

[¹¹C]Choline Positron Emission Tomography/Computerized Tomography to Restage Prostate Cancer Cases With Biochemical Failure After Radical Prostatectomy and No Disease Evidence on Conventional Imaging

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

CT = computerized tomography

PCa = prostate cancer

PET = positron emission tomography

PSA = prostate specific antigen

PSADT = PSA doubling time

RP = radical prostatectomy

Purpose: We assessed the value of [¹¹C]choline positron emission tomography/computerized tomography in patients with prostate cancer in whom biochemical failure developed after radical prostatectomy but who showed no disease evidence on conventional imaging.

Materials and Methods: Considered for this study were 2,124 patients treated with radical prostatectomy who underwent [¹¹C]choline positron emission tomography/computerized tomography to restage disease between December 2004 and January 2007. Study inclusion criteria were 1) previous radical prostatectomy and pelvic lymph node dissection, 2) increasing prostate specific antigen beyond 0.2 ng/ml after radical prostatectomy, 3) no lymph node disease at radical prostatectomy, 4) no evidence of metastatic disease on conventional imaging, 5) no androgen deprivation therapy and 6) no adjuvant or salvage radiotherapy. These criteria were satisfied in 109 of the 2,124 patients (5%).

Results: Median prostate specific antigen at imaging was 0.81 ng/ml (range 0.22 to 16.76 ml). Imaging suggested local recurrence in 4 patients (4%) and pelvic lymph node disease in 8 (7%). Scans were positive in 5%, 15% and 28% of patients with prostate specific antigen less than 1, between 1 and 2, and greater than 2 ng/ml, respectively (p <0.05). Prostate specific antigen was the only significant predictor of tomography results (p <0.05).

Conclusions: Positron emission tomography/computerized tomography detected increased [¹¹C]choline uptake, suggesting recurrent disease in 11% of patients with prostate cancer, increasing prostate specific antigen after radical prostatectomy and no evidence of disease on conventional imaging. This modality may be useful to restage disease but it cannot be used to guide therapy.

Key Words: prostate; tomography, emission-computed; choline; prostate-specific antigen; prostatic neoplasms

AFTER RP in patients with PCa biochemical failure, that is persistently increasing plasma PSA beyond 0.2 ng/ml, develops in 15% to 77% in the first 5 years after surgery.¹ In recent years

[¹¹C]choline PET/CT has proved useful to restage patients with PCa who have biochemical failure.²⁻¹⁰ The greatest appeal of this technique is that it allows assessment of disease recur-

Submitted for publication December 15, 2009.
Study received approval from the Scientific Institute, San Raffaele Hospital ethical committee.

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rence at multiple anatomical sites at a single time.⁴

The positive detection rate of [¹¹C]choline PET/CT varies substantially among studies. de Jong et al failed to detect positive scans in patients with PSA less than 5 ng/ml³ while Krause et al reported a 36% detection rate in patients with PCa who had PSA less than 1 ng/ml.⁷ These disparities may be related to methodological differences in sample population recruitment. Previous PET/CT series included patients with biochemical recurrence only as well as those with clinically proven metastatic disease.^{3–5,7,11} Also, no distinction was made between patients receiving and not receiving ADT. This may represent a significant limitation due to the potential of ADT to interfere with [¹¹C]choline uptake,¹² and to the inclusion of androgen sensitive and androgen resistant patients in the same cohort. Previous studies also included patients who did and did not previously receive radiotherapy.^{4,5,7}

We assessed the ability of [¹¹C]choline PET/CT to detect recurrent disease in patients with PCa and biochemical failure after RP who had no other evidence of disease on conventional imaging.¹³

MATERIALS AND METHODS

Patients

We retrospectively considered 2,124 patients referred to our institution for [¹¹C]choline PET/CT from December 2004 to January 2007 to restage PCa after biochemical failure. Study inclusion criteria were 1) previous RP and pelvic lymph node dissection, 2) biochemical failure, defined as PSA greater than 0.2 ng/ml on at least 2 consecutive measurements 3 months apart, 3) no evidence of lymph node metastasis at RP, 4) no evidence of metastatic disease on clinical examination and several diagnostic conventional imaging techniques, 5) no previous ADT and 6) no previous adjuvant or salvage radiotherapy. At least 1 imaging technique at each analyzed anatomical district had to be negative for metastatic disease. Transrectal ultrasound and transrectal magnetic resonance were used to assess the prostatectomy bed, abdominopelvic CT was used to study lymph nodes, and bone scintigraphy and bone CT were used to assess the skeleton. Imaging was done within 3 months of PET/CT.

