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RESEARCH**

APPLICATION NUMBER:

203155Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	August 31, 2012
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	203-155
Applicant Name	Mayo Clinic PET Radiochemistry Facility (MCPRF)
Date of Submission	December 12, 2011
PDUFA Goal Date	September 12, 2012 (based on a major amendment extension)
Proprietary Name / Established (USAN) Name	Choline C 11 Injection
Dosage Forms / Strength	Supplied as a glass vial containing 40 – 331 mCi (1.48 – 12.247 GBq) of ¹¹ C choline in aqueous 0.9% sodium chloride (approximately 10 mL volume); the mass dose of choline is estimated at no more than 5 mcg per dose
Proposed Indication(s)	<p>“for positron emission tomography (PET) imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging (MRI). In these patients, ¹¹C-choline PET imaging may help identify potential sites of prostate cancer recurrence for subsequent histologic confirmation. Suspected prostate recurrence is based upon elevated blood prostatic specific antigen (PSA) levels following initial therapy. In clinical studies, images were produced with PET/CT co-registration.</p> <p><u>Limitation of Use:</u> ¹¹C-choline PET imaging is not a replacement for histologic verification of recurrent prostate cancer.”</p>
Action/Recommended Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	William Dickerson, MD & Alex Gorovets, MD
Statistical Review	Lan Huang, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Ronald Honchel, PhD & Adebayo Lanionu, PhD (TL)
CMC Review/OBP Review	Ravindra Kasliwal, PhD
Microbiology Review	Robert Mello, PhD
Clinical Pharmacology Review	Christy John, PhD & Gene Williams, PhD (TL)

DDMAC/DPDP	James Dvorsky
DSI	Jong Hoon Lee, MD
CDTL Review	Alex Gorovets, MD
OSE/DMEPA	Kevin Wright, PharmD and Yelena Maslov, PharmD (TL)
OSE/DRISK	Not applicable
Pediatric and Maternal Health	Jeanine Best, MSN, RN
Project Manager	Frank Lutterodt, MS

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication; also known as Division of Professional Drug Promotion (DPDP)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls

1. Introduction:

This document describes the basis for my recommendation to approve the NDA for Choline C11 Injection for the indication cited above. This application was reviewed under a priority review time line but the review cycle was extended by a major amendment that prompted a clinical site inspection. The inspectional findings raised no new concerns. At the time of this document finalization, the review team is working to resolve an outstanding microbiology deficiency and also to revise the proposed labeling to correct typographical and formatting deficiencies.

Choline C11 Injection is one of the positron emission tomography (PET) drugs that has been in clinical use over the past many years, consistent with the provisions of the Food and Drug Administration Modernization Act of 1997 (The Act). This law outlined the process for regulation of PET drugs, including a prohibition against FDA requiring new drug applications (NDAs) for the drugs until the agency published final Current Good Manufacturing Practice (cGMP) regulations. The law allowed PET drugs to be used in clinical medicine even though they were unapproved. The law set a time line for this use of the unapproved drugs; specifically, the use of the unapproved drugs could continue until the FDA published cGMP regulations which were to trigger a timeline for submission of marketing applications. In December, 2009, FDA published the cGMP regulations which triggered the need for sponsors to submit NDAs or ANDAs for all PET drugs in clinical use by June 12, 2012. Choline C11 injection has been in clinical use at the Mayo Clinic and that institution submitted this NDA in order to continue using the drug in clinical practice.

A pre-NDA meeting was hold with the sponsor on February 8, 2011; representatives from FDA Office of Regulatory Policy (ORP) were present to facilitate the discussion of the unique aspects of PET drug regulation, especially the facilitation of NDA submission. The sponsor had proposed submitting an NDA to support the use of Choline C 11 Injection for “PET imaging of prostate cancer patients with known history of the disease.” At the pre-NDA meeting the sponsor indicated that they planned to rely on

published literature to support the drug's efficacy and safety. Consistent with the approval basis for other clinically used PET drugs, FDA clarified that a systematic review of the literature was a reasonable proposal. The major meeting discussion focused upon the need for the sponsor to better develop the proposed indication statement in order for it to align with the current usage of choline C11 injection at their institution; this usage was narrower than the usage identified by the proposed indication statement.

The NDA was submitted with two clinical data sources: 1) the results of a systematic review of the published literature performed by the sponsor and 2) unpublished findings from a retrospective review of the medical records from certain patients managed at the Mayo Clinic. The proposed labeling (package insert) contained a Clinical Studies section that was based entirely upon the Mayo Clinic experience.

The regulatory history of PET drug review and approval consideration is somewhat complicated, in part related to The Act expectations and the precedent for using published literature to support safety and efficacy of the drugs. In 1999, FDA review staff conducted reviews of published literature to try to facilitate the submission of NDA submissions since some of these products had been in relatively wide-spread clinical use. These reviews were not meta-analyses; instead, they relied upon expert FDA review officer appraisal of the ability of the information within the reports to equate to substantial evidence of efficacy. Three reviews culminated in a finding of safety and efficacy, as follows:

- Dr. Florence Houn reviewed published reports of fludeoxyglucose F18 (FDG) to support the drug's use in oncology; FDG had previously been approved only for a neurological indication.

- Dr. Victor Raczkowski reviewed published reports to support FDG use in cardiac evaluations;

- Dr. Florence Houn and Dr. Sonia Castillo also reviewed published reports of ammonia N-13 to support the drug's use in cardiac evaluations. Ammonia N-13 had not been previously approved by the FDA.

These reviews are available on the FDA's external PET website at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm181434.htm>.

In their reviews, the FDA staff emphasized the following as priorities for assessing the quality of evidence in published reports: prospective study designs, comparison of imaging results to pathology or another reference standard, the use of controls to the extent imaging studies are usually controlled, reasonable sample sizes and imaging drug dose information. The reviewers noted that some centers published multiple reports and, in this situation, only the publication with the largest sample size was reviewed. The most clinically important studies were selected by the reviewers for inclusion into labeling. For example, the ammonia N13 label cited only a single clinical study that supported the drug's use; the FDG label cited 16 oncology studies but stated that the

results were variable across the studies; the FDG “cardiology” label similarly summarized the reviewer’s interpretation of the findings from 10 studies without supplying outcome details of any single study. Performance data (sensitivity/specificity) were not supplied in the labeling for any of the drugs approved based upon FDA’s review of published literature.

The FDA medical expert’s review is consistent with the principles described in the 1998 FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products. This guidance describes some of the important limitations of relying solely upon published reports as an evidentiary basis, such as bias toward only “positive” results and the truncation of details within publications. However, the guidance notes that:

“The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

- a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.
- b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.
- c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.
- d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or “evaluable” subset).
- e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

There have been approvals based primarily or exclusively on published reports. Examples include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.”

The published reports reviewed by FDA medical experts in 1999 all had deficiencies; indeed, only two were regarded as adequate and well controlled for the ammonia N-13 efficacy finding and even these two reports contained deficiencies, as detailed by the reviewers. Nevertheless, in the context of carefully crafted labeling, the reviewers regarded the published literature as providing substantial evidence of effectiveness. This experience is relevant to the review of Choline C 11 Injection since regulations for diagnostic radiopharmaceuticals emphasize the importance of the evaluating efficacy as it relates to the drug's proposed indication.

The Diagnostic Radiopharmaceutical regulations (21 CFR 315) state that, "The effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use."

This history of PET drug review (for drugs already in clinical use) impacted the Choline C11 Injection review by providing a precedent for the use of published literature as a source for definitive safety and efficacy information. In this review document, I highlight the sponsor's main basis for asserting the safety and efficacy of Choline C11 injection and I also include a review that I performed of the published literature, following the paradigm performed by Drs. Houn, Raczkowski and Castillo.

During the review process, the sponsor submitted a response to an FDA request that prompted a Major Amendment to the application and extended the review cycle by three months. The sponsor's response elaborated upon some of the details within the Mayo Clinic's summarized experience.

Overall, the NDA's main clinical review items focused upon assessment of efficacy data because the safety concerns related to the product relate predominantly to the nature of the information obtained from PET imaging and the radiation exposure (not toxicity from choline).

2. Background:

Choline is a naturally occurring compound/nutrient involved in multiple aspects of cellular metabolism. The sponsor reports that the C11-radiolabeled choline is identical in molecular structure to naturally occurring choline, exclusive of the radiolabel. Some publications have asserted that *in vitro* prostate cancer cells have a special preference for uptake of choline over glucose and acetate. The basis for prostate carcinoma avidity to choline is unknown but has been proposed to relate to unique prostate cancer cellular membrane lipid metabolism features.

The first published report of Choline C11 PET imaging appeared in 1998. Over the subsequent years, multiple publications have appeared in the literature; almost all clinical publications relate to use of the drug among men with prostate cancer. Because of the unique manufacturing aspects of Choline C11, this type of PET imaging is not widespread and appears largely confined to academic centers with special interest in nuclear medicine and prostate cancer clinical research.

