11C-Choline PET/CT Predicts Prostate Cancer–Specific Survival in Patients with Biochemical Failure During Androgen-Deprivation Therapy

Giampiero Giovacchini[1,2], Maria Picchio[3], Rita Garcia-Parra[4], Alberto Briganti[5], Firas Abdollah[5], Luigi Gianolli[3], Christian Schindler[6], Francesco Montorsi[5], Cristina Messa[4,7,8], and Ferruccio Fazio[3,4]

[1]Department of Radiology, Stadtspital Triemli, Zurich, Switzerland; [2]Department of Radiology and Nuclear Medicine, Stadtspital Waid, Zurich, Switzerland; [3]Department of Nuclear Medicine, San Raffaele Scientific Institute, Milan, Italy; [4]Department of Health Sciences, Tecnomed Foundation, University of Milano-Bicocca, Milan, Italy; [5]Department of Urology, San Raffaele Scientific Institute, Milan, Italy; [6]Swiss Tropical and Public Health Institute, Basel, Switzerland; [7]Institute for Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR), Milan, Italy; and [8]Department of Nuclear Medicine, San Gerardo Hospital, Monza, Italy

Several studies have shown that 11C-choline PET/CT may be useful for restaging prostate cancer (PCa) patients with biochemical failure after radical prostatectomy. However, validation of 11C-choline PET/CT findings scarcely relied on histologic findings, and prognostic implications of 11C-choline PET/CT are currently unknown. The aim of this study was to assess whether 11C-choline PET/CT predicts survival in PCa patients. **Methods:** This retrospective study included 195 PCa patients treated with radical prostatectomy who underwent 11C-choline PET/CT from December 1, 2004, to July 31, 2007, due to biochemical failure (prostate-specific antigen > 0.2 mg/mL) during androgen-deprivation therapy. PCa-specific survival was computed as the interval from radical prostatectomy to PCa-specific death. **Results:** The median interval after radical prostatectomy was 8.9 y (95% confidence interval [CI], 1.7–18.9 y). The median follow-up after 11C-choline PET/CT was 4.5 y (95% CI, 0.4–8.5 y). 11C-choline PET/CT results were positive in 57% of patients. The median PCa-specific survival was 16.4 y (95% CI, 14.0–18.8 y) in patients with negative 11C-choline PET/CT results and 11.2 y (95% CI, 9.8–12.6 y) in patients with positive 11C-choline PET/CT results (log-rank: $\chi^2 = 19.3$, $P < 0001$). At multivariate analysis, statistical significance was obtained for 11C-choline PET/CT (hazard ratio, 2.53; 95% CI, 1.41–4.53; $P = 0.002$), prostate-specific antigen (hazard ratio, 1.03; 95% CI, 1.00–1.05; $P = 0.037$), and Gleason score (>7: hazard ratio, 2.49; 95% CI, 1.25–4.95; $P = 0.009$). Patients with pathologic 11C-choline uptake in the prostatic bed or in pelvic or retroperitoneal lymph nodes had longer PCa-specific survival (median, 12.1 y; 95% CI, 10.5–13.7 y) in comparison to patients with pathologic tracer uptake in the skeleton (median, 9.9 y; 95% CI, 6.8–13.1 y) (log-rank: $\chi^2 = 6.5$, $P = 0.010$). Two internally validated nomograms predicted 10- and 15-y PCa-specific survival probability with an accuracy of 76% and 74%, respectively. In an ancillary analysis, we also showed that 11C-choline PET/CT predicts PCa-specific survival after PET/CT, with similar statistical power. **Conclusion:** 11C-choline PET/CT predicts PCa-specific survival in PCa patients treated with radical prostatectomy who develop biochemical failure during androgen-deprivation therapy. If independent or multicenter confirmation of these findings is obtained, 11C-choline PET/CT might be more widely used in the follow-up of PCa patients for tailoring salvage therapy.

In recent years, PET/CT with radiolabeled choline (either 11C-choline or 18F-fluorocholine) has emerged as a sensitive technique for restaging prostate cancer (PCa) patients who experience biochemical failure after radical prostatectomy (1–12). Studies have shown that several factors predict 11C-choline or 18F-fluorocholine PET/CT, including trigger prostate-specific antigen (PSA), PSA doubling time (PSADT) or PSA velocity, pathologic stage at radical prostatectomy, Gleason score, and previous biochemical failure (2,5–8). These results lent support to a growing clinical application of PET/CT with radiolabeled choline, especially in Europe. The convincing results from an increasing number of studies recently led the Food and Drug Administration to approve 11C-choline PET/CT for PCa (13).

A major drawback of most 11C-choline PET/CT clinical studies lies in the poor assessment of the accuracy of the technique. Histologic confirmation has been obtained in no more than 15% of patients in most studies, whereas clinical and imaging criteria have been applied with variable methodologic consistency (1,2,5–8,10,14). False-positives are a concern because increased 11C-choline uptake is not specific for carcinogenesis (15,16). Accuracy assessment will be particularly important for early restaging of disease and to monitor response to therapy.

An indirect way to support the accuracy of 11C-choline PET/CT is to demonstrate that pathologic findings have prognostic implication. The impact on survival in PCa has been demonstrated for bone scintigraphy (17) and PET/CT with 18F-fluorodeoxyglucose (18F-FDG) (18) but not with 11C-choline PET/CT. This study was aimed at assessing whether 11C-choline PET/CT predicts PCa-specific survival in PCa patients who experienced biochemical failure during androgen-deprivation therapy.

MATERIALS AND METHODS

Study Population

This retrospective study included 195 PCa patients who underwent 11C-choline PET/CT for restaging of disease after biochemical failure.

TABLE 1
Clinical and Pathologic Characteristics of Whole Sample

Parameter	Whole sample (n = 195)	PET/CT negative (n = 83)	PET/CT positive (n = 112)	P
Interval prostatectomy—[11]C-choline PET/CT (y)				0.350
Mean ± SD	4.8 ± 3.0	4.5 ± 2.7	4.9 ± 3.2	
Median	4.2	4.2	4.1	
Range	0.4–14.4	0.4–12.4	0.7–14.4	
Age (y)				0.864
Mean ± SD	68 ± 7	68 ± 6	68 ± 7	
Median	68	68	67	
Range	50–85	50–79	51–85	
PSA (ng/mL)				<0.001
Mean ± SD	5.17 ± 8.45	2.60 ± 5.39	7.08 ± 9.73	
Median	1.82	1.01	3.03	
Range	0.22–48.6	0.22–35.0	0.25–48.6	
PSADT (mo) (n = 76)				0.003
Mean ± SD	6.67 ± 4.82	9.04 ± 5.68	5.23 ± 3.58	
Median	5.47	7.89	4.79	
Range	1.11–23.59	1.13–23.59	1.11–18.37	
Pathologic stage				<0.001
pT2pN0	62 (32)	41 (49)	21 (19)	
pT3pN0 and pT4pN0	82 (42)	28 (34)	54 (48)	
Any T pN1	51 (26)	14 (17)	37 (33)	
Gleason score				0.411
<7	40 (20)	20 (24)	20 (18)	
7	85 (44)	37 (45)	48 (43)	
>7	70 (36)	26 (31)	44 (39)	

Data in parentheses are percentages.