This retrospective, single institution study was approved by the Scientific Institute, San Raffaele Hospital ethical committee. An informed consent form for [¹¹C]choline PET/CT and for anonymous publication of disease related information was signed by each patient according to the Declaration of Helsinki.

PET/CT Acquisition

PET/CT was acquired using 3 integrated PET/CT systems, including DiscoveryTM LS, Discovery ST and Discovery STE. Patients refrained from drinking and fasted at least 6 hours before [¹¹C]choline PET/CT. A CT scout image was acquired to define the body axial extension (from the pelvis to the base of the skull) to be imaged. After low dose CT at 90 mA, 0.8 seconds per rotation and 140 kV 5, 1-minute

frames centered on the pelvis were acquired immediately after injecting about a mean \pm SD of 438 ± 70 MBq [¹¹C]choline. At the end of dynamic scanning, ie 5 minutes after injection, whole body PET was done.¹⁰

Image Interpretation

Image readout was done on a XelerisTM workstation, which enables visualization of PET, CT and fused PET/CT images in the transverse, coronal and sagittal planes. [¹¹C]choline images were read independently by a staff physician (GG) and a senior staff physician (LG) with 3 and 7 years, respectively, of experience with [¹¹C]choline PET/CT. All cases of disagreement (7 of 109 or 6%) were reexamined and a consensus was reached. Each focal tracer accumulation deviating from tracer physiological distribution¹⁴ was considered to suggest disease. [¹¹C]choline PET/CT findings were compared to histological analysis of the surgical lymph node specimen and the vesicourethral anastomosis biopsy, when available.

Group comparisons were done using the t test for continuous variables and the chi-square test for categorical variables. All tests were 2-sided with statistical significance considered at $p < 0.05$.

RESULTS

Of 2,124 patients 109 (5%) met study inclusion criteria. Table 1 lists sample characteristics. Median time from PSA measurement to [¹¹C]choline PET/CT was 18 days. Median PSA was 0.81 ng/ml (mean 1.31 ± 1.91 , range 0.22 to 16.76). Median PSADT¹⁵ in 47 cases was 9.96 months (mean 12.42 ± 8.34 , range 2.90 to 45.33). PET/CT was positive in 12 of 109 patients (11%) and negative in 97 of 109 (89%). Of the 109 patients with positive scans 8 (7%) had increased [¹¹C]choline uptake in the pelvic lymph nodes. A median of 2 lymph nodes (range 1 to 3) had increased [¹¹C]choline uptake and mean maximal diameter was 8.7 ± 1.3 mm (range 5.4 to 9.7). Four patients (4%) had increased [¹¹C]choline uptake in the prostatectomy bed. No patient had concomitant increased [¹¹C]choline uptake in the prostatectomy bed and the lymph nodes. There was no significant [¹¹C]choline uptake in the retroperito-

Table 1. Sample clinical characteristics

Mean \pm SD/median age (range)	66.4 \pm 6.2/67	(51–83)
Mean \pm SD/median ng/ml PSA at PET/CT (range)	1.31 \pm 1.91/0.81	(0.22–16.76)
Mean \pm SD/median mos to biochemical failure (range)	33 \pm 22/24	(7–135)
Mean \pm SD/median mos to trigger PSA (range)	43 \pm 28/36	(9–141)
No. pathological T stage (%):		
pT2	76	(70)
pT3a	17	(15)
pT3b	16	(15)
No. Gleason score (%):		
7 or Less	92	(84)
Greater than 7	17	(16)

Table 2. Clinical and pathological characteristics in 12 patients with positive [¹¹C]choline PET/CT