The major clinical concern for this application relates to the potential use of Choline C11 PET imaging among men with suspected recurrent prostate cancer (following primary treatment of localized disease). The ability to identify men who have localized disease versus men with metastatic disease is clinically important because the types of therapy differ: localized treatment (surgery and/or radiation) for localized disease versus systemic therapy for non-localized disease (chemotherapy and/or radiation).

The Mayo Clinic physicians and surgeons submitting this application have highlighted the role of surgical extirpation of an isolated recurrent site (such as in the prostatic fossa) as well as the potential for curative radiotherapy to the single site. The Mayo physicians note that if metastatic disease is detected, the management is usually more extensive and involves radiotherapy and/or androgen deprivation and/or systemic pharmacotherapies. Hence, the physicians purport that Choline C11 Injection could serve an important clinical role in the situation where the PET imaging helped to identify an isolated prostate recurrence site amenable to local therapy (surgery or radiation).

Currently the only medical imaging drug approved for use in the imaging of patients with prostate cancer is the murine monoclonal antibody, capromab pendetide (Prostascint), an indium 111 radiolabelled compound. The ProstaScint labeling contained many limitations, in part apparently related to the performance characteristics and very limited clinical study data when positive scans suggested metastatic disease (limited truth standard data).

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. Ravindra Kasliwal who verified acceptable manufacturing procedure during the resubmission cycle and recommended approval. Facility inspections are complete and document sufficiency for NDA approval.

The C 11 radionuclide is produced within a cyclotron; the choline is chemically synthesized from a precursor molecule, as noted below.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by Dr. Ronald Honchel who noted that choline is a normal component of the diet (typically in an amount of several hundred milligrams). The applicant did not submit nonclinical studies but did cite the publicly available literature to support the safety of Choline C 11 Injection. Dr. Honchel noted that choline within the drug product (b) (4) which is present in the drug product at approximately (b) (4). Dr. Honchel noted that (b) (4) endogenously by the body, is a food supplement and data supports its safety at ingested doses far greater than those present in Choline C 11 Injection.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer who found the sponsor's submission of data from publications sufficient to characterize the pharmacology of the drug.

6. Clinical Microbiology:

I agree with Dr. Robert Mello's observations that the sponsor needs to resolve one deficiency pertaining to the description of the media fill microbiology testing procedure. This morning Dr. Mello spoke with the applicant who has committed to submitting the required document revision within the next few days. Dr. Mello is to document his findings once the applicant submits this information.

7. Clinical/Statistical-Efficacy:

Dr. William Dickerson provided the main clinical review and Dr. Lan Huang and Dr. Jyoti Zalikar provided the main statistical review for the submission. Dr. Alex Gorovets provided a secondary clinical review.

My review is divided into two sections: 1) a summary of the sponsor's major clinical data submission and 2) my review of the published literature (performed independent of the submission). I will not describe the sponsor's major clinical data in detail since Dr. Dickerson and Dr. Huang provide extensive detail.

1) Sponsor's data submission: The sponsor cites two data sources, as follows:

a. A systematic review of the published literature (located in Section 5.4 of the submission, titled, "Choline C11 Injection Literature Search).

The literature search used the following terms: choline, prostate and PET to examine the following databases for reports: PubMed and MedLine. The search revealed 183 publications; the sponsor eliminated study reports if they:

- a. Included < 30 subjects
- b. Focused on tracer radiochemistry or biodistribution
- c. Had no described method of verification of choline PET imaging findings
- d. Were technology update or technology improvement focused articles or
- e. Were at high risk of inclusion of duplicate data from another publication included in the final acceptable group.

Using the above criteria, the sponsor detected 20 publications; 11 were pertinent to the proposed indication in that they focused on restaging prostate cancer patients after initial therapy. The submission contains the selected 11 publications as well as narrative summaries of the publications (two of these publications actually studied choline F18, not choline C11). The Mayo researchers identified three studies that used prospective designs and six studies that used retrospective designs. I will not duplicate the information from these studies since it is covered in my own review (below) of the published literature.

b. A summary of the Mayo Clinic experience with choline C11 imaging consists of a retrospective review of medical records for selected patients who had undergone choline C11 imaging at the Mayo Clinic.

The sponsor supplies a study report and SAS datasets (following a request by the FDA; the datasets were not supplied initially by the sponsor). The study was not based on a protocol; instead a data collection format (a table) was developed to contain information extracted from medical records. The study was exempted from IRB review and patients did not provide consent; study report findings are not traceable back to original source data. The study examined patients who underwent Choline C11 PET imaging between September 2007 and November 2010. Among 231 patients who underwent the PET imaging during this time period, 176 met the following criteria: men with documented “BCR” (biochemical recurrence) defined as at least 2 separate prostate specific antigen (PSA) measurements acquired 3 months apart for retropubic prostatectomy (RP) patients, nadir plus 2 ng/mL for patients treated with radiation or primary cytoablation, or a steady rise in PSA for men treated with primary androgen deprivation therapy (ADT).

In an amendment submitted to the NDA on February 6, 2012, the sponsor stated, “The data presented to support this NDA were collected in compliance with GCP standards to the extent that the institution and regulatory agencies required for a retrospective chart review. The data collection on the human subjects was done with IRB oversight and approval in accordance with the research plan. Data were recorded in a manner to protect subject confidentiality as well as maintain the quality of the data collected.”

The February 6, 2012 submission also contained a statistical analytical plan (SAP) for the retrospective chart review. The SAP was dated February 2, 2011 and stated, “This was a retrospective review of data extracted and statistically analyzed from hospital charts of patients who developed biochemical recurrence (BCR) after primary treatment failure of prostate cancer. Patients’ charts were consecutively selected if they underwent a Choline C 11 PET scan at Mayo Clinic within the time interval September 2007 through November 2010 so as not to exclude or select cases. This time frame was selected because the Mayo Clinic clinical program in Choline C 11 PET began in September, 2007.”

In an April 17, 2012 NDA submission, the sponsor further clarified that, “Follow-up of the patients was not part of this retrospective study. Any reference to recurrence was to the status of disease at the time of the Choline scan and/or immediate medical status as determined by the summation of all of the testing at that time. Therefore there is no follow-up data on the 35 patients. We likewise have no information on what prompted biopsy as the data was not collected prospectively as to what information was used to make this decision or how a decision was made on selecting a location for biopsy.”

Reviewer’s comment: During a telephone conversation, the sponsor clarified that this retrospective chart review was exempted from IRB detailed review because all data were

to be anonymized—i.e., the data collection process did not contain a link of extracted variables back to source data. Hence, the presented data cannot be source verified back to the original data; in essence, the Mayo Clinic experience is relatively similar to a single site published report. Unlike a published report, FDA was supplied with the extracted case report tabulations that supported the final report's observations.

The sponsor's major findings are described in Dr. Wilkerson's reports (e.g., sensitivity/specificity, etc). The "positive" truth standard definition includes "a decrease in PSA > 50% after selective irradiation of choline-avid lesions" or histologic confirmation or confirmation by conventional imaging. A "true negative" was denoted by negative histopathology or "negative conventional imaging." Images were interpreted with knowledge of clinical findings.

Among the 176 reported patients, 44 were reported as "negative" and 114 were reported as "positive." A truth standard was missing for 17 of the 176 subjects; among the remaining 159 subjects the sensitivity was reported as 93% and the specificity as 76%. The report notes that the sensitivity (95%) and specificity results (86%) are numerically higher in the subset of men who had undergone primary RP (n = 126) in whom the truth standard was confined to pathology or imaging. The report notes that PET images were more likely to be positive for men with higher PSA values, compared to men with lower values.

The results in the subset of men with negative conventional imaging studies are especially notable and are summarized in Dr. Huang's review.

The Mayo clinic experience is summarized in a couple of abstracts published in The Journal of Urology, as cited in the proposed labeling.

2) My review of the published literature:

In a search of PubMed database on May 8, 2011, the following search terms were entered: C11 choline + prostate cancer. From this search of reports published over the past 10 years, 102 publications were obtained. Multiple citations referred to use of Choline C11 in the primary prostate cancer setting and/or animal models. Abstracts of all publications were reviewed to identify those that related to use of Choline C 11 in the prostate cancer recurrence setting. Twenty-nine publications met these criteria (see appendix).

From the listing of 29 publications, reports were selected for detailed review if all of the following criteria were met: English, report of a study that included at least 10 subjects (not a review or letter to the editor) and use of C11 choline (not F18 choline). Based on these criteria the following were identified:

- five reports of prospectively conducted clinical studies
- 13 reports of retrospective reviews of patient records

The review of the publications showed that some clinical sites provided multiple publications in a manner that precludes the ability to rule out duplicate reporting of patients. The following were found:

- The University of Bologna in Bologna, Italy is cited as author representation on three of the published reports (all retrospective in study design)
- The University of Ulm in Ulm, Germany and the Katholieke Universiteit Leuven in Leuven, Belgium is cited as author representation on two of the published reports (both retrospective in study design).