Briefly, 2,124 consecutive patients referred to our institution for ^{11}C-choline PET/CT from December 1, 2004, to July 31, 2007, were initially considered for eligibility in this study. Enrollment required histologically confirmed adenocarcinoma of the prostate, primary treatment with radical prostatectomy, rising PSA (PSA > 0.2 ng/mL after previous evidence of nonmeasureable PSA) during androgen-deprivation therapy, clinical and pathologic features of interest for multivariate Cox regression analysis, follow-up information regarding the survival status, and informed consent agreement. Because of the retrospective design of the study, only a minor number of patients (10%) satisfied all inclusion criteria. The exclusion of initially considered patients was due to lack of complete clinical and pathologic information necessary for survival analysis, primary therapy other than prostatectomy, no treatment with antiandrogenic drugs, and refusal to sign informed consent. This single-institution study was approved by the ethical committee of the Scientific Institute San Raffaele Hospital. An informed consent form for the execution of the ^{11}C-choline PET/CT scan and for anonymous publication of disease-related information according to the Declaration of Helsinki was signed by each patient.

Follow-up

Clinical surveillance included PSA determinations and rectal examinations every 3–12 mo. The use of imaging techniques, including computer tomography, ultrasonography, MR, and bone scintigraphy was variable among patients.

The median interval after radical prostatectomy was 8.9 y (95% confidence interval [CI], 1.7–18.9 y), and median follow-up after ^{11}C-choline PET/CT was 4.5 y (95% CI, 0.4–8.5 y). At last follow-up, 84 of 195 (43%) patients had died: 79 of 195 (41%) patients had died of PCa and 5 of 84 (2%) died of causes not related to PCa. PCa-specific survival was chosen as a primary endpoint. PCa-specific death was defined as death in any patient with metastases that showed progression

after hormonal therapy without another obvious cause of death (19). Metastases in patients with negative ^{11}C-choline PET/CT findings were documented with different techniques, including bone scintigraphy, contrast-enhanced CT, MR, or subsequent ^{11}C-choline PET/CT. PCa-specific survival was defined as the time between radical prostatectomy and the time of PCa-specific death (19–22). Survival times of patients who were alive at the last follow-up contact were censored.
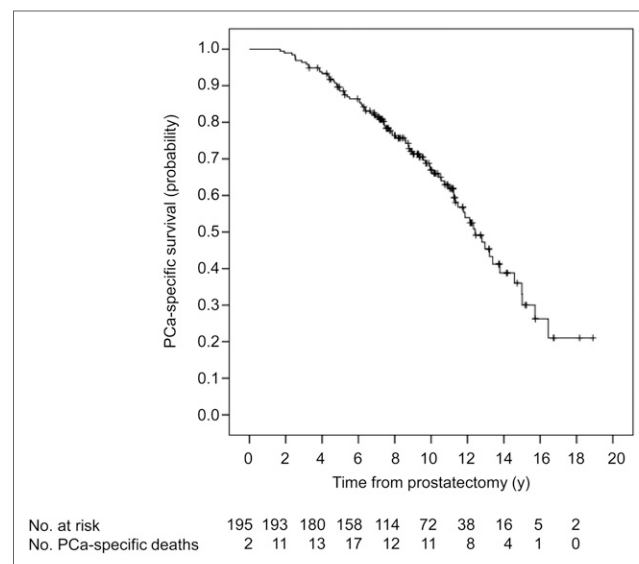

	0	2	4	6	8	10	12	14	16	18	20
No. at risk	195	193	180	158	114	72	38	16	5	2	
No. PCa-specific deaths	2	11	13	17	12	11	8	4	1	0	

FIGURE 1. Twenty-year actuarial Kaplan–Meier PCa-specific survival probability curve in whole sample. Numbers indicate patients at risk at time t_n and number of PCa-specific deaths occurred between t_n and $t_n + 2$.
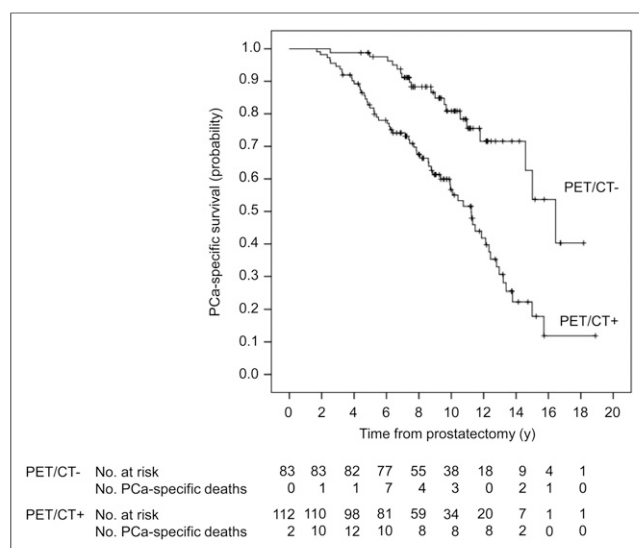
FIGURE 2. Kaplan–Meier PCa-specific survival probability curves in patients with negative ^{11}C-choline PET/CT and in patients with positive ^{11}C-choline PET/CT. Numbers indicate patients at risk at time t_n and number of PCa-specific deaths occurred between t_n and $t_n + 2$.

PET/CT Acquisition

PET/CT studies were acquired by means of 3 integrated PET/CT systems, namely, Discovery LS, Discovery ST, and Discovery STE (GE Healthcare). Patients refrained from drinking and fasted for at least 6 h before ^{11}C-choline PET/CT. A CT scout scan was initially acquired to define the body axial extension (from the pelvis to the base of the skull) to be imaged. After an unenhanced CT scan (90 mAs, 0.8 s per rotation, 140 kV, 4.25-mm reconstructed section thickness) from the pelvis to the base of the skull, five 1-min frames centered on the pelvis were acquired immediately after the injection of 406 ± 48 MBq of ^{11}C-choline using dynamic acquisition. At the end of dynamic imaging, that is, about 5 min after injection, a whole-body PET scan was acquired starting from the pelvis. Images were acquired in 2-dimensional mode (4 min per bed) with the Discovery LS and ST scanners and in 3-dimensional mode (2.5 min per bed) with the Discovery STE scanner. PET images were corrected for random, scatter, and attenuation and reconstructed on a 128×128 image matrix using iterative algorithms (8). The axial spatial resolution of the 3 tomographs ranges between 5 and 6 mm (8). A previous study showed no significant differences in the accuracy of the 3 scanners for detection of recurrent disease in PCa patients (8).