Pt No.—Age	PSA at PET/CT (ng/ml)	Gleason Score	T Stage	Lymph Nodes		PET	
				No.	Max Diameter (mm)	Lymph Nodes	Prostatectomy Bed
1—66	0.35	4 + 3	pT2a	1	8.6	Pos	Neg
2—61	0.46	2 + 2	pT2b	3	9.1	Pos	Neg
3—64	0.51	4 + 4	pT2b	Not applicable	Not applicable	Neg	Pos
4—71	1.07	3 + 3	pT2c	2	7.3	Pos	Neg
5—72	1.76	2 + 3	pT3b	Not applicable	Not applicable	Neg	Pos
6—69	1.81	4 + 3	pT3a	Not applicable	Not applicable	Neg	Pos
7—60	1.93	3 + 4	pT2b	Not applicable	Not applicable	Neg	Pos
8—63	2.32	3 + 4	pT2b	2	5.4	Pos	Neg
9—68	2.68	4 + 4	pT2b	1	8.1	Pos	Neg
10—72	5.4	3 + 4	pT3b	2	8.8	Pos	Neg
11—58	8.41	4 + 3	pT3b	1	9	Pos	Neg
12—67	16.76	4 + 3	pT3a	2	9.7	Pos	Neg

neal lymph nodes or the skeleton. Table 2 lists details on the 12 patients with positive [¹¹C]choline PET/CT. Figure 1 shows 1 patient with lymph node disease.

Time to biochemical failure did not significantly differ in patients with positive vs negative PET/CT findings (24 ± 15 vs 33 ± 23 months, $p = 0.24$). PSA at imaging was significantly higher in patients with positive vs negative findings (3.62 ± 4.75 vs 1.03 ± 0.88 ng/ml). PSA velocity was significantly higher in patients with positive vs negative findings (2.31 ± 2.86 vs 0.76 ± 0.71 ng/ml per year, $p < 0.05$). Conversely PSADT was significantly shorter in patients with positive vs negative PET/CT results (6.82 ± 3.78 vs 13.74 ± 8.60 months, $p < 0.05$). However, there was no significant difference in PSA ($p = 0.29$), PSADT ($p = 0.98$) or PSA velocity ($p = 0.18$) in patients with [¹¹C]choline uptake in the pelvic lymph nodes vs the prostatectomy bed.

The percent of positive [¹¹C]choline PET/CT scans increased with increasing PSA. Imaging was positive in 3 of 65 (5%), 4 of 26 (15%) and 5 of 18 patients (28%) with PSA between 0.2 and 1, between 1 and 2, and greater than 2 ng/ml, respectively ($p < 0.05$, fig. 2). The incidence of positive results did not significantly

differ in patients with Gleason score 7 or less vs greater than 7 (10.9% vs 11.8%, $p = 0.91$) or in those with pT2 vs pT3 (9.2% vs 15.2%, $p = 0.36$).

Vesicourethral anastomosis biopsy was done in 13 of 109 patients. Three of these 13 patients had focal [¹¹C]choline uptake in the prostatectomy bed and 10 had negative [¹¹C]choline PET/CT results. Biopsy was positive in all 3 patients with positive findings and in 2 of 10 with negative findings. Biopsy was negative in 8 of 10 patients with negative [¹¹C]choline PET/CT. Only 1 patient with pelvic lymph node [¹¹C]choline uptake underwent surgery. PCa metastasis was detected in the surgical specimen.

DISCUSSION

PSA relapse after RP represents a clinical dilemma. The increase in PSA may occur many years before clinical evidence of recurrence, a change in lymph node size on abdominopelvic CT or positive bone scintigraphy.^{16,17} Thus, there is ongoing debate on when treatment should be started and which treatment modality is most appropriate in each patient. A critical step in this decision making process is the distinction between local and systemic disease,¹⁸ for