Because several of the published retrospective reviews came from institutions that appeared to have duplicate reporting of patients, I limited my review to 10 of the 13 publications and included the publication with the largest sample size as the representative publication for each of the two clinical sites that appeared to have had duplicate reporting of patients.

I have assigned the greatest potential importance to the prospectively designed clinical studies and provide the following table and narrative summaries:

Prospective Study Reports

Study	N	Imaging/Dose	Status	PSA	Imaging field
1	25	PET/CT ~ 370 MBq	All Post-RP	Median 2.0 Range 0.2 – 23.1	Pelvis to neck
2	15	PET/CT ~ 1000 MBq	All Post-RP	Median 2.0 Range 1.0 – 8.0	Pelvis to neck
3	70	PET ~ 370 MBq	All Post-RT	Median 10.7 Range 0.6 – 54.7	Pelvis to lower abd
4	73	PET for 18; PET/CT for 55; ~ 370 MBq	Post-RP 49; Post-RT 24	Median 2.7 Range 1.1 – 5.4	Pelvis to upper 1/3 abd
5	38	PET/CT ~ 650 MBq	Post-RP 20; Post RT 18	Range 0.8 – 9.5	Pelvis to neck

1 = Eurorology 2007; 52:423-420

2 = Urologia 2008; 81:191 – 197

3 = Int J Radiation Oncol 2010; 77:160-164 (includes 10 control subjects/70 patients)

4 = Mol Imaging Biol 2010; 12:210-217

5 = Rev Esp Med Nucl 2009; 28:95-100

In most of the reports, authors report that patients were fasted for six to eight hours prior to administration of radioactive choline.

Reports of Prospective Clinical Studies

Similar to the criteria used by Dr. Houn and Dr. Raczkowski in their review of published literature for unapproved but clinically used PET drugs, I examined the published reports

of the Choline C11 clinical studies that used a prospective design and assessed the strengths and weaknesses of the reports, focusing upon the following criteria that have previously been used by FDA to help identify “adequate and well controlled studies” in published literature:

- prospective design
- adequate patient disposition description
- a method for evaluating success
- description of measures to control bias in patient selection and image interpretation
- a description of study drug dose
- a description of hypotheses for testing and analytical procedures

My greatest focus is upon the reports of studies that used prospective designs since these studies are likely less vulnerable to the multiple biases inherent in retrospective reviews of previously obtained patient data. The studies are presented in the order of my assessment of their usefulness, the strongest first. Some of the studies used a truth standard composite consisting of histopathology, alternate imaging results and the response to the “salvage” cancer therapy (similar to the Mayo Clinic report). My comments on the studies are denoted in italics.

1. Scattoni, V, Picchio, M, Suardi, N, et. al. Detection of lymph-node metastases with integrated C 11 choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. European Urology 2007; 52:423-429.

Design:

Single arm, single center study in which patients were to be enrolled if they had choline C 11 PET scans and/or conventional imaging that indicated lymph node cancer recurrence and surgery (lymphadenectomy) was to be performed and the patients met the full eligibility criteria.

Eligibility:

Inclusion criteria:

- provide written consent
- scheduled for surgical resection of pelvic-retroperitoneal disease
- prior choline C11 PET/CT or conventional imaging demonstrating pelvic-retroperitoneal lymph node disease
- prior RP as primary therapy for prostate cancer
- “PSA relapse” documented by PSA > 0.2 ng/mL

Exclusion criteria:

- evidence of bone metastases
- evidence of local recurrence detected by trans-rectal ultrasound (TRUS) prostatic fossa biopsy, CT or MR, choline C11 PET
- PSA doubling time of < 6 months

Choline C 11 dose:

-approximately 370 mBq

Evaluations:

- restaging with choline C11 PET/CT scans, bone scans, digital rectal exam, CT or MR, TRUS-guided prostate fossa biopsy
- surgical resection of lymph nodes with histopathological examination of tissue; all performed by the same surgeon

Image protocol:

- PET/CT done with an integrated scanner with whole body imaging (pelvis to neck)
- PET/CT images interpreted by two independent nuclear medicine physicians using prespecified criteria for positive/negative lymph nodes (does not explicitly state that readers were masked to clinical information)
- conventional imaging (MR or CT) interpreted by a single radiologist using pre-specified criteria based on lymph node size

Objective:

The pre-specified objective was to: “evaluate the accuracy of choline C11 PET/CT in the detection of tumor lymph node involvement, with the use of histologic results as the standard of reference, in patients undergoing retroperitoneal and/or pelvic lymph node dissection because of a rising PSA level and isolated evidence of nodal recurrence.”

Outcome assessments:

“accuracy” measures based on comparison of choline C11 images to histopathology (sensitivity/specificity/PPV/NPV/Accuracy); a criterion for success is not described in the study report.

Results:

Conduct: The study was conducted between 2002 and 2005 at clinical sites affiliated with the University of Milano-Bicocca in Milan, Italy.

Patient disposition: 85 patients screened, 25 enrolled; all 25 completed the study.

Efficacy: The primary outcome measures of choline C11 “accuracy” were:

- sensitivity 100%
- specificity 66%
- PPV 90%
- NPV 100%
- accuracy 92%

Overall, histopathology was positive in 19 patients and negative in 6 patients.

With respect to imaging,

-choline C11 PET/CT was positive in 21/25 patients and of these 21 patients, histopathology was positive in 19 patients; The report does not describe the histopathological finding in the two false positive situations.

-conventional imaging was positive in 12/25 patients and of these 12 patients, histopathology was positive in 8 patients.

The serum PSA median was 1.98 (range of 0.23 – 23.12 ng/mL). The authors report the best performance characteristics among the subset of patients with PSA levels > 2.0 ng/mL.

The supplied information within the report is sufficient to identify patients with non-informative conventional imaging. Specifically, the report notes that “All patients underwent a digital rectal examination, C 11 choline PET/CT, bone scan, morphologic imaging (CT or MR) and transrectal ultrasound-guided prostatic fossa biopsy to restage the disease.” The text further clarifies that patients with local recurrence or bone metastases were excluded from the study.

The report identifies 13 patients as having histopathology but negative conventional imaging. Specifically, the text notes, “PET/CT contributed true positive information beyond conventional CT/MR in 11 patients (58%).” Consequently, this text indicates that 11 patients had negative conventional imaging and positive PET/CT. The text also notes, “In 8 cases (67%) positive results were obtained by both PET/CT and conventional imaging.” The text further indicates that, overall, conventional imaging was negative in 13 patients since it states, “Choline C 11 PET/CT results were positive in 21 patients (13 at pelvic sites and 8 at retroperitoneum site) and conventional CT or MR imaging results were positive in 12 cases (9 at pelvic sites and 3 at retroperitoneum site).

The preceding statements allow a summary of the distribution by image result as follows:

Table 1 Distribution of Patients by Imaging Results (all have histopathology)

Patients		
8	PET +	Conventional +
4	PET -	Conventional +
11	PET +	Conventional -
2	PET +	Conventional -

Safety: The report does not describe safety outcomes.

Eight patients had both positive PET/CT and positive conventional imaging. The four patients with negative PET/CT and positive conventional imaging all had negative histology. Examination of lymph node cancer “positivity” in comparison to blood PSA levels, suggested that the higher the PSA level, the more likely a lymph node contained cancer; similarly the lymph node was more likely to be choline C 11 positive.

All positive PET/CT scans were at the pelvic or retroperitoneal sites.

Reviewer's comment: This study is remarkable for the detail within the publication. The study specifically examined patients with suspected local lymph node metastases—not prostate fossa loco-regional recurrence. Nevertheless, the performance characteristics within patients with suspected lymph node metastases is clinically important information in that it may help guide the choice for pelvic irradiation over systemic therapy or potential surgical resection of the pelvic disease. The authors noted that one limitation of the study was the fact that the surgeon had knowledge of the pre-surgical imaging which could have impacted the lymphadenectomy procedure. The authors noted that the surgical procedure was performed in a standardized manner that was intended to minimize this bias (with a systematic evaluation of specific anatomic sites).

The study provides some useful information for the 13 patients who have negative conventional imaging (11 were choline true positive and 2 were choline false positive). The true negative results cannot be estimated however since none of the patients in this subset had negative results (all PET/CT were positive).

Regarding other limitations, the study's sample size is small (in comparison to most phase 3 studies) and the study comes from a single center. Additionally, no PET/CT scans were positive at body sites remote from the pelvis-retroperitoneal area so the ability of the scan to detect systemic metastatic disease is not evaluated. Another limitation of this report is the lack of safety information; the study involved surgery which would have likely confounded any delayed PET/CT safety observations.

2. Rinnab, L, Mottaghy, F, Simon, J, et. al. 11C choline PET/CT for targeted salvage lymph node dissection in patients with biochemical recurrence after primary curative therapy for prostate cancer. Urologia Internationalis 2008; 81:191-197.