Image Interpretation

Image readout was performed on a Xeleris WorkStation (GE Healthcare). ^{11}C-choline PET/CT images were read independently by 2 experienced nuclear medicine physicians. Cases of disagreement were reexamined, and a consensus was reached. A ^{11}C-choline PET/CT scan was called positive in the presence of focal uptake deviating from the physiologic distribution of the tracer independently by semiquantitative uptake values (1,5). For lymph nodes, focal ^{11}C-choline uptake was considered pathologic when greater than background or blood pool independently by lymph node size (5,8). Because the parameter of interest was represented by PCa-specific survival, we made no attempt to validate PET/CT findings versus clinical data or other imaging modalities.

Statistical Analysis

Continuous variables between 2 groups were compared using the t test. The χ^2 test was used for categoric variables. The normality of the distribution of continuous variables was assessed with the Kolmogorov–Smirnov test. Nonnormally distributed continuous variables between 2 groups were compared using the Mann–Whitney U test.

PCa-specific survival was estimated using Kaplan–Meier curves. Differences between survival curves of patients with positive ^{11}C-choline PET/CT and negative ^{11}C-choline PET/CT findings were evaluated using the log-rank test. Survival rates and their 95% CIs were also derived from Kaplan–Meier curves.

The association between ^{11}C-choline PET/CT and PCa-specific survival was assessed using Cox proportional hazards regression models. To minimize biases on survival times introduced by therapy successive to ^{11}C-choline PET/CT, additional therapy (radiotherapy or chemotherapy) after ^{11}C-choline PET/CT was included in the analysis. Other variables were age, trigger PSA, pathologic stage, and Gleason score. The effect estimates were expressed as hazard ratios (HRs) with 95% CIs. To assess the additive value of ^{11}C-choline PET/CT in the prediction of survival, a 2-block Cox regression survival analysis was performed. In the first block, all clinical and pathologic variables except ^{11}C-choline PET/CT were included, whereas in the second block ^{11}C-choline PET/CT was added. Results were compared with the Akaike information criterion and χ^2 improvement. The proportional hazards assumption was formally tested using interaction terms between independent variables and time. All these interactions had a P value greater than 0.1. Statistical significance was defined as a P value less than 0.05. Survival analysis was performed using a statistical software package (SPSS, version 18; SPSS Inc.).

The coefficients of the covariates included in the Cox regression analysis were used to develop novel nomograms predicting PCa-specific survival probability. The discrimination of the model was quantified using Harrell's concordance index. One thousand bootstrap resamples were used to internally validate the estimations of the model. Subsequently, the relationship between the nomogram-predicted probabilities and the observed survival rates was graphically explored with calibration plots using the val.prob function at each specific examined time point (R statistical package system; R Foundation for Statistical Computing).

RESULTS

The clinical and pathologic characteristics of the sample are reported in Table 1. ^{11}C-choline PET/CT results were positive in 112 of 195 patients (57%). On an anatomic basis, pathologic ^{11}C-choline uptake was observed in pelvic or retroperitoneal lymph nodes (64/195, 33%), in the skeleton (49/195, 25%), and in the postsurgical prostate bed (36/195, 18%). After ^{11}C-choline PET/CT, radiotherapy or chemotherapy was performed in 23% of patients with negative ^{11}C-choline PET/CT and in 71% of patients with positive ^{11}C-choline PET/CT ($P < 0.05$). Patients with positive ^{11}C-choline PET/CT had significantly ($P < 0.05$) higher PSA, more advanced pathologic stage, and shorter PSADT than patients with negative PET/CT (Table 1).

TABLE 2
PCa-Specific Survival Probabilities (%)

Survival (y)	PET/CT negative ($n = 83$)	PET/CT positive ($n = 112$)
5	97.5% (95.8%–99.2%)	81.8% (78.1%–85.5%)
10	80.9% (76.0%–85.8%)	55.0% (49.6%–60.4%)
15	53.7% (41.6%–65.8%)	17.8% (11.5%–24.1%)

Data in parentheses are 95% CI.

TABLE 3
Cox Regression Analysis of Factors Predicting PCa-Specific Survival in Whole Sample ($n = 195$)

Parameter	Univariate analysis		Multivariate analysis	
	HR	P	HR	P
[11]C-choline PET/CT	3.02 (1.80–5.08)	<0.001	2.53 (1.41–4.53)	0.002
Age (y)	1.00 (0.97–1.04)	0.738	1.01 (0.98–1.05)	0.469
PSA (ng/mL)	1.04 (1.02–1.06)	0.001	1.03 (1.00–1.05)	0.037
Pathologic stage		0.007		0.065
pT2pN0	1 (reference)		1 (reference)	
pT3pN0 and pT4pN0	1.24 (0.70–2.17)	0.458	0.79 (0.42–1.46)	0.453
Any T pN1	2.33 (1.32–4.09)	0.003	1.48 (0.82–2.69)	0.191
Gleason score		0.001		0.025
<7	1 (reference)		1 (reference)	
7	1.81 (0.95–3.45)	0.069	1.57 (0.81–3.04)	0.176
>7	3.26 (1.68–6.35)	<0.001	2.49 (1.25–4.95)	0.009
Additional therapy	1.83 (1.17–2.86)	0.008	1.20 (0.73–1.97)	0.451

Data in parentheses are 95% CI.

In the whole group, the 5-, 10-, and 15-y PCa-specific survival probabilities were, respectively, 88.6% (95% CI, 86.3%–90.9%), 66.0% (95% CI, 62.2%–69.8%), and 30.0% (95% CI, 23.7%–36.3%) (Fig. 1).

Figure 2 shows Kaplan–Meier PCa-specific survival curves stratified by ^{11}C-choline PET/CT. The median PCa-specific survival was 16.4 y (95% CI, 14.0–18.8 y) in patients with negative ^{11}C-choline PET/CT and 11.2 (95% CI, 9.8–12.6 y) in patients with positive ^{11}C-choline PET/CT (log-rank: $\chi^2 = 19.3$, $P < 0001$). The 5-, 10-, and 15-y PCa-specific survival probabilities for the 2 groups are reported in Table 2.

Results of univariate and multivariate Cox regression analysis are shown in Table 3. At multivariate analysis, statistical significance was obtained for ^{11}C-choline PET/CT (HR, 2.53; 95% CI, 1.41–4.53; $P = 0.002$), PSA (HR, 1.03; 95% CI, 1.00–1.05; $P = 0.037$), and Gleason score (>7: HR, 2.49; 95% CI, 1.25–4.95; $P = 0.009$).