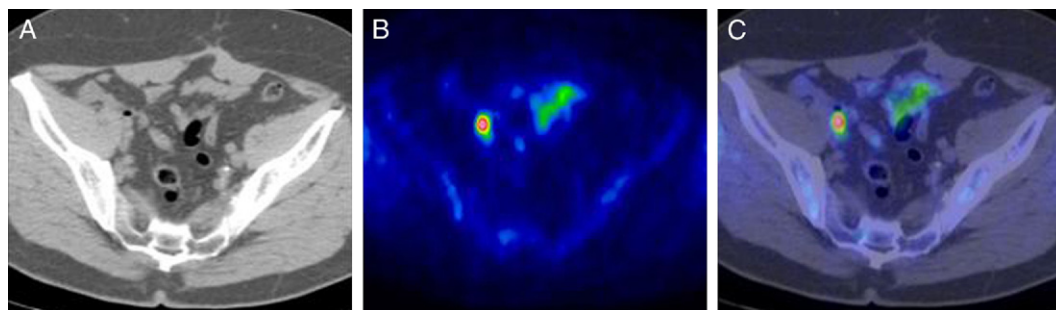


Figure 1. CT (A), PET (B) and fused PET/CT (C) show pathologically increased [¹¹C]choline uptake in patient with right external iliac lymph node. No other pathological uptake sites were noted. Trigger PSA was 2.68 ng/ml. Pelvic lymph nodal area was irradiated with 50 Gy during 5 weeks. PSA was undetectable 3 months after therapy end.

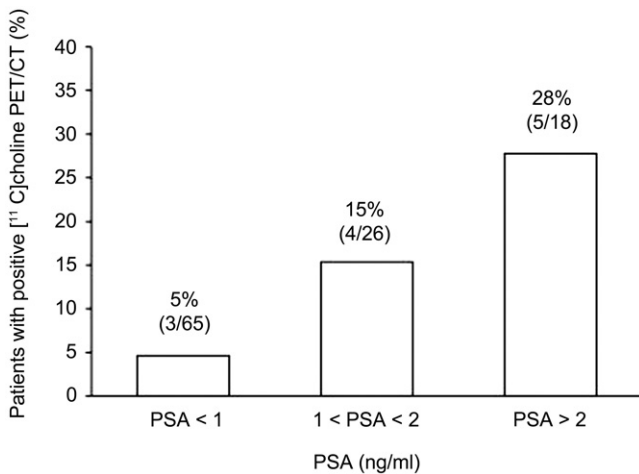


Figure 2. Positive [¹¹C]choline PET/CT incidence in patients with PSA less than 1, between 1 and 2, and greater than 2 ng/ml.

which PSA kinetics has been used to evaluate. For example, PSADT greater than 10 months is more likely related to local recurrence while PSADT less than 4 months is predominantly seen in patients with distant disease.^{19,20} Nomograms combining different risk factors have also been used to predict the likelihood of metastasis.²¹ Imaging can be used to differentiate local recurrence from distant disease.^{17,22} However, current imaging techniques, including transrectal ultrasound, lack the sensitivity needed to detect cancer recurrence when PSA is relatively low.^{16,17,22} Although imaging provides prognostic information,²³ routine imaging is not recommended in the followup of patients with PCa. In most cases PSA, PSA kinetics and clinical examination suffice to choose treatment type and timing.¹⁸

In recent years [¹¹C]choline PET/CT has emerged as a promising technique to restage PCa cases with biochemical failure.^{2–8,10,11} However, PET/CT is currently not recommended to detect metastasis since it is still considered investigational.^{13,18} To our knowledge our study differs from all previous studies in the rigorous patient selection criteria. Despite the retrospective design great care was taken to select only patients with no disease evidence on conventional imaging, in accordance with Prostate Specific Antigen Working Group guidelines.¹³ Previous ADT and radiotherapy were additional study exclusion criteria.

A high [¹¹C]choline PET/CT positive detection rate for low PSA would be desirable to guide therapy. Urologists and radiotherapists wish to use imaging for PSA lower than 1 ng/ml since in such cases disease is more likely to be locally confined and salvage therapy is expected to be more efficacious.¹⁸ In this select sample with a limited disease burden the positive detection rate of [¹¹C]choline PET/CT

was low (range 5% for PSA between 0.2 and 1 ng/ml to 28% for greater than 2 ng/ml). This technique may be useful to restaging PCa cases with biochemical failure and no other evidence of disease but it cannot be used to guide therapy. Our results may form the basis for future investigations in prospective fashion. In patients with characteristics similar to those in this sample [¹¹C]choline PET/CT is most useful for PSA greater than 2 ng/ml.