Design:

Single arm, two center study in which patients were to be enrolled if they had positive choline C 11 PET/CT scans that indicated pelvic loco-regional lymph node cancer recurrence and surgery (lymphadenectomy) was to be performed and the patients met the full eligibility criteria. Excluded were patients who had positive conventional imaging (MRI, CT, bone scintigraphy) and patients who hadn't had prior radical prostatectomy.

Eligibility:

Inclusion criteria:

- provide written consent
- scheduled for surgical resection of loco-regional disease
- prior positive choline C11 PET/CT imaging demonstrating loco-regional disease
- prior RP as primary therapy for prostate cancer

- “PSA relapse” documented by PSA “rising in three consecutive drawings or a PSA doubling time > 0.75 ng/mL yearly”
- negative conventional imaging (MRI, CT, bone scintigraphy)

Exclusion criteria:

- evidence of bone metastases

Choline C 11 dose:

- approximately 1,122 mBq

Evaluations:

- surgical resection of lymph nodes with histopathological examination of tissue; all performed by surgeons who had knowledge of imaging results

Image protocol:

- PET/CT done with an integrated scanner with imaging from pelvis to an unspecified upper area
- PET/CT images interpreted by two independent nuclear medicine physicians and two radiologists masked to clinical information

Objective:

- to compare choline C 11 images to histologic outcomes

Outcome assessments:

- Summary of findings

Results:

Conduct: The study was initiated in 2004 at the University of Ulm in Ulm, Germany.

Patient disposition: 15 patients enrolled and studied

Efficacy:

Since all patients had positive choline C 11 images at baseline, the results were notable for finding that 7/15 patients had no cancer detected in resected tissue (i.e., seven false positive scans); 8/15 had true positive scans.

The serum PSA median was 1.98 (range of 1.0 – 8.0 ng/mL). The authors report the best performance characteristics among the subset of patients with PSA levels > 2.0 ng/mL.

Safety: The report does not describe safety outcomes.

Reviewer’s comment: This report is especially notable for describing nearly half of the positive C 11 choline images as false positives. The authors speculate that this finding may have been due to failure to resect the “hot” tissue/nodes detected on the scans. The report does not describe the specific histopathology within the “false” nodes. The report

is also notable in the very brief comments about the follow-up of the patients; the authors summarize by noting that all patients had progressive disease after the lymphadenectomy and they speculate that lymphadenectomy may have very little (if any) role in controlling recurrent disease. The study is very small in sample size. Still, the results seem remarkable for the number of false positives (especially in comparison to prospective study number 1). The distribution of baseline PSA levels appeared relatively similar between studies 1 and 2; however, the dose of choline C 11 in study two was nearly twice that in study one and the extent to which this higher dose may have contributed to the higher false positive rate is unknown.

The True Negative and False Negative outcomes for PET/CT cannot be determined from this report since all patients had positive PET/CT results.

3. Detection of local, regional, and distant recurrence in patients with psa relapse after external-beam radiotherapy using (11)C-choline positron emission tomography. Breeuwsma AJ, Pruim J, van den Bergh AC, Leliveld AM, Nijman RJ, Dierckx RA, de Jong IJ. Int J Radiat Oncol Biol Phys. 2010 May 1;77(1):160-4. Epub 2009 Sep 23. PMID: 19783375

Design:

Single center study in which patients were to be prospectively enrolled if they had “biochemical recurrence as defined by the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus statement;” coincident with this enrollment at least 10 patients who did not have biochemical recurrence by the consensus statement were to be enrolled and were to serve as a control group. All patients had to have undergone initial external beam radiotherapy (EBRT). All patients were to undergo choline C 11 PET (not co-registered with CT) with a goal of determining “the accuracy of choline C 11 PET in detecting the site of recurrence...”

The ASTRO consensus statement (J Clin Oncol 1999; 17:1155-1163; based upon a 1997 “Consensus Panel”) defines “secure evidence of a PSA failure” as a level of 0.5 ng/mL. The publication notes that the study relied upon an updated statement as published in 2006 (Int J Radiat Oncol Biol Phys 2006; 65(4):965-74) which defined a “biochemical failure” as a PSA “rise by 2 ng/mL or more above the nadir PSA be considered the standard definition for biochemical failure after EBRT with or without HT.”

Eligibility:

Inclusion criteria:

- prior EBRT for prostate cancer
- biochemical recurrence as outlined above
- and 10 “control” patients without biochemical recurrence

Exclusion criteria:

- adjuvant hormonal therapy within past one year

Choline C 11 dose:

-approximately 400 mBq

Evaluations:

- choline C11 PET scans
- transrectal ultrasound with prostate biopsy as indicated
- bone scan if PSA exceeded 20 ng/mL or patient symptomatic
- CT or MR imaging if choline C11 scans were positive

Image protocol:

- PET scanning was performed without CT
- two “independent” PET readers who were blinded to clinical data
- readers used pre-specified criteria for definition of local recurrence

Objective:

The pre-specified objective was to: “determine the accuracy of choline C11 PET in detecting the site of recurrence in patients with BCR after EBRT...”

Outcome assessments:

“accuracy” measures based on comparison of choline C11 images to a truth standard of: biopsy, confirmation on additional imaging tests (CT, ultrasound, MR, bone scan) and follow up data showing a response to therapy.

Results:

Conduct: The study was conducted at the University of Groningen in Groningen, The Netherlands. The time period for conduct of the study was not stated.

Patient disposition: 70 patients enrolled as recurrence; 10 patients enrolled as a control, non-recurrence group. Histopathology and imaging populations summarized below.

Efficacy: The primary outcome measures of choline C11 “accuracy” were:

- sensitivity 81% (57/70)
- specificity 100% (10/10)
- PPV 100%
- NPV 44%
- accuracy 84%

In these performance estimates the presence of BCR was regarded as “truth.” Hence, the specificity estimate is derived only from the 10 “controls” who lacked BCR.

Overall, histopathology was obtained in 33 patients (30 histo positive/3 histo negative); alternative imaging showed positive cancer imaging in 12 patients (4 bone scans, 8 CT).

Overall 57 of the 70 recurrence patients had positive choline C11 scans; all choline C11 scans were negative in the 10 control patients.

Among the 57 patients with positive choline C11 scans, true positives were confirmed in 41 (72%) patients (by histopathology or alternate imaging tests). In addition to these more solid definitions of true positive, the authors reported that fifteen patients were regarded as true positive based upon clinical response to therapy. One patient was described as a “false positive” because the PET scan was positive in a loco-regional pattern but surgical lymphadenectomy revealed no metastatic disease. The authors specifically divide the 57 positive PET scans into:

- patients with local disease: n = 41 and of these: 26 had histo confirming cancer and 15 had a response to therapy

- patient with loco-regional disease: n = 16 and of these: 8 had positive conventional imaging (CT/MR); 1 was found to actually have no cancer at pelvic lymphadenectomy; 1 had histo positive and 6 had bone scans that were also positive in the areas where the PET indicated bone lesions.

Among the 13 patients with negative choline C11 scans, the authors regarded all 13 as false negatives, given that the patients had biochemical recurrence. However, they note that prostate biopsies were performed in five of the 13 patients, in three of the five, histology was positive.

The authors report, “The PSA doubling time, PSA velocity and disease-free interval were clearly correlated with the site of recurrence as identified by PET.” The authors do not describe the histopathology results in the false positive Choline C 11 situations.

The serum PSA median was 10.7 (range of 0.6 – 54.7 ng/mL). The authors report the highest sensitivity (87%) among a subset of patients with PSA levels > 10 ng/mL.

Safety: The report does not describe safety outcomes.

Reviewer’s comment: This study is notable in that it used a prospective design and enrolled only patients who had previously undergone EBRT (a group not commonly described in publications). Patients with prior EBRT are generally recognized as having higher post-treatment PSA values compared to patients who undergo prostatectomy. Hence, the potential for restaging errors is probably greater in this population than in the post-prostatectomy population. The study’s performance strength comes from the finding that:

- of 57 patients with positive PET scans, histology or alternative imaging tests were positive in 41 (72%) of the patients, 15 were positive based on follow-up response to local therapy and one was a false positive (no cancer found at pelvic lymphadenectomy)*

- of the 6 patients with PET scans positive for bone lesions, bone scans were also positive in these areas.*

-of the 13 patients with negative PET scans, 5 patients had biopsy and 3 were positive for cancer.

The study's main weakness is the lack of solid truth standard data (histology or alternative imaging) for 23 patients (15 who had positive PET scans and 8 with negative PET scans). The study provides much information but lacks sufficient detail to allow identification of patients with negative conventional imaging and a histopathology truth standard. The lack of safety data also is of note.

4. Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment. Richter JA, Rodríguez M, Rioja J, Peñuelas I, Martí-Climent J, Garrastachu P, Quincoes G, Zudaire J, García-Velloso MJ. Mol Imaging Biol. 2010 Apr; 12(2):210-7. Epub 2009 Jun 19. PMID: 19543774

Design:

Single center, single arm prospective study in which men with suspected prostate cancer recurrence (post either radiotherapy or prostatectomy) were to undergo Choline C11 and FDG PET scans; the study was to compare performance of the two imaging tests. The standard of truth was based upon histology and alternative imaging (when available) or the PSA response during follow-up.