In the 2-block survival analysis, the block that additionally included ^{11}C-choline PET/CT yielded a significantly better prediction than the block that included only PSA, age, pathologic stage, Gleason score, and additional therapy (change from previous block: $\chi^2 = 10.8$, $P = 0.001$; Akaike information criterion with and without ^{11}C-choline PET/CT: 267.2 vs. 274.1, respectively).

Cox regression analysis was repeated in patients for whom PSADT was available ($n = 76$) (Table 4). At bivariate analysis, both ^{11}C-choline PET/CT (HR, 2.75; 95% CI, 1.04–7.32; $P = 0.042$) and PSADT (HR, 0.88; 95% CI, 0.79–0.98; $P = 0.029$) attained statistical significance.

Patients with pathologic ^{11}C-choline uptake in the prostatic bed or in pelvic or retroperitoneal lymph nodes but no evidence of pathologic bone uptake had shorter PCa-specific survival (median, 12.1 y; 95% CI, 10.5–13.7 y) in comparison to patients with negative PET/CT (log-rank: $\chi^2 = 8.9$, $P = 0.003$) but longer PCa-specific survival in comparison to patients with pathologic tracer uptake in the skeleton (median, 9.9 y; 95% CI, 6.8–13.1 y) (log-rank: $\chi^2 = 6.5$, $P = 0.011$) (Fig. 3). Patients with pathologic tracer uptake in the skeleton had shorter PCa-specific survival than patients with negative PET/CT (log-rank: $\chi^2 = 27.8$, $P < 0.001$). PCa-specific survival probabilities for these groups are reported in Table 5. We also assessed survival according to the TNM classification of the American Joint Committee on Cancer (23), assuming ^{11}C-choline PET/CT as a gold standard for identification of disease. Contrasting patients with pathologic ^{11}C-choline uptake in the skeleton (M1b) or in retroperitoneal lymph nodes (M1a) to patients with pathologic ^{11}C-choline uptake in pelvic lymph nodes (N1 M0) or in the prostate bed (N0) provided similar results, even though group differences in survival, as expected, were somehow increased (Table 5).

To assess the sensitivity of our results to the definition of PCa-specific survival, an ancillary Cox regression analysis was performed in which PCa-specific survival was computed as the interval between the date of ^{11}C-choline PET/CT and the date of PCa-specific death. At multivariate analysis, statistical significance was obtained for ^{11}C-choline PET/CT (HR, 3.16; 95% CI, 1.72–5.78; $P < 0.001$), age (HR, 1.06; 95% CI, 1.02–1.10; $P = 0.002$), PSA (HR, 1.05; 95% CI, 1.02–1.07; $P < 0.001$), and

TABLE 4
Cox Regression Analysis of Factors Predicting PCa-Specific Survival in Patients with PSADT ($n = 76$)

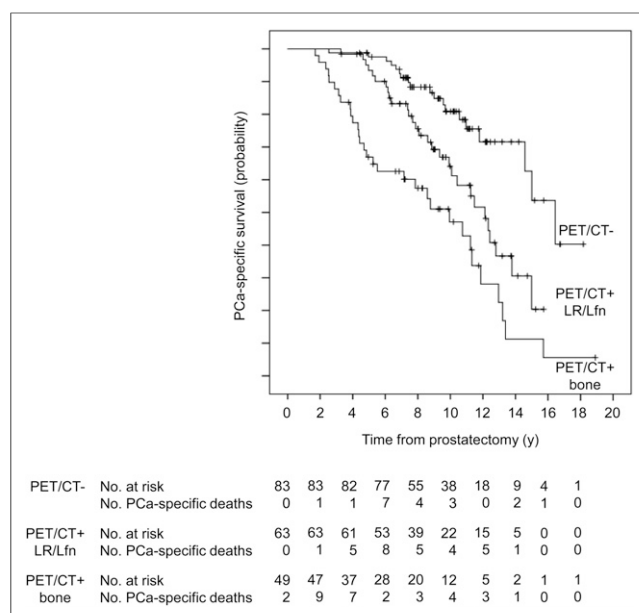| Parameter	Univariate analysis		Bivariate analysis	
	HR	P	HR	P
[11]C-choline PET/CT	3.83 (1.48–9.92)	0.006	2.75 (1.04–7.32)	0.042
PSADT (mo)	0.86 (0.77–0.95)	0.004	0.88 (0.79–0.98)	0.029

Data in parentheses are 95% CI.

FIGURE 3. Kaplan–Meier PCa-specific survival probability curves in patients with negative ^{11}C-choline PET/CT (PET/CT−), in patients with ^{11}C-choline PET/CT suggestive of local recurrence or lymph node disease (PET/CT+ LR/Lfn), and in patients with ^{11}C-choline PET/CT suggestive of bone metastases (PET/CT+ bone). Numbers indicate patients at risk at time t_n and number of PCa-specific deaths occurred between t_n and $t_n + 2$.

pathologic stage (any T pN1: HR, 1.85; 95% CI, 1.02–3.38; $P = 0.043$) (Table 6). Median PCa-specific survival after ^{11}C-choline PET/CT was 7.9 y (95% CI, 5.3–10.5 y) in patients with negative ^{11}C-choline PET/CT and 4.1 y (95% CI, 2.5–5.6 y) in patients with positive ^{11}C-choline PET/CT (log-rank: $\chi^2 = 30.9$, $P < 0.001$). The 5-y PCa-specific survival probability after ^{11}C-choline PET/CT was 82.9% (95% CI, 78.6%–87.2%) in patients with negative ^{11}C-choline PET/CT and 44.7% (95% CI, 39.5%–49.9%) in patients with positive ^{11}C-choline PET/CT. At bivariate Cox regression analysis in patients with PSADT ($n = 76$) (Table 7), ^{11}C-choline PET/CT (HR, 4.51; 95% CI, 1.68–12.11; $P = 0.003$) but not PSADT (HR, 0.93; 95% CI, 0.84–1.03; $P = 0.178$) attained statistical significance.

The nomograms predicting 10- and 15-y PCa-specific survival probability after radical prostatectomy and 5-y PCa-specific survival probability after ^{11}C-choline PET/CT together with their calibration plots are shown in Figures 4–6. The internally vali-

dated discriminations of the model were, respectively, 76%, 74%, and 73%. The calibration plots between nomogram-predicted-probability PCa-specific survival rate and observed surviving fraction indicate good prediction throughout the range of predicted probabilities. However, the nomogram that predicts the 15-y PCa-specific probability tended to overestimate the real rate of survival (Fig. 5B).

