatectomy, radiotherapy or both (Table 2). The highest proportion of management changes was observed in patients having had both (57%). Intended management change (Q1/2) was not considerably different among patients currently undergoing vs. not undergoing androgen deprivation therapy.

Triggered or prevented Diagnostic Tests

Table 3 lists diagnostic tests planned before and prevented or triggered after PSMA PET according to the referring physicians. Before PSMA PET, referring physicians intended to perform 443 tests in 382 patients. According to Q2, a total of 150 tests were prevented. One test was prevented in 45 of 382 patients (12%), and multiple tests were prevented in 48 of 382 patients (13%). Mostly bone scans/NaF-PET (52 of 150 tests, 35%) and CT Scans (43 of 150 tests, 29%) were prevented by PSMA PET. Following PSMA

PET, 73 diagnostic tests were triggered in 70 patients. One test was triggered in 67 of 382 patients (18%), and two tests were triggered in 3 of 382 patients (1%). Biopsies to confirm PSMA PET-positive sites of disease (44 of 73 tests, 60%) were triggered most often.

Implemented Management

Management implementation rates are given in Table 4. According to Q3 responses, intended management was implemented in 160 (78%) patients. Management was implemented in 98 of 135 (72%) of patients with intended change. Continuation of pre-PET management was implemented in 62 of 70 (89%) of cases. Implementation rate was consistent and ranged from 66 to 78% for the several management change pathways (Table 5).

DISCUSSION

For clinical impact, diagnostics tests need to translate into relevant changes in management. Analyses of the National Oncologic PET Registry (NOPR) demonstrated a change of management in 37% of cases following ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) in cancer patients and resulted in FDG PET reimbursement for a wide range of indications in the US (*15*). However, a subanalysis of the NOPR study revealed a somewhat lower change of management rate for prostate cancer as compared to other entities, possibly due to low FDG uptake and limited lesion detection (*16*). Since NOPR completion, several novel radiotracers have been introduced for prostate cancer imaging. Of these, radiolabeled PSMA-ligands have been studied extensively since their introduction. Recently, high positive predictive value, detection rate and inter-reader agreement were reported for PSMA PET in a prospective multicenter trial

(*10*). Here, we present NOPR-like survey-based impact on management data, a secondary endpoint of this prospective study.

PSMA PET resulted in change in management in more than half of patients undergoing PSMA PET for localization of biochemically recurrent prostate cancer. Referring physicians frequently accepted reported site of disease according to post-PET surveys. Subsequent management pathways were consistent with PSMA PET disease locations, i.e. local disease was considered more often for local treatment (54 of 126 patients, 44%) versus systemic disease was associated more often with intended change towards systemic or combination approaches (106 of 153 patients, 69%). Our findings demonstrate that the accuracy of PSMA PET translates into change in disease stage and management, both consistent with PET-positive sites of recurrent prostate cancer.

Following PSMA PET, the proportion of patients with unknown sites of disease declined from about two thirds to one third according to the referring clinicians. PSMA PET disease location was frequently accepted by referring physicians. Individual management pathways are diverse (Supplemental Figure 5). However, changes demonstrate detectable patterns: Patients without detectable disease by PSMA PET more often experienced intended major de-escalation towards active surveillance (47%), whereas patients with locoregional disease had intended major transition towards focal therapy (56%). In case of extra-pelvic nodal disease (M1a), clinicians tended towards major change to systemic therapy (65%). In patients with bone metastasis (M1b) or visceral metastasis (M1c), major systemic and/or local treatment changes were most common (43% and 33%, respectively).