The author's text does not explicitly state the study design was prospective but the description of the study provides detail that verifies the prospective nature. For example, the text specifically refers to eligibility criteria for enrollment and the text also describes the study's protocol. Hence, the study description verifies the prospective design.

Eligibility:

Inclusion criteria:

- prior radiotherapy or prostatectomy for prostate cancer
- biochemical recurrence defined as:
 - post prostatectomy: increase in PSA of > 0.2 ng/mL in two or more consecutive blood samples
 - post radiotherapy: three consecutive increases in PSA above the peak values

Exclusion criteria:

- patients with PSA > 20 ng/mL
- a prior imaging test that demonstrates relapse
- treatment initiated prior to PET scans

Choline C 11 dose:

- approximately 370 mBq

Evaluations:

- choline C11 PET scans followed by FDG scans (separated by at least 3 hours)
- bone scan if PSA > 10 ng/mL
- MR or CT to be performed after PET
- “clinical outcome” was to be determined after PET scans (histo, imaging, clinical PSA “response”)

Image protocol:

- PET scanning was to be performed without CT for the first 18 patients; then with CT for the remaining 55 patients
- two “independent” PET readers who were masked to clinical data
- readers used pre-specified criteria for definition of local recurrence

Objective:

To compare “the efficacy of FDG and choline C11 PET in the early phase of biochemical recurrence of prostate cancer after radical treatment.”

Outcome assessments:

A statistical analytical section of the report states that sensitivity, specificity, accuracy and positive/negative predictive values were to be calculated for each PET test.

Results:

Conduct: The study was conducted at the Universidad de Navarra in Pamplona, Spain. The time period for conduct of the study was not stated.

Patient disposition: 73 patients enrolled; all scanned. Histo and imaging populations summarized below; nearly half the patients lacked histo or follow-up imaging. Hence, the truth standard was heavily impacted by clinical follow-up assessments.

Efficacy: Overall, almost all patients had disease based upon clinical course and/or histo and/or imaging (71 of 73 had disease). Only two patients had no disease based upon the truth standard criteria.

Overall, 43 patients had positive choline C 11 scans and 30 had negative scans. With respect to FDG, 22 had positive scans and 51 had negative scans. The stated performance characteristics of the two scans were:

	Choline C11	FDG
Sensitivity	61% (43/71)	31% (22/71)
Specificity	100% (2/2)	100% (2/2)

The very low number of patients without disease may have contributed to the limited discussion of performance characteristics.

Histology confirmed cancer in 10 patients (all choline C 11 *or* FDG positive) and alternate imaging confirmed cancer in 13 additional patients (all choline C 11 positive); so a total of 23 patients with positive PET scans (23/43) had a truth standard for cancer confirmation defined in a relatively traditional manner of histology or conventional imaging. The authors do not describe the histopathology results in the false positive Choline C 11 situations.

The serum PSA median was not described for the aggregated population of 73 patients; instead, the PSA was described in categories where 45/73 patients had a PSA > 2 ng/mL. “A PSA value higher than 1.9 ng/mL determines a significant increase in the diagnostic yield.’

Safety: The report does not describe safety outcomes.

Reviewer’s comment: This study’s main strength is its prospective design and nominal comparison of FDG to Choline C11. The major report weakness is the paucity of detail about histological and conventional imaging outcomes. Some of these outcomes are described but they are provided in a manner that does not allow dissection of the FDG results from the choline C11 results. The study provides very little information other than the observation of nominally more positive lesions detected with Choline C11 than with FDG.

5. PET/CT with (11)C-choline and (18)F-FDG in patients with elevated PSA after radical treatment of a prostate cancer. García JR, Soler M, Blanch MA, Ramírez I, Riera E, Lozano P, Pérez X, Delgado E, Carrio I, Lomeña F. Rev Esp Med Nucl. 2009 May-Jun;28(3):95-100. PMID: 19558948

Design:

Single center, single arm prospective study in which men with suspected prostate cancer recurrence (post either radiotherapy or prostatectomy) were to undergo choline C11 PET/CT and FDG PET/CT scans; the study was to compare performance of the two imaging tests. The standard of truth was based upon histology and alternative imaging (when available) or the PSA response during follow-up.

The author’s text does not explicitly state the study design was prospective but the description of the study provides detail that verifies the prospective nature. For example, the text specifically refers to the study’s protocol.

Eligibility:

Inclusion criteria:

- prior radiotherapy or prostatectomy for prostate cancer
- biochemical recurrence defined as “increased PSA, between 0.8 – 9.5 ng/mL”

Exclusion criteria:

- not stated

Choline C 11 dose:

-approximately 656 mBq

Evaluations:

-choline C11 PET/CT scans followed by FDG PET/CT scans

Image protocol:

-two image readers who “jointly” interpreted images; were masked to clinical data

Objective:

To compare “the diagnostic accuracy of PET/CT with FDG and choline C 11...”

Outcome assessments:

Not elaborated upon beyond the description of the objective

Results:

Conduct: The study was conducted at the Esplungues de Llobregat in Barcelona, Spain. The time period for conduct of the study was not stated.

Patient disposition: 38 patients enrolled; all scanned.

Efficacy: The report does not describe the truth standard outcomes in a manner sufficient to account for the enrolled population of 38 subjects. The main description of outcomes reports that:

Choline C11 scans were positive in 26/38 (68%) of patients
FDG scans were positive in 13/38 (34%)

The report notes that recurrence was confirmed by biopsy in 10 patients (8 local recurrence, 2 mediastinal); Three patients had bone lesions positive (with both choline C11 and FDG) and bone scans were also positive in the three patients.

PSA data are not described in an aggregated manner although the report states, “Choline C 11 sensitivity was clearly related to PSA levels, was higher in patients with surgery and did not seem to be modified by hormonal therapy.” Furthermore, “¹¹C choline was able to detect 40% of recurrences in patients with PSA < 1 ng/mL, 50% of recurrences in patients with PSA 1 – 4 ng/mL and 87% of recurrences with PSA > 4 ng/mL.”

Safety: The report does not describe safety outcomes.

Reviewer’s comment: *This study’s main strength is its prospective design and nominal comparison of FDG to choline C11. The report contains a marked paucity of truth standard data and is nominally useful in suggesting that choline C11 likely detects more*

prostate cancer recurrence than FDG. The findings in this study are relatively similar to those in the prior study.

Overall, the four prospective studies described above are most notable for:

- summarizing the results from single centers
- finding point estimates of sensitivity/specificity that exceed 50%
- showing that Choline C 11 imaging appeared more useful than F18 FDG imaging, when these two modalities were compared in the same patient

Reports of Retrospective Clinical Studies

The reports of retrospectively summarized clinical data are confined to ten publications, as summarized in the following table and in the synopses:

Study	N	All PET/CT/Dose in MBq	Status	PSA	Imaging field
1	78	~ 370	Post-RP or RT	Average 21.0 Range 0.2 – 500.0	Whole body
2	210	~ 555	Post-RP or RT	Average 6 ± 20 (SD)	Pelvis to skull base
3	14	~ 690	Post-RP	Average 17 Range 0.3 – 170	Mid-thigh to skull base
4	37	~ 690	Post-RP	Median 9.8 Range 0.8 – 35.6	Mid-thigh to mid-thorax
5	190	~ 370 to 555	Post-RP	Median 2.1 Range 0.2 – 25.4	Mid-thigh to skull base
6	170	~ 1000	Post-RP	Median 1.2 Range 0.2 – 48.6	Pelvis to skull base
7	50	~ 1000	Post-RP or RT	Median 2.4 Range 0.4 – 13.1	Pelvis to undefined
8	10	~ 650 to 850	Post-RP or RT	Average 10.9 Range 0.7 – 24.8	Mid-thigh to skull base
9	63	~ 650	Post-RP or RT	Median 2.2 Range 0.2 – 39.0	Mid-thigh to skull base
10	49	~ 1000	Post-RP	BCR average 2.0 Range 0.3 – 12.1	Pelvis to undefined

1. Picchio, A, Spinapolice, E, Fallanca, F, Crivellaro, C, Giovacchini, G, Gianolli, Messa, C. ¹¹C Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. Eur J Nucl Med Mol Imaging 2012; 39:13-26.

In this single center experience (Milan, IT), 78 patients with elevated blood PSA levels had bone scans and also Choline C 11 PET/CT scans. The truth standard was histopathology, conventional imaging or clinical follow-up. The authors regard the most notable finding that the sensitivity for Choline C 11 (approximately 90%) appeared lower than that for bone scans (approximately 100%) but the specificity appeared similar or better for Choline C 11 (100% for Choline C11 versus 75% for bone scans). The Choline C 11 dose was approximately 370 MBq.

Reviewer's comment: Much data is provided but insufficient detail to identify those patients with negative conventional imaging and a histopathology truth standard.