DISCUSSION

Over the last years, there has been growing evidence that PET/CT with radiolabeled choline may be useful for restaging PCa patients with biochemical failure after radical prostatectomy (1–12). For this reason, the Food and Drug Administration recently approved ^{11}C-choline PET/CT for PCa (13). However, in most recent guidelines of international oncologic and urologic societies ^{11}C-choline PET/CT is not recommended either for restaging PCa patients with biochemical failure or for evaluation of response in clinical trials (24–26), and the role of ^{11}C-choline PET/CT was recently debated between members of the European Association of Urology and of the European Association of Nuclear Medicine and Molecular Imaging (26,27).

In our opinion, there are 3 main reasons that give support to the limited acceptance of ^{11}C-choline PET/CT among clinicians worldwide. First, most clinical studies with PET/CT and either ^{11}C-choline or ^{18}F-fluorocholine offered only poor validation of PET/CT findings. Histologic confirmation has been obtained in no more than 15% of patients of most ^{11}C-choline PET/CT studies, whereas clinical and imaging criteria have been applied with variable methodologic consistency (1,2,5–8,10,14). Methodologic problems related to this issue have been previously discussed (6–8,10,14) and represented a motivation for the present study. False-positive ^{11}C-choline PET/CT findings are a concern because increased ^{11}C-choline uptake is not specific for carcinogenesis (15,16). In studies with largest samples, false-positives were reported in about 15% of patients who underwent salvage lymphadenectomy (28,29). On the other hand, the limited spatial resolution of PET/CT significantly limits the detection of microscopic disease and underestimates the extent of lymph node disease, as assessed by histologic analysis (28,29).

The second reason is that change of management has not been the focus of most studies. Soyka et al. did report change of management using PET/CT with ^{18}F-fluorocholine in 48% of PCa patients (30). However, in this study change of management was assessed retrospectively a minimum of 14 mo after PET/CT.

TABLE 5
PCa-Specific Survival Probabilities (%) in Patients With Pathologic ^{11}C-Choline Uptake and in Patients Without (M0) and With (M1) Distant Metastases

	PET/CT positive			
Survival (y)	Prostatic bed/lymph nodes ($n = 63$)*	Skeleton ($n = 49$)	M0, prostatic bed/pelvic lymph nodes ($n = 46$)[†]	M1, retroperitoneal lymph nodes/skeleton ($n = 66$)[†]
5	92.6% (89.3%–95.9%)	65.9% (59.0%–72.8%)	97.8% (95.6%–1.00%)	69.6% (63.9%–75.3%)
10	61.2% (54.1%–68.3%)	47.1% (39.0%–55.2%)	75.5% (68.1%–82.9%)	55.0% (47.9%–62.1%)
15	20.4% (10.2%–30.6%)	5.6% (0.3%–10.9%)	25.0% (12.5%–37.5%)	4.7% (0.2%–9.2%)

*Without bone involvement.
[†][11]C-choline PET/CT according to American Joint Committee on Cancer staging system.
Data in parentheses are 95% CI.

TABLE 6
Cox Regression Analysis of Factors Predicting PCa-Specific Survival (Calculated from Time of
[11]C-Choline PET/CT) in Whole Sample (n = 195)

Parameter	Univariate analysis		Multivariate analysis	
	HR	P	HR	P
[11]C-choline PET/CT	4.03 (2.37–6.87)	<0.001	3.16 (1.72–5.78)	<0.001
Age (y)	1.04 (1.00–1.07)	0.045	1.06 (1.02–1.10)	0.002
PSA (ng/mL)	1.05 (1.02–1.07)	<0.001	1.05 (1.02–1.07)	<0.001
Pathologic stage		0.005		0.017
pT2pN0	1 (reference)		1 (reference)	
pT3pN0 and pT4pN0	1.22 (0.69–2.14)	0.485	0.89 (0.49–1.64)	0.727
Any T pN1	2.38 (1.35–4.19)	0.003	1.85 (1.02–3.38)	0.043
Gleason score		0.276		0.610
<7	1 (reference)		1 (reference)	
7	1.29 (0.69–2.42)	0.415	1.11 (0.58–2.12)	0.732
>7	1.65 (0.87–3.11)	0.119	1.35 (0.70–2.60)	0.366
Additional therapy	2.01 (1.28–3.15)	0.002	1.15 (0.69–1.91)	0.576

Data in parentheses are 95% CI.

The third and possibly most important reason is that prognostic implications of ^{11}C-choline PET/CT have been so far scarcely investigated. This is due to the fact that most studies were cross-sectional and had small sample size and limited follow-up. To the best of our knowledge, only Breeuwsma et al. preliminary reported on this issue (31). In this study that included 64 patients, 10 patients died during follow-up, of which 5 patients died due to metastasized disease. For this reason, the study was not powered to detect significant differences in PCa-specific survival. Kaplan–Meier curves did show shorter overall survival in patients with positive ^{11}C-choline, but median overall survival was not achieved (31). Bone scintigraphy and PET/CT with ^{18}F-FDG are currently considered in the nuclear medicine community less sensitive or less accurate than ^{11}C-choline PET/CT for restaging PCa patients after biochemical failure (1,7,10,32,33). However, previous studies showed that bone scintigraphy (17) and PET/CT with ^{18}F-FDG (18) predict survival in PCa patients.

In the current study, we performed survival analysis in PCa patients who developed biochemical failure during androgen-deprivation therapy. These patients are at a higher risk of PCa-specific mortality in comparison to androgen-sensitive patients (25), and they also have a higher likelihood of positive ^{11}C-choline PET/CT in comparison to patients who are hormone-naïve (8,34). We followed up the present cohort for a median interval of 4.5 y (95% CI, 0.4–8.5 y) after ^{11}C-choline PET/CT. The median PCa-specific survival (calculated from radical prostatectomy) was 16.4 y (95% CI, 14.0–18.8 y) in patients with negative ^{11}C-choline

PET/CT and 11.2 y (95% CI, 9.8–12.6 y) in patients with positive ^{11}C-choline PET/CT. The median PCa-specific survival after ^{11}C-choline PET/CT was 7.9 y (95% CI, 5.3–10.5 y) in patients with negative ^{11}C-choline PET/CT and 4.1 y (95% CI, 2.5–5.6 y) in patients with positive ^{11}C-choline PET/CT.

Several clinical and pathologic factors have been shown in larger studies to predict PCa-specific mortality, including Gleason score, pathologic stage, PSA, PSADT, and PSA velocity (19–22). In the current study, when ^{11}C-choline PET/CT was added to the regression model including clinical and pathologic factors the stratification of PCa-specific death risk significantly improved.