The overall 11% positive detection rate of [¹¹C]choline PET/CT in this sample is the lowest among previous PET/CT studies using radiolabeled choline.^{2,4–7,9,10,24–26} Values range from 23%²⁵ to 86%⁶ and most series show a positive detection rate similar to or greater than 40%.^{4–7,9,10,24,26} This apparent discrepancy may be attributable to the peculiar clinical and pathological characteristics of our sample. By definition our sample included only patients with negative conventional imaging and, thus, those at low risk. Median PSA, which is the primary determinant of the [¹¹C]choline positive detection rate, was the lowest compared to rates in previous studies. Also, none of our patients had received salvage radiotherapy or antiandrogen therapy. These variables were previously reported to affect the probability of positive [¹¹C]choline PET/CT results.¹⁰

We found no difference in PSADT or PSA velocity in patients with pathological [¹¹C]choline uptake in the pelvic lymph nodes vs the prostatectomy bed.⁹ This finding is most likely attributable to the few patients with positive [¹¹C]choline PET/CT and the lack of patients with skeletal disease.^{19,20}

In addition to PSA, in the clinical setting other variables are commonly considered for diagnostic or therapeutic purposes, primarily Gleason score and pathological stage. An unexpected finding in our study was that the positive [¹¹C]choline PET/CT rate did not significantly differ in patients with Gleason score 7 or less vs greater than 7 or in those with pT2 vs pT3 disease. While Gleason score and pathological stage are well established predictive factors of disease-free survival and overall survival in patients with PCa treated with RP,²⁷ their ability to predict imaging findings is less robust.¹⁷ Trigger PSA is measured at PET/CT while Gleason score and pathological stage are measured at RP. Thus, PSA may more closely correlate with disease activity at restaging. Alternatively a type II error may have occurred due to the small number of patients with positive [¹¹C]choline PET/CT.¹⁰

Several previous groups related radiolabeled choline PET/CT findings to conventional imaging but failed to provide compelling evidence of the superiority of [¹¹C]choline PET/CT over conventional imaging.^{4,5,7,8,11} Thus, [¹¹C]choline PET/CT has traditionally been considered complementary to conventional

imaging.⁴ We report that in a restricted group of patients with PCa and no disease evidence on conventional imaging PET/CT detected pathological [¹¹C]choline uptake sites, suggesting disease in 11%. Thus, in this specific patient group with a limited disease burden [¹¹C]choline PET/CT may be considered a valid choice of technique for disease restaging.

A study limitation is its retrospective design. Thus, selection bias cannot be excluded. However, we tried to minimize such bias by outlining a priori inclusion criteria and considering all consecutive patients referred to our institution for [¹¹C]choline PET/CT in a continuous 2-year period. Also, histological confirmation of [¹¹C]choline PET/CT positive findings was possible in only 4 patients since salvage pelvic lymph node dissection is not considered an established treatment in those with biochemical recurrence and evidence of nodal disease after RP.^{11,28,29} Moreover, anastomotic biopsy may have a low positive detection rate, especially for PSA less than 1 ng/ml.³⁰ The lack of histological confirmation and followup information makes this investigation primarily observational. The issue of possible false-positive findings is of critical importance because increased [¹¹C]choline uptake is not specific for car-

cinogenesis. Histological signs of inflammation has been found in lymph nodes with pathological [¹¹C]choline uptake that was erroneously attributed to recurrent disease.^{11,28,29} Histological evidence of PCa metastasis has been found in 70% to 90% of patients with pathological [¹¹C]choline uptake in the pelvic or retroperitoneal lymph nodes.^{11,28,29} False-positive findings may also occur in the prostatectomy bed, although false-negative results are the greatest concern at this anatomical district.^{4,8} The resolution of [¹¹C]choline PET/CT, which is about 6 mm, limits the ability to detect small lymph node metastasis and micrometastasis. This contributes to the low positive detection rate of [¹¹C]choline PET/CT and accounts for the 2 patients with false-negative findings in the prostatectomy bed compared to anastomotic biopsy findings.

CONCLUSIONS

PET/CT detected increased [¹¹C]choline uptake, suggesting recurrent disease, in 11% of patients with PCa who had increasing PSA after RP and no disease evidence on conventional imaging. In this population with a limited disease burden [¹¹C]choline PET/CT may be useful to restage disease but it cannot be used to guide therapy.

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