2. Bertagna, F, Abuhilal, M, Bosio, G, Simeone, C, Rossini, C, et. al. Role of 11C-choline positron emission tomography/computed tomography in evaluating patients affected by prostate cancer with suspected relapse due to prostate-specific antigen elevation. Jpn J Radiol 2011; 29:394-404.

In this single center experience (Brescia, IT), the medical records were examined for 210 patients with suspected prostate cancer recurrence (based on PSA results) and Choline C 11 PET/CT images. The Choline C 11 dose was approximately 555 MBq. The truth standard is not described but appears to be based upon histopathology, conventional imaging or clinical follow-up. Choline C 11 PET/CT was positive in 116 patients and negative in 94 patients. Receiver operating characteristic (ROC) results suggested that the scan's "highest accuracy" occurred among the subset of patients with PSA levels greater than 1.26 ng/mL.

3. Fuccio, C, Schiavina, R, Castellucci, P, Rubello, D, et al. Androgen deprivation therapy influences the uptake of ¹¹C-choline in patients with recurrent prostate cancer: the preliminary results of a sequential PET/CT study. Eur J Nucl Med Mol Imaging 2011; 38:1985-1989.

In this single center experience (Bologna, IT), the medical records of 14 patients were reviewed to examine the Choline C 11 image results among patients who had radical prostatectomy followed by androgen deprivation therapy. The average serum PSA before androgen deprivation therapy was 17 ng/mL and was reduced by approximately 2.5 ng/mL after six months on the therapy. Before starting the therapy, Choline C 11 images had been positive in 13/14 patients; after six months of therapy, images were positive in 9/14 patients.

4. Souvatzoglou, M, Krause, B, Purschel, A, et al. Influence of (11)C-choline PET/CT on the treatment planning for salvage radiation therapy in patients with biochemical recurrence of prostate cancer. Radiother Oncol 2011; 99(2):193-200.

In this study from Munchen, Germany, the authors report the medical record review for 37 patients who were undergoing salvage radiotherapy and who also had Choline C11 scans. The authors specifically examined how the Choline C11 scans impacted the planning target value (PTV) for the radiotherapy. Among the 37 patients, 11 had positive

choline scans and 5 of these were in areas outside of the prostatic fossa (potentially increasing the size of the PTV). Patients with positive scans had higher blood PSA values than patients with negative scans.

5. Castellucci, P, Fuccio, C, Nanni, C, et al. Influence of trigger PSA and PSA kinetics on ¹¹C-choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. J Nucl Med 2009; 50: 1394-1400.

In this study from Bologna, Italy, the medical records were reviewed from 190 patients who had elevations of blood PSA levels after radical prostatectomy. The dose of Choline C 11 was 370 to 555 MBq. The authors summarized the occurrence of positive Choline C 11 PET/CT scans by blood PSA levels. Overall, 74 of 190 Patients (39%) had positive Choline C 11 scans. The occurrence of positivity was associated with the baseline PSA level. “Receiver operating characteristic analysis showed an optimal cutoff point for trigger PSA of 2.43 ng/mL (areas under the curve, 0.76).”

This publication is cited as potentially containing results from patients who were also described in the following publications from authors affiliated with this institution (Bologna, IT):

-Castellucci, P, Fuccio, C, Rubello, D, et al. Is there a role for ¹¹C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase < 1.5 ng/mL? Eur J Nucl Med Mol Imaging 2011; 38:55-63. A report of 102 patients.

-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. A report of 25 patients.

6. Giovacchini, G, Picchio, M, Scattoni, V, et al. PSA doubling time for prediction of ¹¹C-choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy.

In this study from Milan, Italy, the PSA doubling time (PSADT) was analyzed among 170 patients “with biochemical failure after radical prostatectomy” and who also had Choline C 11 PET/CT scans. The dose of Choline C 11 was approximately 438 MBq. Among the 170 patients, 75 had positive scans. Multivariate logistic regression showed that higher baseline PSA and short PSADT were significant predictors of positive scan results.

7. Rinnab, L, Mottaghy, F, Blumstein, N, et al. Evaluation of ¹¹C-choline positron-emission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer. BJU International 2007; 100: 786-793.

In this report from Leuven, Belgium, the authors summarized the Choline C11 PET/CT findings from 50 patients who had either radical prostatectomy (40), external beam radiotherapy (3) or brachytherapy (7) after suspected prostate cancer recurrence. The Choline C 11 dose was approximately 1056 MBq. Among the patients, 38 patients had positive scans. The authors found that the occurrence of positive scans appeared to increase with the level of PSA. The authors did not identify a PSA “trigger” or threshold but proposed that the scan could be useful in patients who had undergone radical prostatectomy with PSA levels < 2.5 ng/mL.

This publication is cited as potentially containing results from patients who were also described in the following publications from authors affiliated with this institution (Leuven, Belgium): Rinnab, L, Simon, J, Hautmann, R. ¹¹C Choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy. World J Urol 2009; 27: 619-625. A study of 41 patients.

8. Schilling, D, Schlemmer, H, Wagner, P, et al. Histological verification of 11C-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. BJU International 2008; 102:446-451.

In this report from Tübingen, Germany, medical records were reviewed from 10 patients who had laparoscopic resection of lymph nodes for suspected prostate cancer recurrence, based on Choline C 11 PET/CT results. Three of the patients had no cancer detected on histologic analyses of lymph nodes; instead inflammation was detected. The dose of Choline C 11 was 650 to 850 MBq.

Reviewer’s comment: This study report indicates that many patients also had positive CT localization of suspected prostate cancer recurrence sites in lymph nodes. Study details are insufficient to identify which patients had negative conventional imaging.

9. Krause, B, Souvatzoglou, M, Tunel, M, et al. The detection rate of 11Ccholine-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.

In this report from Munich, Germany, the medical records for 63 patients were reviewed if the patients had elevated PSA levels after primary prostate cancer therapy (surgery in 42 and radiotherapy/other in 21). Choline C 11 PET/CT had been performed in all the patients; the dose was approximately 650 MBq. Positive images were observed in 35 (56%) and the occurrence of positive images appeared more likely for patients with higher PSA levels. Truth standard data are not available.

10. Reske, S, Blumstein, N, Glatting, G. ¹¹C Choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. Eur J Nucl Med Mol Imaging 2008; 35:9-17.

In this report from Ulm, Germany, medical records were reviewed for 36 patients with PSA-based suspected recurrent prostate cancer; all 36 patients underwent biopsy of the prostate bed. The 36 patients all had negative conventional imaging for metastatic disease, including transrectal ultrasound; all underwent Choline C 11 PET/CT. This group was compared to 13 patients without suspected prostate recurrence (normal PSA) who also underwent Choline C 11 PET/CT imaging. Of the 36 patients with suspected recurrence, biopsy was positive for cancer in 33 patients and of these, the PET/CT was positive in 23 (70%); 10 patients were false negative by the PET/CT. Three patients (of the 36) were negative for cancer at biopsy and one of these patients had a positive PET/CT (one false positive). Within the control group of 13 patients, all PET/CT scans were negative except for one (a presumed false positive). The most remarkable finding from this study was that Choline C11 PET/CT failed to detect 10 of the 33 patients with localized cancer; most of these patients had a PSA level of < 2 ng/mL (8/10). However, the scans were positive in 23/33; no scans showed metastatic disease.

The study report provides considerable detail, especially for the 33 patients with histology confirmed recurrence (PSA values are provided for each patient along with PET/CT results for each patient). The data show that the median PSA was 2.6 ng/mL (range 0.6 – 12.1 ng/mL) among the 23 patients with true positive images; most patients with false negative or positive results (9/11) had PSA levels < 2 ng/mL.

Reviewer's comment: This study supplies sufficient detail to determine that 36 patients had negative conventional imaging and of these: 23 had true positive PET/CT scans, 1 had a false positive PET/CT scan; 2 patients had true negative PET/CT scans and 10 had false negative PET/CT scans. One patient in the control group (subjects with no recurrence suspected) had a positive PET/CT (presumed false positive in a patient with PSA level < 1 ng/mL).

Overall, the available data (my review findings plus the sponsor's submitted information) support the following excerpt from the proposed labeling. The footnote citations are present within the labeling and are not repeated here.

“A systematic review of published reports identified four studies that contained data sufficient to compare ¹¹C-choline PET imaging to histopathology (truth standard) among patients with suspected prostate cancer recurrence and non-informative conventional imaging (for most patients, CT or MRI). In general, the suspected recurrence criteria consisted of at least two sequential PSA levels of > 0.2 ng/mL for men who had undergone prostatectomy and PSA levels of ≥ 2 ng/mL above the post-therapy nadir for men who had undergone radiotherapy. The studies were predominantly single clinical site experiences and image acquisition generally surveyed radioactivity from the base of the pelvis to the base of the skull.

Prospective studies: Two studies examined the ability of ¹¹C-choline PET/CT to detect prostate cancer in pelvic and/or retroperitoneal lymph nodes among patients who had previously undergone radical prostatectomy. Both studies used a truth standard of lymph node histopathology. ¹¹C-choline images were interpreted by readers masked to clinical

information; surgical resection of lymph nodes was performed by surgeons aware of the ¹¹C-choline PET/CT results.

In Study One³, 25 patients who underwent ¹¹C-choline PET/CT and conventional imaging (CT or MRI) were scheduled to undergo pelvic or pelvic plus retroperitoneal lymphadenectomy following the imaging identification of suspected lymph node metastases. The median PSA was 2.0 ng/mL (range 0.2 to 23.1 ng/mL). The study excluded subjects with metastatic disease detected by bone scintigraphy or isolated prostatic fossa recurrence. Among the 25 patients, 21 had positive ¹¹C-choline PET/CT scans; histopathology verified cancer in 19 of these patients. Lymph node histopathology detected no cancer among the four patients who had surgery based only on positive conventional imaging; ¹¹C-choline PET/CT was negative in all four patients. The study report included information for patients who had non-informative conventional imaging (CT or MRI, bone scintigraphy and transrectal ultrasound), as shown in Table 1.

In Study Two⁴, 15 patients were scheduled to undergo pelvic or pelvis plus retroperitoneal lymphadenectomy solely based upon positive ¹¹C-choline PET/CT imaging in the setting of negative conventional imaging (ultrasound and/or CT and/or MRI and/or bone scintigraphy). The median PSA was 2.0 ng/mL (range 1.0 to 8.0 ng/mL); all patients had previously undergone radical prostatectomy. Eight of the 15 patients had cancer verified by lymph node histology; histology detected no cancer in seven patients.

Retrospective Studies: Two studies were retrospective reviews of patients who underwent ¹¹C-choline PET/CT and had histopathology obtained from biopsy of the prostatic fossa or other suspected recurrence sites.

In Study Three⁵, ¹¹C-choline PET/CT imaging was performed among 36 patients with suspected prostate cancer recurrence and 13 subjects without suspected recurrence (controls). Prostatic fossa biopsies were performed among the patients with suspected recurrence. All the patients and control subjects had previously undergone radical prostatectomy; patient with suspected recurrence had no evidence of cancer on conventional clinical evaluations, including trans-rectal ultrasound and bone scintigraphy. PET/CT scans were interpreted by readers masked to clinical information. Median PSA was 2.0 ng/mL (range 0.3 – 12.1 ng/mL) for patients with suspected recurrence and 0.1 ng/mL (range 0.0 – 0.2 ng/mL) in control subjects. Prostatic fossa biopsy showed cancer in 33 of the 36 patients with suspected recurrence. PET/CT scans were positive in 25 of the 36 patients; two patients had false positive scans (one scan in a control subject and one scan in a suspected recurrence subject who had no cancer detected on prostatic fossa biopsy). Among the 13 control subjects, 12 had negative PET/CT scans.

In Study Four⁶, 34 patients with negative conventional imaging underwent ¹¹C-choline PET/CT and subsequently had biopsies of suspected recurrence sites. The median PSA level of the 34 patients was 3.9 ng/mL (range 0.2 to 65.0 ng/mL); 22 of the patients had previously undergone radical prostatectomy and 12 had received other therapy (radiotherapy, anti-androgen therapy or cryotherapy). ¹¹C-choline PET/CT images were

positive in 30 patients and negative in four patients. Cancer was verified by histopathology in 29 patients; 25 had positive PET/CT images and 4 had negative PET/CT images. Five patients with positive PET/CT images did not have cancer confirmed with histopathology.

As shown in Table 1, within each study at least half the patients with non-informative conventional imaging had positive ¹¹C-choline PET/CT images and histologically verified recurrent prostate cancer.

Table 1 ¹¹C-Choline PET/CT Results among Patients with Non-informative Conventional Imaging and a Histopathology Truth Standard

Study	Patients, n				
	Total	True Positive	False Positive	True Negative	False Negative
One	13	11	2	ND*	ND*
Two	15	8	7	ND*	ND*
Three	36	23	1	2	10
Four	34	25	5	0	4

*ND = not determined

In Studies Three and Four, PSA levels were generally lower for patients with negative ¹¹C-choline PET/CT results than for patients with positive results. In Study Three, the median PSA was 2.6 ng/mL (range 0.6 – 12.1 ng/mL) among the 23 patients with true positive images; nine out of eleven patients with false negative or false positive images had PSA levels < 2 ng/mL. In Study Four, the median PSA was 4.2 ng/mL (range 0.2 – 65.0 ng/mL) among the 25 patients with true positive images; PSA levels < 2 ng/mL were observed in four of the nine patients with false negative or false positive images. These data, combined with other published reports, suggest that ¹¹C-choline PET imaging performance may be more reliable among patients with blood PSA levels > 2 ng/mL, compared to patients with lower levels.”

8. Safety:

The main safety findings relate to a single occurrence of an injection site reaction in the Mayo Clinic experience. No safety concerns were reported in published literature (exclusive of concern about misinterpretation of images, particularly the risk for false positive scan results that might erroneously prompt systemic therapy).

The radiation exposure from a choline C 11 PET/CT consists of the CT dose (estimated at approximately 0.8 rads (maximum) and the PET radiation (estimated at maximum of 0.03 rem/mCi) such that the typical PET/CT (no more than 20 mCi) would likely result in an radiation dose of approximately 0.6 mSv from the PET and approximately 8 mSv from the CT for a maximum total effective dose of 8.6 mSv.

Post-marketing Requirements (PMR):

None.

Post-marketing Commitments (PMC):

None.

9. Advisory Committee Meeting:

This application was not reviewed at an Advisory Committee because the review team regarded the supplied data as not raising unique questions that necessitated advice, particularly since the drug has been legally marketed for several years with no reports of important adverse reactions or notable efficacy concerns identified in published reports; the review precedent for this drug follows that established approximately 10 years ago for certain PET drugs in a similar regulatory situation (fludeoxyglucose F18, ammonia N 13).

10. Pediatrics:

The PREA committee agreed to grant a full waiver for PREA-related studies; the committee noted that the applicable disease/condition does not exist in children. The committee's concurrence was documented in an email correspondence from Courtney Suggs that reported the results of the April 4, 2012 committee meeting.

11. Other Relevant Regulatory Issues

FDA's inspection of the Mayo Clinic clinical report data tabulations disclosed no inconsistency between information at the clinical site and that submitted to the NDA. The Mayo clinical study was a retrospective review that was exempted from IRB review because of the patient anonymity associated with the process; hence, the FDA review did not verify consistency of data tabulations with patient medical records.

Appendix 1. Initial Publication Listings from May 8, 2012 PubMed Search

1. ¹¹C-Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. Picchio M, Spinapolice EG, Fallanca F, Crivellaro C, Giovacchini G, Gianolli L, Messa C. *Eur J Nucl Med Mol Imaging*. 2012 Jan;39(1):13-26. Epub 2011 Sep 20; PMID: 21932120 (included in review as retrospective study number 1).
2. The Role of C-Choline-PET/CT-Guided Secondary Lymphadenectomy in Patients with PSA Failure after Radical Prostatectomy: Lessons Learned from Eight Cases. Martini T, Mayr R, Trenti E, Palermo S, Comploj E, Pycha A, Zywicka M, Lodde M. *Adv Urol*. 2012;2012:601572. Epub 2011 Jul 31. PMID: 21822429 (not included in review due to sample size < 10).
3. Role of ¹¹C-choline positron emission tomography/computed tomography in evaluating patients affected by prostate cancer with suspected relapse due to prostate-specific antigen elevation. Bertagna F, Abuhilal M, Bosio G, Simeone C, Rossini P, Pizzocaro C, Orlando E, Finamanti M, Biasiotto G, Rodella C, Cosciani Cunico S, Giubbini R. *Jpn J Radiol*. 2011 Jul;29(6):394-404. Epub 2011 Jul 24. PMID: 21786095 (included in review as retrospective study number 2)
4. Androgen deprivation therapy influences the uptake of ¹¹C-choline in patients with recurrent prostate cancer: the preliminary results of a sequential PET/CT study. Fuccio C, Schiavina R, Castellucci P, Rubello D, Martorana G, Celli M, Malizia C, Profitos MB, Marzola MC, Pettinato V, Fanti S. *Eur J Nucl Med Mol Imaging*. 2011 Nov;38(11):1985-9. Epub 2011 Jul 6. PMID: 21732105 (included in review as retrospective study number 3).
5. Influence of (¹¹C)-choline PET/CT on the treatment planning for salvage radiation therapy in patients with biochemical recurrence of prostate cancer. Souvatzoglou M, Krause BJ, Pürschel A, Thamm R, Schuster T, Buck AK, Zimmermann F, Molls M, Schwaiger M, Geinitz H. *Radiother Oncol*. 2011 May;99(2):193-200. Epub 2011 May 26. PMID: 21620494 (included in review as retrospective study number 4).
6. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, Schmid HP, Van der Kwast T, Wiegel T, Zattoni F, Heidenreich A. *Eur Urol*. 2011 Apr;59(4):572-83. Epub 2011 Jan 25. PMID: 21315502 (not included in review because this is a review).
7. Is there a role for ¹¹C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/ml? Castellucci P, Fuccio C, Rubello D, Schiavina R, Santi I, Nanni C, Allegri V, Montini GC, Ambrosini V, Boschi S, Martorana G, Marzola MC, Fanti S. *Eur J Nucl Med Mol*

Imaging. 2011 Jan;38(1):55-63. Epub 2010 Sep 17 (*included in review as subset/suspected duplicate patient reporting under retrospective study number 5*).

8. Role of 11C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. Fuccio C, Castellucci P, Schiavina R, Santi I, Allegri V, Pettinato V, Boschi S, Martorana G, Al-Nahhas A, Rubello D, Fanti S. *Ann Nucl Med*. 2010 Jul;24(6):485-92. Epub 2010 Jun 11. PMID: 20544323 (*included in review as subset/suspected duplicate patient reporting under retrospective study number 5*).

9. PSA doubling time for prediction of [(11)C]choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy. Giovacchini G, Picchio M, Scattoni V, Garcia Parra R, Briganti A, Gianolli L, Montorsi F, Messa C. *Eur J Nucl Med Mol Imaging*. 2010 Jun;37(6):1106-16. Epub 2010 Mar 20. PMID: 20306038 (*included in review as retrospective study number 6*).

10. First results of [11C]choline PET/CT-guided secondary lymph node surgery in patients with PSA failure and single lymph node recurrence after radical retropubic prostatectomy. Winter A, Uphoff J, Henke RP, Wawroschek F. *Urol Int*. 2010;84(4):418-23. Epub 2010 Mar 17. PMID: 20299773 (*not included in review because report is published in German/English version not available*).

11. Influence of trigger PSA and PSA kinetics on (11)C-choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. Jadvar H. *J Nucl Med*. 2010 Mar;51(3):498-9; author reply 499-500. Epub 2010 Feb 11. No abstract available. PMID: 20150273 (a letter to editor) (*not included in review because this is a letter to the editor*).

12. Detection of local, regional, and distant recurrence in patients with psa relapse after external-beam radiotherapy using (11)C-choline positron emission tomography. Breeuwsma AJ, Pruijm J, van den Bergh AC, Leliveld AM, Nijman RJ, Dierckx RA, de Jong IJ. *Int J Radiat Oncol Biol Phys*. 2010 May 1;77(1):160-4. Epub 2009 Sep 23. PMID: 19783375 (*included in review as prospective study number 2*).

13. Influence of trigger PSA and PSA kinetics on 11C-Choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. Castellucci P, Fuccio C, Nanni C, Santi I, Rizzello A, Lodi F, Franceschelli A, Martorana G, Manfredi F, Fanti S. *J Nucl Med*. 2009 Sep;50(9):1394-400. Epub 2009 Aug 18. Erratum in: *J Nucl Med*. 2009 Oct;50(10):1578. PMID: 19690023 (*included in review as retrospective study number 5*).

14. [PET/CT with (11)C-choline and (18)F-FDG in patients with elevated PSA after radical treatment of a prostate cancer]. García JR, Soler M, Blanch MA, Ramírez I, Riera E, Lozano P, Pérez X, Delgado E, Carrio I, Lomeña F. *Rev Esp Med Nucl*. 2009 May-Jun;28(3):95-100. Spanish. PMID: 19558948 (*not included in review because the report is in Spanish; English version not available*).

15. Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment. Richter JA, Rodríguez M, Rioja J, Peñuelas I, Martí-Climent J, Garrastachu P, Quincoces G, Zudaire J, García-Velloso MJ. *Mol Imaging Biol.* 2010 Apr;12(2):210-7. Epub 2009 Jun 19. PMID: 19543774 (*included in review as prospective study number 3*).
16. [First results of PET / CT-guided secondary lymph node surgery on patients with a PSA relapse after radical prostatectomy]. Winter A, Uphoff J, Henke RP, Wawroschek F. *Aktuelle Urol.* 2009 Sep;40(5):294-9. Epub 2009 Jun 16. German. PMID: 19533582 (*not included in review because the report is in German; English version not available*).
17. [Which imaging methods should be used prior to salvage radiotherapy after prostatectomy for prostate cancer?]. Pasquier D, Hugentobler A, Masson P. *Cancer Radiother.* 2009 Jun;13(3):173-81. Epub 2009 May 2. Review. French. PMID: 19414277 (*not included in review because the report is in French; English version not available*).
18. ¹¹C choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy. Rinnab L, Simon J, Hautmann RE, Cronauer MV, Hohl K, Buck AK, Reske SN, Mottaghy FM. *World J Urol.* 2009 Oct;27(5):619-25. Epub 2009 Feb 21. PMID: 19234708 (*not included in review because it appears to be a subset/duplicate patient reporting to the retrospective study number 7*).
19. [¹¹C]Choline PET/CT for targeted salvage lymph node dissection in patients with biochemical recurrence after primary curative therapy for prostate cancer. Preliminary results of a prospective study. Rinnab L, Mottaghy FM, Simon J, Volkmer BG, de Petriconi R, Hautmann RE, Wittbrodt M, Egghart G, Moeller P, Blumstein N, Reske S, Kuefer R. *Urol Int.* 2008;81(2):191-7. Epub 2008 Aug 29. PMID: 18758218 (*included in review as prospective study number 5*)).
20. Histological verification of 11C-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. Schilling D, Schlemmer HP, Wagner PH, Böttcher P, Merseburger AS, Aschoff P, Bares R, Pfannenbergl C, Ganswindt U, Corvin S, Stenzl A. *BJU Int.* 2008 Aug;102(4):446-51. Epub 2008 Apr 11. PMID: 18410442 (*included in review as retrospective study number 8*).
21. The role of imaging in the detection of prostate cancer local recurrence after radiation therapy and surgery. Pucar D, Sella T, Schöder H. *Curr Opin Urol.* 2008 Jan;18(1):87-97. Review. PMID: 18090496 (*not included in this review because the report is a review article*).
22. The detection rate of [¹¹C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. Krause BJ, Souvatzoglou M, Tuncel M, Herrmann K, Buck AK, Praus C, Schuster T, Geinitz H, Treiber U, Schwaiger M. *Eur J Nucl Med Mol Imaging.* 2008 Jan;35(1):18-23. Epub 2007 Sep 22. PMID: 17891394 (*included in review as retrospective study number 9*).

23. [11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. Reske SN, Blumstein NM, Glatting G. Eur J Nucl Med Mol Imaging. 2008 Jan;35(1):9-17. Epub 2007 Sep 9. PMID: 17828534 (*included in review as retrospective study number 10*).
24. Evaluation of [11C]-choline positron-emission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer. Rinnab L, Mottaghy FM, Blumstein NM, Reske SN, Hautmann RE, Hohl K, Möller P, Wiegel T, Kuefer R, Gschwend JE. BJU Int. 2007 Oct;100(4):786-93. PMID: 17822459 (*included in review as retrospective study number 7*).
25. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy. Veas H, Buchegger F, Albrecht S, Khan H, Husarik D, Zaidi H, Soloviev D, Hany TF, Miralbell R. BJU Int. 2007 Jun;99(6):1415-20. Epub 2007 Apr 8. PMID: 17428249 (*not included in review because this is F18*).
26. Detection of lymph-node metastases with integrated [11C]choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. Scattoni V, Picchio M, Suardi N, Messa C, Freschi M, Roscigno M, Da Pozzo L, Bocciardi A, Rigatti P, Fazio F. Eur Urol. 2007 Aug;52(2):423-9. Epub 2007 Mar 20. PMID: 17397992 (*included in review as prospective study number 1*).
27. Distant metastasis of prostate cancer: early detection of recurrent tumor with dual-phase carbon-11 choline positron emission tomography/computed tomography in two cases. Maeda T, Tateishi U, Komiyama M, Fujimoto H, Watanabe S, Terauchi T, Moriyama N, Arai Y, Sugimura K, Kakizoe T. Jpn J Clin Oncol. 2006 Sep;36(9):598-601. Epub 2006 Jul 14. PMID: 16844733 (*not included in review because of small sample size; only two patients*).
28. Positron emission tomography/computed tomography with F-18-fluorocholine for restaging of prostate cancer patients: meaningful at PSA < 5 ng/ml? Heinisch M, Dirisamer A, Loidl W, Stoiber F, Gruy B, Haim S, Langsteger W. Mol Imaging Biol. 2006 Jan-Feb;8(1):43-8 (*not included in review because this is F18*).
29. PET in the management of urologic malignancies. Kumar R, Zhuang H, Alavi A. Radiol Clin North Am. 2004 Nov;42(6):1141-53, ix. Review. PMID: 15488563 (*not included in review because this publication is also a review*).

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RAFEL D RIEVES
08/31/2012