Patients with ^{11}C-choline PET/CT findings suggestive of skeletal metastases had shorter survival in comparison to patients with PET/CT findings suggestive of lymph node metastases or local recurrence (Fig. 3; Table 5) consistent with the observation that skeletal metastases represent the primary source of morbidity and mortality in PCa patients (17,35). Analysis according to the American Joint Committee on Cancer staging system provided similar results (Table 5). In patients experiencing biochemical failure, it is important to identify the site of recurrence to stratify the risk of death. Patients at high risk of death are those who require more aggressive treatment, whereas overtreatment could be reduced in patients who are less likely to rapidly progress (21). If images suggest pelvic lymph node disease, pelvic lymph nodes can be included in the radiation plan (36). Combined treatment of prostate bed and lymph nodes might improve progression-free survival (37). Our results suggest that ^{11}C-choline PET/CT might be a suit-

TABLE 7
Cox Regression Analysis of Factors Predicting PCa-Specific Survival (Calculated from Time of
[11]C-Choline PET/CT) in Patients with PSADT (n = 76)

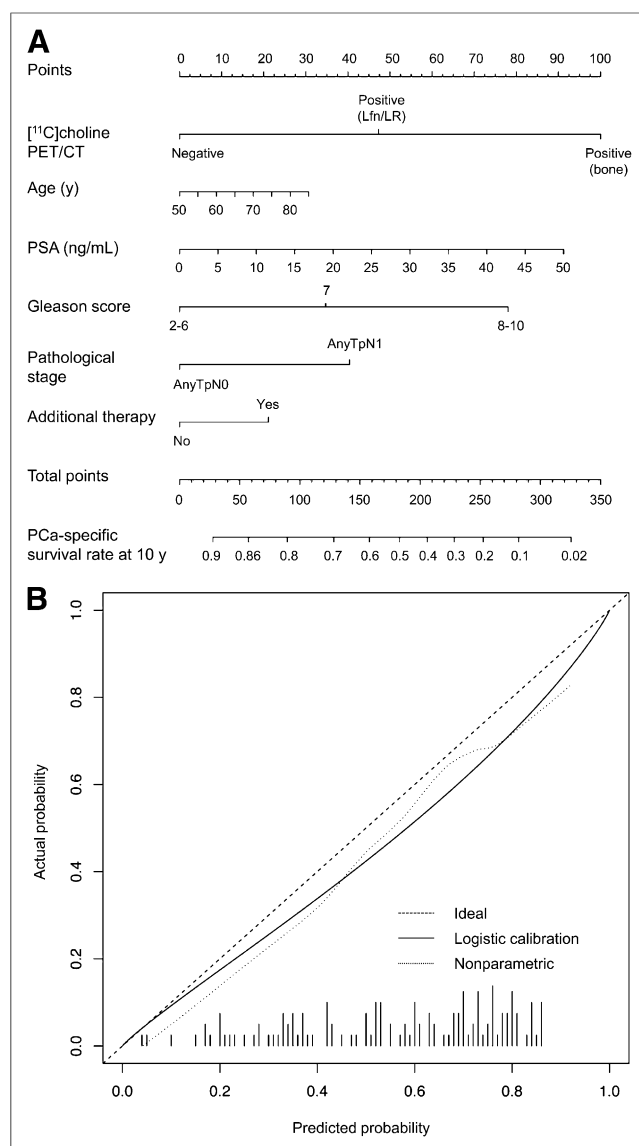| Parameter	Univariate analysis		Bivariate analysis	
	HR	P	HR	P
[11]C-choline PET/CT	5.61 (2.16–14.53)	<0.001	4.51 (1.68–12.11)	0.003
PSADT (mo)	0.88 (0.80–0.97)	0.012	0.93 (0.84–1.03)	0.178

Data in parentheses are 95% CI.

FIGURE 4. Nomogram (A) and calibration factor (B) predicting 10-y PCa-specific survival probability (calculated from radical prostatectomy). Perfect prediction would correspond to diagonal 45° broken line. Dotted line indicates actual nomogram performance. Expected performance on future data is represented through solid line.

statistical significance only if survival time is computed from radical prostatectomy, whereas the predictive power of age, PSA, and pathologic stage is more robust when survival is computed starting from the date of PET/CT. This differential sensitivity may have methodologic and biologic explanations. For example, Gleason score at radical prostatectomy may not accurately reflect Gleason score at recurrence (38). High PSA measured at the time of PET/CT is intuitively more related to residual survival time rather than to survival from radical prostatectomy. On the contrary, ^{11}C-choline PET/CT was highly significant at multivariate analysis independent of the method chosen for the calculation of survival time. Therefore, among the considered variables ^{11}C-choline PET/CT appears to be the most powerful and reliable predictor of PCa-specific survival. This means that ^{11}C-choline PET/CT can be used to accurately predict PCa-specific survival from radical prostatectomy and PCa-specific survival after PET/CT.

Fast PSA kinetics, expressed either as PSADT or PSA velocity, has been often reported as the single most important factor
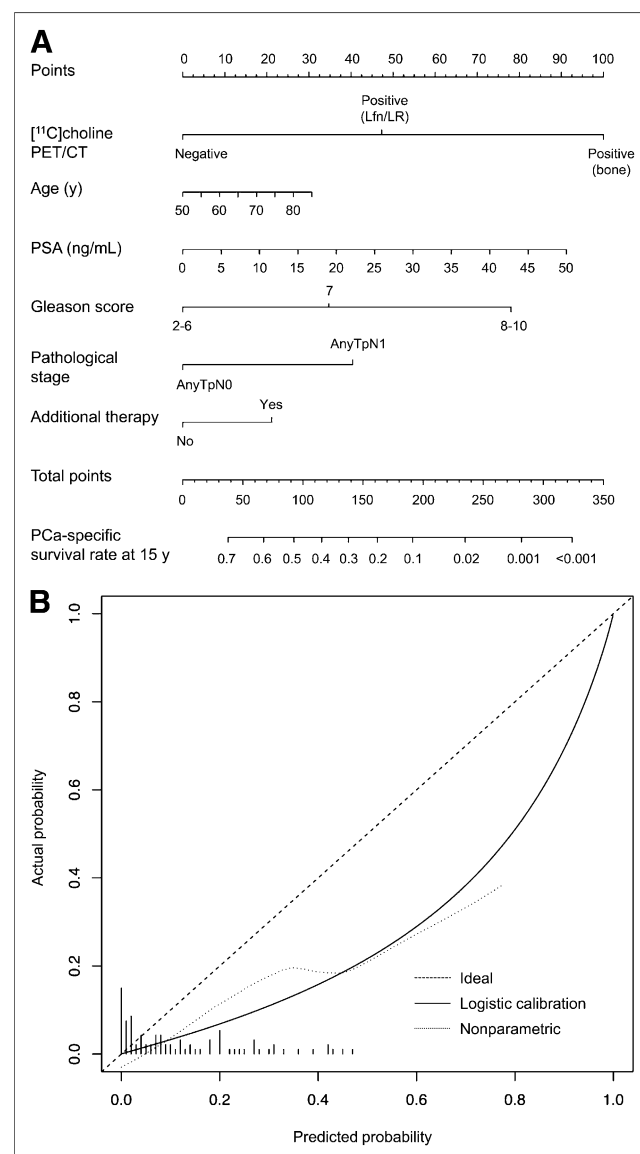
able technique to identify patients with different prognosis for potential stratification for salvage lymphadenectomy or radiotherapy in oncologic trials.