Accurate localization of disease is a critical early step in the management of patients with biochemical recurrence of prostate cancer. Focal and salvage therapies

need accurate target delineation. On the other hand, the presence of distant metastases may trigger additional or alternative systemic therapy (*3*). Therefore, the updated EAU guidelines recommend PSMA PET in BCR after radical prostatectomy if the results will influence subsequent treatment decisions (*3*). In this study, major changes occurred most often in patients with PSA of 0.5 to <2.0 ng/mL. However, impact on subsequent treatment decisions occurred also in patients with undetectable or extensive disease. We further demonstrate that detectable management pathways follow guideline recommendations: Focal or salvage therapy is offered for local disease, and systemic treatment is recommended in case of metastatic spread (*3*). Whether PSMA PET induced management changes translate into survival benefits remains unknown. Prospective studies with long-term follow-up are required to answer this question. In this intent, trials investigating PSMA PET guided therapy are currently underway (*17,18*).

A previous study reports management changes based on surveys and chart review in an initial UCLA cohort (n=101) of the presented study (*5*). Systematic chart review confirms that intended management changes frequently differ from implemented changes based on subsequent diagnostic tests, tumor board decisions or patient preference (*5*). However, even when considering subsequent modification, the overall proportion of patients experiencing major implemented management change remains high (*5*). In our expanded cohort (n=382), survey-based implemented management differed from intended management in 22% of cases overall; discrepancy was somewhat higher in patients with intended management change (38%). The proportion of management change was similar in the biochemical failure cohort of a recent Australian multicenter study finding altered management in 62% of patients (*6*). Similarly, Muller et al. found a 60% management change in a retrospective cohort of recurrent prostate cancer and, of

note, a high response rate to subsequent focal therapy (*19*). Overall, impact on management was higher than reported in a recent meta-analysis of 1163 patients at primary diagnosis and biochemical recurrence with a change of management occurring in 54% of cases (95%CI: 47-60%) (*9*). In this study, we report in more detail, how management pathways are associate with PET-stage indicating high confidence of referring physicians in PSMA PET findings.

One hundred fifty diagnostic tests were prevented by PSMA PET according to survey response. Most of these were CT-scans (43 cases) or bone scans/^{18}F–Sodium Fluoride (NaF) PET/CTs (52 cases). Decision for omitting these diagnostic tests is in line with several studies that demonstrate superior accuracy of PSMA PET when compared with one or a combination of the prevented diagnostic instruments for prostate cancer localization (*8,12,20,21*). Specifically, PSMA PET demonstrated superior detection sensitivity when compared head-to-head with bone scan or recently approved ^{18}F-fluciclovine, especially at PSA≤2 ng/mL (*20,21*). Although more diagnostic tests were prevented than triggered, the addition of PSMA PET increases total diagnostic work-up. On the other hand, at the time of enrollment referring physicians had little experience with PSMA PET and part of diagnostic tests, including biopsies (44/382, 12%), were encouraged by the study protocol for lesion validation. Histopathology validation resulted in a positive predictive value of PSMA PET of 84% both on a per-patient and per-region basis (*10*). As availability improves, by an increasing number of clinical trials or a planned approval of PSMA-ligand PET, additional tests, especially potentially burdensome biopsies, may be ordered less frequently in the future clinical setting.

While this study benefits from a large cohort, missing questionnaires are a limitation to our study. More specifically, 60% of cases had completed questionnaires Q1 and Q2,

and all three questionnaires were available in 32% of patients only. More frequent reply by proponents of new imaging technologies may have introduced a responder bias. Furthermore, information on implemented management was not confirmed by file review and potential discrepancy between intended and finally implemented management, reported previously (*5*), was not resolved. Low Q3 rate may be due to late request to respond, i.e. 3 to 6 months after PSMA PET, disconnected from the PET report and outside typical clinical timelines. Also, more frequent Q3-response for closely monitored or high-risk patients, might have led to an overestimation of the management implementation rate. On the other hand, similar patient characteristics of the intended versus implemented management cohorts (Table 1) indicate no relevant selection bias. Only a small proportion of patients were African-American. This underrepresentation may have led to a selection bias and findings might not be entirely applicable to this ethnic group.

CONCLUSION

PSMA PET findings were accepted by referring physicians and induced management changes in more than half of patients with biochemically recurrent prostate cancer. Management pathways aligned with PET disease location: Focal or salvage therapy for local disease; systemic treatment for distant metastases. Future randomized trials aim to evaluate the impact of management changes on oncologic outcomes.

DISCLOSURE

Wolfgang Fendler is a consultant for Ipsen, Endocyte, and BTG, and he received personal fees from RadioMedix outside of the submitted work. Matthias Eiber is consultant for ABX and Blue Earth Diagnostics. Johannes Czernin is a founder, board member, and holds equity in Sofie Biosciences and Trethera Therapeutics. Intellectual property patented by the University of California is licensed to Sofie Biosciences and Trethera Therapeutics. Johannes Czernin serves on the medical advisory board of Actinium and is a member of the VISION trial steering committee, a clinical trial sponsored by Endocyte. Robert Flavell receives grant support from Fukushima SiC. Thomas Hope is a consultant for Curium and Ipsen and receives grant support from Philips. Matthew Rettig is speaker and advisory board member for Janssen and Bayer and receives research funding from Novartis; he consults for Amgen and Ambrx. Ken Herrmann reports personal fees from Bayer, other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, outside the submitted work. No other potential conflicts of interest relevant to this article exist.

Author contributions

Wolfgang Fendler and Thomas Hope 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: Matthias Eiber, Wolfgang Fendler, Justin Ferdinandus, Ken Herrmann, Thomas Hope

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Drafting of the manuscript: Wolfgang Fendler, Justin Ferdinandus, Thomas Hope

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Administrative, technical, or material support: Jeannine Gartmann, Roger Slavik

Supervision: Johannes Czernin, Thomas Hope

Other: -

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Key Points

QUESTION: Does PSMA PET impact the management of men with biochemically recurrent prostate cancer?

PERTINENT FINDINGS: We demonstrate that PSMA PET findings were frequently accepted by referring physicians and induced management changes in 260/382 (68%) patients with biochemically recurrent prostate cancer. Furthermore, management pathways aligned with PET disease location: Local therapy was chosen more often for local disease; change towards systemic treatment was seen more often for distant metastases.

IMPLICATIONS FOR PATIENT CARE: We demonstrate that ^{68}Ga-PSMA-11 PET accuracy translates into change in management for patients with recurrent prostate cancer. The potential benefit of PSMA PET guided management now needs to be assessed in prospective trials with oncologic outcome.

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FIGURES

Figure 1: Patient Flow and Study design

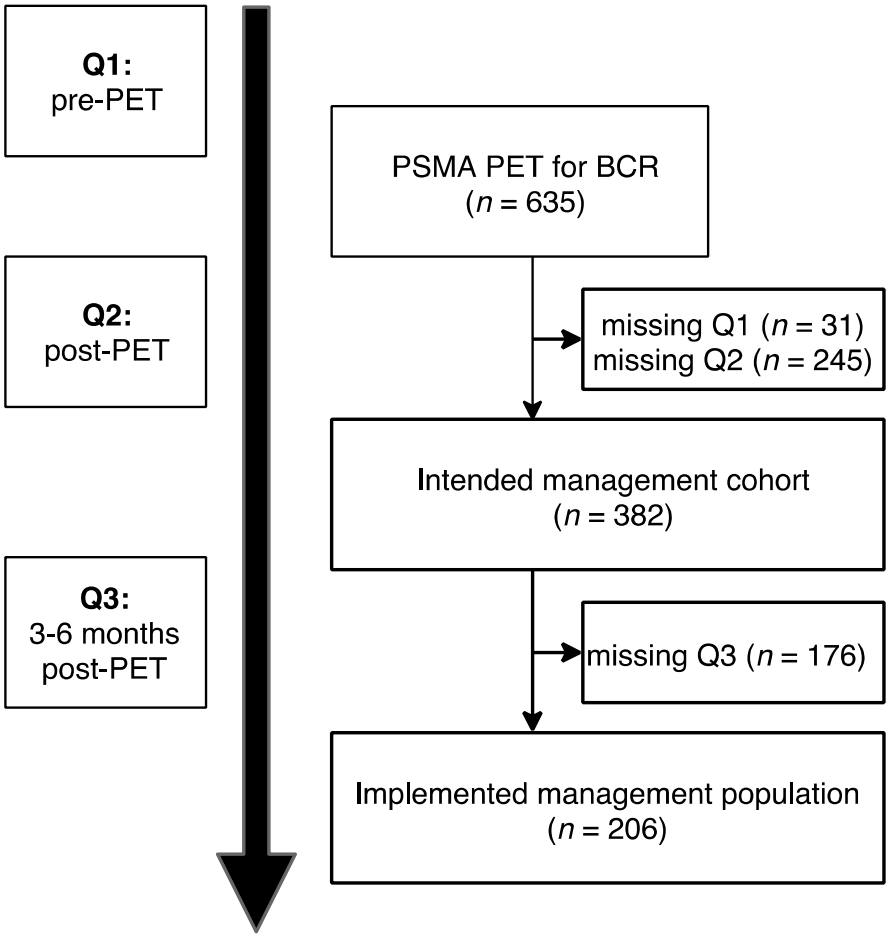
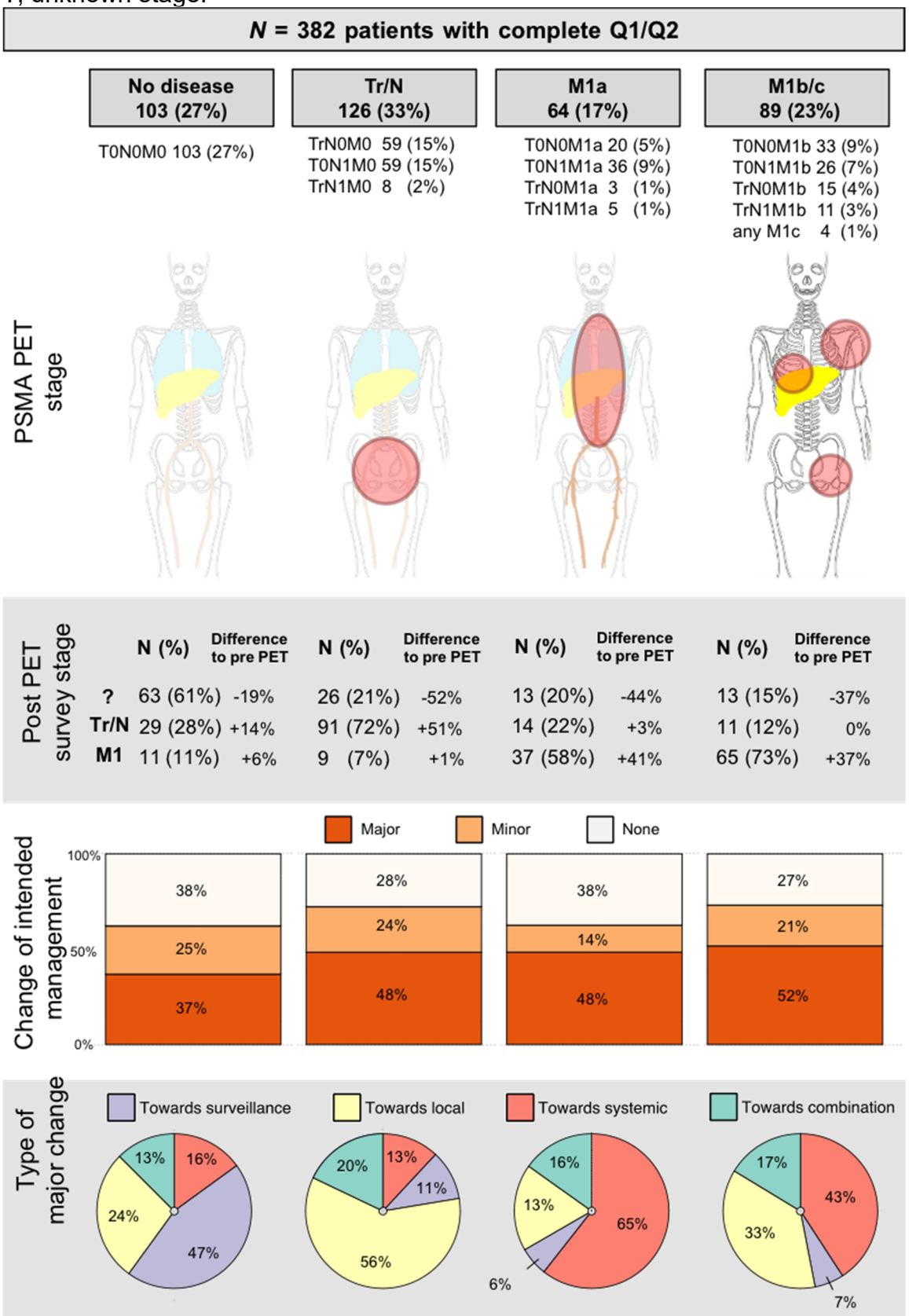


Figure 2: Summary of intended management change after PSMA PET. Abbreviation: ?, unknown stage.



TABLES

Table 1: Characteristics of the intended (n=382) and implemented management cohorts (n=206)

Characteristic		Median	(Range)	Intended cohort N (%)	Implemented cohort N (%)
Age (years)		70,1	(43,8-95,3)		
Ethnicity/Race					
	White American			333 (87%)	177 (86%)
	Black or African American			8 (2%)	2 (1%)
	Asian American			10 (3%)	4 (2%)
	Other			14 (4%)	7 (3%)
	Missing data			17 (5%)	15 (7%)
Initial therapy					
	Prostatectomy only			166 (44%)	86 (42%)
	Radiotherapy only			101 (26%)	50 (24%)
	Prostatectomy and Salvage Radiotherapy			115 (30%)	70 (34%)
Other prior therapy					
	Local salvage therapy			56 (15%)	19 (9%)
	ADT			145 (38%)	80 (39%)
	Abiraterone/Enzalutamide			11 (3%)	4 (2%)
	Chemotherapy			12 (3%)	3 (1%)
	Bone targeted treatment			4 (1%)	1 (0%)
	Other			24 (6%)	3 (1%)
Gleason Score					
	<8			237 (62%)	125 (61%)
	≥8			112 (29%)	62 (30%)
	Missing data			33 (9%)	19 (9%)
PSA					
	Intended cohort	1,86	(0,05-425)		
	Implemented cohort	1,75	(0,2-425)		
dtPSA*		6,30	(0,43-5018)		
	<6 months			150 (39%)	83 (40%)
	≥6 months			160 (42%)	94 (46%)
	Missing data			72 (19%)	19 (9%)
Prior staging examination within 6 months of PSMA PET					
	Negative for prostate cancer			101 (26%)	56 (27%)
	Positive for prostate cancer			46 (12%)	24 (12%)
	Equivocal			25 (7%)	14 (7%)
	None			210 (55%)	112 (54%)
***in accordance with Pound et al. JAMA. 1999;281:1591-1597 (*22*)**					

Table 2: Change of intended management stratified by previous therapy and hormone status (n=382)

	Previous therapy			Hormone status	
Change Category	**Prostatectomy**	**Prostatectomy + Radiotherapy**	**Radiotherapy**	**No current ADT**	**Current ADT**
	(n=166)	**(n=115)**	**(n=101)**	**(n=328)**	**(n=54)**
Major change (n=176)	63 (38%)	66 (57%)	47 (46%)	150 (46%)	26 (48%)
Minor change (n=84)	46 (28%)	11 (10%)	27 (27%)	75 (23%)	9 (17%)
No change (n=122)	57 (34%)	38 (33%)	25 (27%)	103 (31%)	19 (35%)

ADT = androgen deprivation therapy

Table 3: Diagnostic tests triggered or prevented after PSMA PET

	MRI	CT	PET	NaF / Bone scan	Biopsy	Other	Total
Tests planned before PSMA PET (Q1)	56 (13%)	77 (17%)	145 (33%)	144 (33%)	8 (2%)	13 (3%)	443
Tests prevented by PSMA PET (Q2)	16 (11%)	43 (29%)	17 (11%)	52 (35%)	18 (12%)	4 (3%)	150
Tests triggered after PSMA PET (Q2)	8 (11%)	7 (10%)	2 (3%)	5 (7%)	44 (60%)	7 (10%)	73

Table 4: Management implementation (n=206)

Management Change	Implemented	Not implemented
Change intended (n=136)	98 (72%)	38 (28%)
No change intended (n=70)	62 (89%)	8 (11%)

Table 5: Management implementation details (n=206)

Change Category	Implemented	Not implemented
Major change to combination (n=16)	11 (69%)	5 (31%)
Major change to local (n=34)	26 (76%)	8 (24%)
Major change to surveillance (n=17)	11 (65%)	6 (35%)
Major change to systemic (n=29)	19 (66%)	10 (34%)
Minor change (n=40)	31 78%)	9 (22%)
No change (n=70)	62 (89%)	8 (11%)

SUPPLEMENTAL MATERIAL

Supplemental Table 1: Post-PET Management Pathway Category Details (n=382)

Intended management before PSMA PET	Intended management after PSMA PET	Change category	N (%)
Local	Local	No Change	23 (6%)
	Systemic	Major Change	16 (4%)
	Active Surveillance	Major Change	14 (4%)
	Modify Therapy	Minor Change	3 (1%)
	Local + Systemic	Major Change[1]	23 (6%)
	„other“	Minor Change	5 (1%)
Systemic	Local	Major Change	43 (11%)
	Systemic	No Change[2]	83 (22%)
	Active Surveillance	Major Change	11 (3%)
	Modify Therapy	Minor Change	1 (0%)
	Local + Systemic	Major Change	19 (5%)
	Other	Minor Change	19 (5%)
Active Surveillance	Local	Major Change	19 (5%)
	Systemic	Major Change	8 (2%)
	Active Surveillance	No Change	17 (5%)
	Modify Therapy	Minor Change	0 (0%)
	Local + Systemic	Major Change	10 (3%)
	Other	Minor Change	1 (0%)
Other	Local	Minor Change	7 (2%)
	Systemic	Minor Change	5 (1%)
	Active Surveillance	Minor Change	3 (1%)
	Modify Therapy	Minor Change	0 (0%)
	Local + Systemic	Minor Change	3 (1%)
	Other	No Change	2 (1%)
Local + Systemic	Local	Major Change[3]	13 (3%)
	Systemic	Major Change	4 (1%)
	Active Surveillance	Major Change	5 (1%)
	Modify Therapy	Minor Change	0 (0%)
	Local + Systemic	No Change	23 (6%)
	Other	Minor Change	2 (1%)

[1]Exception: Addition of ADT considered Minor Change (n=22); [2]Exception: Switch to different type of systemic therapy considered Major Change (n=26); [3]Exception: Removal of ADT considered Minor Change (n=13)

Supplemental Figure 1: Q1 survey

Q1: SURVEY BEFORE PSMA PET/CT Ga-68 PSMA-11 SCAN BCR

PATIENT INFORMATION

Last name: _____ First Name: _____

Date of Birth: _____ Medical Record Number: _____

1. **Indicate pre ^{68}Ga-PSMA PET working clinical summary for recurrence location:**
   Recurrence is localized in (select all that apply)
   - ☐ unknown recurrence location
   - ☐ the prostate bed
   - ☐ pelvis outside of prostate bed and/or intrapelvic lymph nodes
   - ☐ extrapelvic soft tissue, lymph nodes and/or organ metastases (non-bone)
   - ☐ bone

2. **If ^{68}Ga-PSMA PET was not available, which additional imaging test would you order?**
   - ☐ MRI
   - ☐ CT
   - ☐ FDG/Choline/Acetate/Fluciclovine PET
   - ☐ Bone scan/Fluoride PET
   - ☐ ProstaScint
   - ☐ Biopsy, image guided
   - ☐ Other: _____

3. **What would be your next step in management, if you were not to order this study?**
   - ☐ Surgery
   - ☐ External-beam radiation therapy
   - ☐ ADT for hormone dependent cancer
   - ☐ Abiraterone/Enzalutamide
   - ☐ Chemotherapy
   - ☐ Radionuclide therapy (Ra-223)
   - ☐ Bone targeted therapy
   - ☐ Modify dose of existing therapy
   - ☐ Active surveillance
   - ☐ Other (please describe below)

   Other: _____

   Referring Physician Name: _____

   Date: _____ Signature: _____

Supplemental Figure 2: Q2 survey

Q2: SURVEY WITHIN 4 WEEKS AFTER PSMA PET/CT Ga-68 PSMA-11 SCAN BCR

PATIENT INFORMATION

Last name: _____ First Name: _____

Date of Birth: _____ Medical Record Number: _____

1. **Indicate post ^{68}Ga-PSMA PET working clinical summary for recurrence location:**
   Recurrence is localized in (select all that apply)
   - ☐ unknown recurrence location
   - ☐ the prostate bed
   - ☐ pelvis outside of prostate bed and/or intrapelvic lymph nodes
   - ☐ extrapelvic soft tissue, lymph nodes and/or organ metastases (non-bone)
   - ☐ bone

2. **Did the ^{68}Ga-PSMA PET enable you to avoid any test or procedure?**
   - ☐ Yes
   - ☐ No

   If yes, which test/procedure was avoided? _____

3. **Did the ^{68}Ga-PSMA PET result in any additional test or procedure?**
   - ☐ Yes
   - ☐ No

   If yes, which test/procedure was added? _____

4. **Did ^{68}Ga-PSMA PET findings trigger a planned biopsy?**
   - ☐ Yes
   - ☐ No

5. **Based on ^{68}Ga-PSMA PET findings what is your treatment plan? (select all that apply)**
   - ☐ Surgery
   - ☐ External-beam radiation therapy
   - ☐ ADT for hormone dependent cancer
   - ☐ Abiraterone/Enzalutamide
   - ☐ Chemotherapy
   - ☐ Radionuclide therapy (Ra-223)
   - ☐ Bone targeted therapy
   - ☐ Modify dose of existing therapy
   - ☐ Active surveillance
   - ☐ Other (please describe below)

   Other: _____

   Referring Physician Name: _____

   Date: _____ Signature: _____

Supplemental Figure 3: Q3 survey

Q3: SURVEY 3 TO 6 MONTHS AFTER PSMA PET/CT Ga-68 PSMA-11 SCAN BCR

PATIENT INFORMATION

Last name: _____ First Name: _____

Date of Birth: _____ Medical Record Number: _____

1. **On the post scan questionnaire (questionnaire #2) you indicated an intended treatment management of:**
   - ☐ Surgery
   - ☐ External-beam radiation therapy (EBRT)
   - ☐ Modify EBRT planning
   - ☐ ADT for hormone dependent cancer
   - ☐ Abiraterone/Enzalutamide
   - ☐ Chemotherapy
   - ☐ Radionuclide therapy (Ra-223)
   - ☐ Bone targeted therapy
   - ☐ Modify dose of existing therapy
   - ☐ Active surveillance
   - ☐ Other (please describe below)

   Other: _____

2. **Please indicate whether the intended management noted on the post scan questionnaire (questionnaire #2) was implemented:**

   - ☐ Yes
   - ☐ No

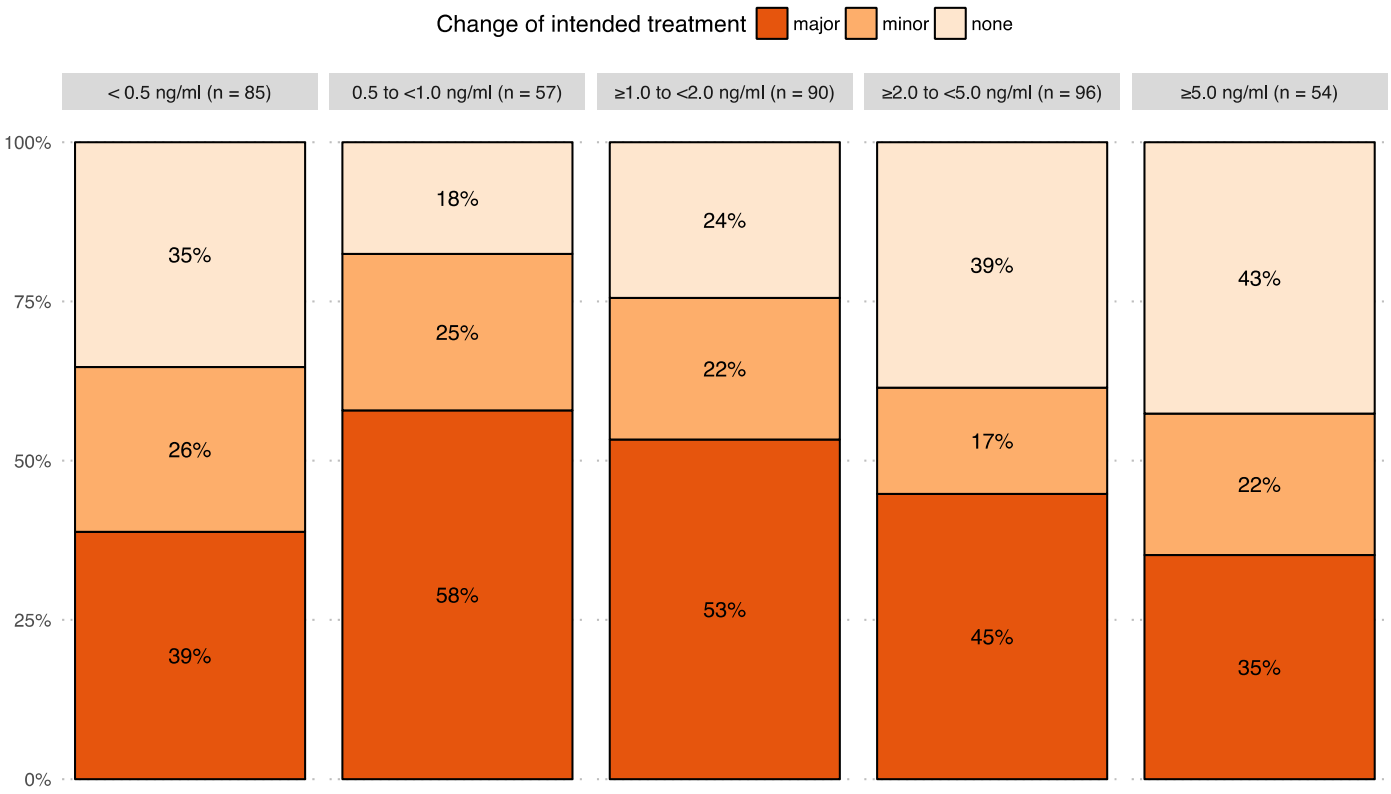
   If No, please indicate why: _____

_____

Referring Physician Name: _____

Date: _____ Signature: _____

Supplemental Figure 4: Intended management change after PSMA PET stratified by PSA



Supplemental Figure 5: Sankey diagram for pre- to post-PET change of intended management (n=382)