PCa-specific survival was traditionally computed as the interval between radical prostatectomy and PCa-specific death. This was motivated by the fact that ^{11}C-choline PET/CT was performed neither at a fixed trigger PSA value nor at the fixed time after radical prostatectomy. If so calculated, survival time is standardized for all patients and it is not influenced by several biases, including modality of referral to ^{11}C-choline PET/CT. On the other hand, computation of survival time starting from the date of ^{11}C-choline PET/CT may be more practical information for patient counseling and therapy decision. Comparison of Table 3 with Table 6 and Table 4 with Table 7 does indicate that the predictive role of most chosen variables is influenced by the definition of survival time. For example, Gleason score and PSADT attained

FIGURE 5. Nomogram (A) and calibration factor (B) predicting 15-y PCa-specific survival probability (calculated from radical prostatectomy).
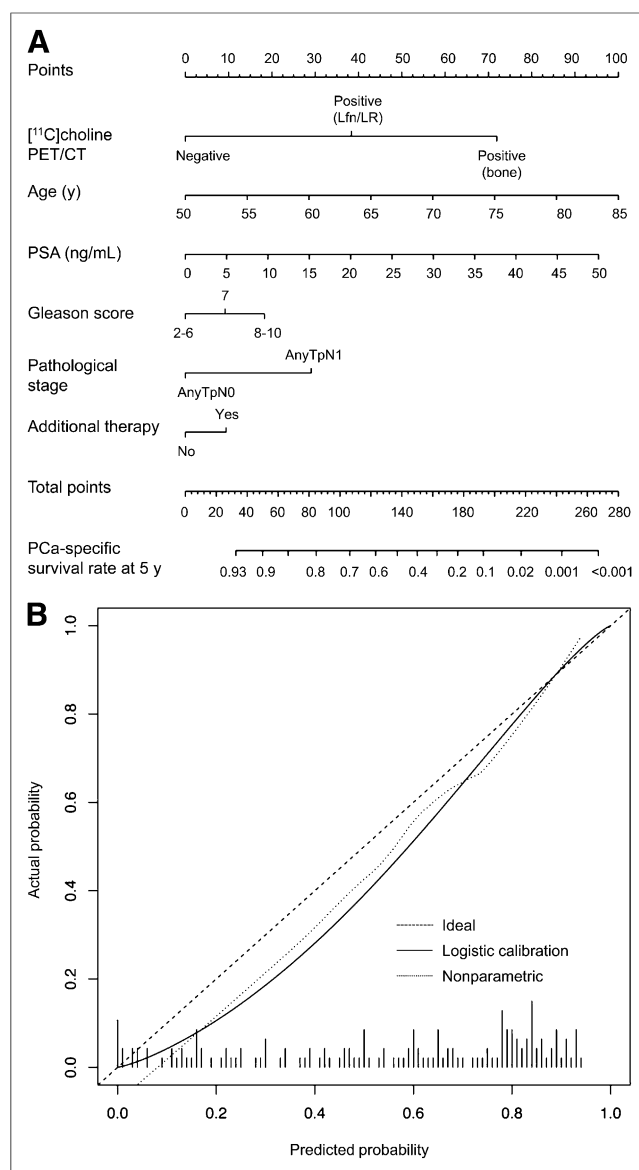
FIGURE 6. Nomogram (A) and calibration factor (B) predicting 5-y PCa-specific survival probability (calculated from ^{11}C-choline PET/CT).

predicting survival in PCa (19–21). Because of the retrospective design of the study, PSADT was available only for 39% of patients, so that PSADT was not included in the main analysis. In this small sample, ^{11}C-choline PET/CT appears to be superior to PSADT for the prediction of PCa-specific survival after ^{11}C-choline PET/CT (Table 7).

Potential limitations of this study need to be considered. This study was designed retrospectively. ^{11}C-choline PET/CT was defined as positive only on the basis of tracer uptake, independently by radiologic findings. Time-dependent changes in bone uptake of radiolabeled choline as a function of changes in Hounsfield units of bone metastases are currently under investigation (14). Finally, therapeutic interventions, which certainly took place after ^{11}C-choline PET/CT, were not further considered in the framework of this data analysis although they might have added relevant information for the raised question. Future prospective studies should assess the comparative value of ^{11}C-choline PET/CT versus conventional imaging for management of PCa patients and prediction of survival.

CONCLUSION

The present observational study indicates that positive ^{11}C-choline PET/CT in PCa patients who develop biochemical failure during androgen-deprivation therapy predicts shorter PCa-specific survival. The prediction of PCa-specific survival is robust and independent of the method of calculation of survival time. Patients with ^{11}C-choline PET/CT scans suggesting local recurrence or lymph node disease had longer PCa-specific survival than patients with presumed bone metastases. If independent or multicenter confirmation of these findings is obtained, ^{11}C-choline PET/CT might be more widely used in the follow-up of PCa patients for tailoring salvage therapy.

DISCLOSURE

REFERENCES

1. Picchio M, Messa C, Landoni C, et al. Value of [11]choline-positron emission tomography for re-staging prostate cancer: a comparison with [18F]fluorodeoxyglucose-positron emission tomography. *J Urol.* 2003;169:1337–1340.
2. Cimitan M, Bortolus R, Morassut S, et al. [18F]fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients. *Eur J Nucl Med Mol Imaging.* 2006;33:1387–1398.
3. Rinnab L, Blumstein NM, Mottaghy FM, et al. ^{11}C-choline positron-emission tomography/computed tomography and transrectal ultrasonography for staging localized prostate cancer. *BJU Int.* 2007;99:1421–1426.
4. Reske SN, Blumstein NM, Glatting G. [^{11}C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. *Eur J Nucl Med Mol Imaging.* 2008;35:9–17.
5. Krause BJ, Souvatzoglou M, Tuncel M, et al. The detection rate of [^{11}C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. *Eur J Nucl Med Mol Imaging.* 2008;35:18–23.
6. Castellucci P, Fuccio C, Nanni C, et al. Influence of trigger PSA and PSA kinetics on ^{11}C-choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. *J Nucl Med.* 2009;50:1394–1400.
7. Giovacchini G, Picchio M, Briganti A, et al. [^{11}C]choline positron emission tomography/computerized tomography to restage prostate cancer cases with biochemical failure after radical prostatectomy and no disease evidence on conventional imaging. *J Urol.* 2010;184:938–943.
8. Giovacchini G, Picchio M, Coradeschi E, et al. Predictive factors of [^{11}C]choline PET/CT in patients with biochemical failure after radical prostatectomy. *Eur J Nucl Med Mol Imaging.* 2010;37:301–309.
9. Giovacchini G, Picchio M, Scattoni V, et al. PSA doubling time for prediction of [^{11}C]choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy. *Eur J Nucl Med Mol Imaging.* 2010;37:1106–1116.
10. McCarthy M, Siew T, Campbell A, et al. ^{18}F-fluoromethylcholine (FCH) PET imaging in patients with castration-resistant prostate cancer: prospective comparison with standard imaging. *Eur J Nucl Med Mol Imaging.* 2011;38:14–22.
11. Graute V, Jansen N, Ubleis C, et al. Relationship between PSA kinetics and [18F]fluorocholine PET/CT detection rates of recurrence in patients with prostate cancer after total prostatectomy. *Eur J Nucl Med Mol Imaging.* 2012;39:271–282.
12. Beheshti M, Haim S, Zakavi R, et al. Impact of ^{18}F-choline PET/CT in prostate cancer patients with biochemical recurrence: influence of androgen deprivation therapy and correlation with PSA kinetics. *J Nucl Med.* 2013;54:833–840.
13. FDA approves ^{11}C-choline for PET in prostate cancer [Newsline]. *J Nucl Med.* 2012;53:11N.
14. Beheshti M, Vali R, Waldenberger P, et al. The use of F-18 choline PET in the assessment of bone metastases in prostate cancer: correlation with morphological changes on CT. *Mol Imaging Biol.* 2010;12:98–107.
15. Schilling D, Schlemmer HP, Wagner PH, et al. Histological verification of ^{11}C-choline-positron emission/computed tomography-positive lymph nodes in patients

with biochemical failure after treatment for localized prostate cancer. *BJU Int.* 2008;102:446–451.

16. Giovacchini G, Gajate AM, Messa C, Fazio F. Increased C-11 choline uptake in pagetic bone in a patient with coexisting skeletal metastases from prostate cancer. *Clin Nucl Med.* 2008;33:797–798.

17. Sabbatini P, Larson SM, Kremer A, et al. Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer. *J Clin Oncol.* 1999;17:948–957.

18. Meirelles GS, Schoder H, Ravizzini GC, et al. Prognostic value of baseline [18F]fluorodeoxyglucose positron emission tomography and 99mTc-MDP bone scan in progressing metastatic prostate cancer. *Clin Cancer Res.* 2010;16:6093–6099.

19. Freedland SJ, Humphreys EB, Mangold LA, et al. Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. *J Clin Oncol.* 2007;25:1765–1771.

20. D'Amico AV, Moul JW, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Natl Cancer Inst.* 2003;95:1376–1383.

21. Zhou P, Chen MH, McLeod D, Carroll PR, Moul JW, D'Amico AV. Predictors of prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Clin Oncol.* 2005;23:6992–6998.

22. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol.* 2007;25:2035–2041.

23. American Joint Committee on Cancer. In: Edge SB, Byrd DR, Compton CC, April GF, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual.* New York, NY; 2010:457–464.

24. Scher HI, Eisenberger M, D'Amico AV, et al. Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol.* 2004;22:537–556.

25. Scher HI, Morris MJ, Basch E, Heller G. End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice. *J Clin Oncol.* 2011;29:3695–3704.

26. Mottet N, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol.* 2011;59:572–583.

27. Fanti S, Krause B, Weber W, et al. Re: Nicolas Mottet, Joaquim Bellmunt, Michel Bolla, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol.* 2011;60: e37–38; author reply e39–41.

28. Rigatti P, Suardi N, Briganti A, et al. Pelvic/retroperitoneal salvage lymph node dissection for patients treated with radical prostatectomy with biochemical recurrence and nodal recurrence detected by [11C]choline positron emission tomography/computed tomography. *Eur Urol.* 2011;60:935–943.

29. Tilki D, Reich O, Graser A, et al. 18F-fluoroethylcholine PET/CT identifies lymph node metastasis in patients with prostate-specific antigen failure after radical prostatectomy but underestimates its extent. *Eur Urol.* 2013;63:792–796.

30. Soyka JD, Muster MA, Schmid DT, et al. Clinical impact of 18F-choline PET/CT in patients with recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2012; 39:936–943.

31. Breeuwsma AJ, Rybalov M, Leliveld AM, Pruim J, de Jong IJ. Correlation of [11C]choline PET-CT with time to treatment and disease-specific survival in men with recurrent prostate cancer after radical prostatectomy. *Q J Nucl Med Mol Imaging.* 2012;56:440–446.

32. Price DT, Coleman RE, Liao RP, Robertson CN, Polascik TJ, DeGrado TR. Comparison of [18F]fluorocholine and [18F]fluorodeoxyglucose for positron emission tomography of androgen dependent and androgen independent prostate cancer. *J Urol.* 2002;168:273–280.

33. Fuccio C, Castellucci P, Schiavina R, et al. Role of 11C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. *Ann Nucl Med.* 2010;24:485–492.

34. Husarik DB, Miralbell R, Dubs M, et al. Evaluation of [18F]-choline PET/CT for staging and restaging of prostate cancer. *Eur J Nucl Med Mol Imaging.* 2008;35: 253–263.

35. Soloway MS, Hardeman SW, Hickey D, et al. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer.* 1988;61:195–202.

36. Souvatzoglou M, Krause BJ, Purschel A, et al. Influence of 11C-choline PET/CT on the treatment planning for salvage radiation therapy in patients with biochemical recurrence of prostate cancer. *Radiother Oncol.* 2011;99:193–200.

37. Roach M 3rd, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol.* 2003;21:1904–1911.

38. Cheng L, Slezak J, Bergstralh EJ, et al. Dedifferentiation in the metastatic progression of prostate carcinoma. *Cancer.* 1999;86:657–663.

11C-Choline PET/CT Predicts Prostate Cancer–Specific Survival in Patients with Biochemical Failure During Androgen-Deprivation Therapy

Giampiero Giovacchini, Maria Picchio, Rita Garcia-Parra, Alberto Briganti, Firas Abdollah, Luigi Gianolli, Christian Schindler, Francesco Montorsi, Cristina Messa and Ferruccio Fazio

This article and updated information are available at:
http://jnm.snmjournals.org/content/55/2/233

Information about reproducing figures, tables, or other portions of this article can be found online at:
http://jnm.snmjournals.org/site/misc/permission.xhtml

Information about subscriptions to JNM can be found at:
http://jnm.snmjournals.org/site/subscriptions/online.xhtml

SNMMI | SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING