[^{11}C]Choline PET/CT Impacts Treatment Decision Making in Patients With Prostate Cancer Referred for Radiotherapy

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Introduction

Prostate cancer is one of the most common tumors in men and one of the main causes of cancer death. Prostate cancer management is based on the prostate-specific antigen (PSA) value, tumor features and stage, and patient characteristics.[1] Increase in PSA levels suggest the presence of disease, which is often difficult to localize.

Over the years, numerous imaging modalities have been investigated, aiming to improve diagnosis, staging, therapy, and follow-up

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of prostate cancer.[2-4] [^{11}C]choline–positron emission tomography/computed tomography (cho-PET/CT) is among these modalities, but its potential role in clinical practice is still under investigation. In regard to diagnosis and staging, cho-PET/CT should not be used routinely because there are insufficient published data. Conversely, cho-PET/CT has proved useful in detecting recurrences of prostate cancer in patients with biochemical relapse after various primary treatments.[5-8] Furthermore, several studies have reported an increase in the sensitivity of cho-PET/CT with increasing PSA values.[9-11]

Radiotherapy is one of the treatment options for prostate cancer. It can be performed with curative, postoperative, salvage, or palliative intent.[1] Radiotherapy is a form of local approach; therefore, the correct delineation of the volume to be targeted is of vital importance. In some clinical situations, radiotherapy is administered to the area of clinically evident disease (curative radiotherapy), whereas in others the choice is driven by the high probability of residual cancer after previous therapy (postoperative radiotherapy, salvage irradiation). Regardless of the specific situation, there is a general consensus that imaging modalities capable of detecting prostate cancer cells at anatomical sites that were considered negative on conventional imaging are extremely useful to enhance the therapeutic outcomes of the therapy.

The aim of the present retrospective study was to analyze the role of cho-PET/CT in the management of patients with prostate cancer referred for radiotherapy. In particular, the study focused on the impact of cho-PET/CT on the definition of the specific therapeutic approach.

Patients and Methods

Inclusion Criteria

The inclusion criteria for this retrospective study were (1) diagnosis of prostate cancer (at any disease stage), (2) referral for a first course of radiotherapy (for primary or recurrent tumor) between February 2007 and July 2010, and (3) performance of cho-PET/CT. All cho-PET/CT exams were performed at the Nuclear Medicine Department of the Humanitas Clinical and Research Institute in Milan, Italy, and all patients were treated with radiotherapy at the Radiotherapy Division of the European Institute of Oncology, Milan, Italy. According to the institutional rules, the European Institute of Oncology Ethical Committee has been informed about this retrospective study.

Patient Data

For each patient, we collected data regarding the diagnosis of prostate cancer (age, histologic type, initial PSA measurements, Gleason score, disease stage), information on the treatment performed before cho-PET/CT, before cho-PET/CT PSA measurement and androgen deprivation treatment, outcome of cho-PET/CT, and confirmation of the cho-PET/CT results.

Cho-PET/CT

Cho-PET/CT was requested by either the referring urologist or the radiation oncologist on the basis of the PSA value.

Carbon-11 was produced using a 18-MeV cyclotron (Cyclone 18/9 from IBA [IBA RadioPharma Solutions, Louvain-la-Neuve, Belgium]), and [^{11}C]choline was synthesized using a TrcerLab FX C Pro module (General Electric Healthcare, Waukesha, WI) in the radiopharmacy laboratory of the Nuclear Medicine Department of Humanitas. Quality control according to Italian legislation demonstrated a radiochemical purity of > 98%.

Patients fasted for 6 hours before the injection of 250 to 400 MBq of [^{11}C]choline. Total body images were acquired 10 minutes after the radiopharmaceutical injection using a Siemens Biograph 6 LSO PET/CT scanner (Siemens Medical Systems, Erlangen, Germany).

All cho-PET/CT studies were reviewed on a medical work station (Syngo Leonardo, Siemens Medical Systems) by 2 board-certified nuclear medicine physicians (AC, MR), and the outcome was classified as positive in the prostate/prostate bed (T), pelvic lymph nodes (N), and distant metastases (M) or as negative. The therapeutic strategy based on the cho-PET/CT evaluation was compared with the strategy that would have been proposed had cho-PET/CT imaging not been available. The generally approved national and international guidelines (Rete Oncologica Lombarda, European Association of Urology and National Comprehensive Cancer Network) were applied to define the therapeutic strategy based on the available clinical and imaging information (before and after cho-PET/CT).[12-15]

Results

Study Population

We analyzed data from 82 cho-PET/CT studies performed in 74 patients who were referred for the first course of radiotherapy between February 28, 2007 and July 26, 2010. Median age at the time of cho-PET/CT was 67.7 years (range, 50-83 years) (Table 1). The histologic type was prostate adenocarcinoma in all patients. Median initial PSA level and Gleason score were 11.5 ng/mL (range, 2.6-995 ng/mL) and 7 (range, 4-9), respectively. The initial treatment (before cho-PET/CT) included surgery, surgery followed by androgen deprivation, androgen deprivation, or no therapy in 26 (35%), 25 (34%), 14 (19%), and 9 patients (12%), respectively.

Median PSA level at the time of cho-PET/CT was 1.6 ng/mL (range, 0.1-150 mg/mL; mean, 10.7 ng/mL). In 23 patients (28%), cho-PET/CT was performed during androgen deprivation therapy.

Cho-PET/CT Findings and Change in Therapeutic Strategy

Cho-PET/CT was positive in 49 studies (60%), with the following classifications: T in 22 cases (27% of all studies and 45% of all positive studies); N in 4 cases (5% of all studies and 8% of all positive studies); T in combination with N in 3 cases (4% of all studies and 6% of all positive studies); M in combination with T or N, or both, in 16 cases (19% of all studies and 33% of all positive studies). Four cases could not be evaluated because of missing data at the time of the retrospective evaluation (5% of all studies and 8% of all positive studies). In 11 cho-PET/CT–positive evaluations (22% of all positive studies), the findings were confirmed by biopsy, contrast-enhanced CT, magnetic resonance imaging, and radiography in 7, 2, 1, and 1 case, respectively.

Thirty-three cho-PET/CT studies (40%) were judged negative. The median pre–cho-PET/CT PSA levels in T-positive and N/M-positive cases was 7.4 ng/mL (range, 2.7-150 ng/mL) and

Table 1 Patient Characteristics (N = 74 Patients per 82 Cho-PET/CT Examinations) and Treatment Strategy Data

Series Characteristics	All Patients N = 74 (%)	All Cho-PET/CT N = 82 (%)	Post-prostatectomy Patients* N = 51 (%)	All Cho-PET/CT in Post-prostatectomy Patients* N = 55 (%)
Age (years) at cho-PET/CT				
Mean ± standard deviation	–	68 ± 7		68 ± 6
Median (range)		67 (50-83)		67 (50-83)
Initial PSA level (ng/mL)				
Median (range)	11.5 (2.6-995)	–	10.1 (2.6-44.6)	–
Initial Gleason Score				
Median (range)	7 (4-9)	–	7 (4-9)	–
Initial TNM stage				
Localized T1-2 N0M0	11 (15)	–	7 (14)	–
Locally advanced T3-4 N0M0	19 (26)	–	16 (31)	–
Regional metastases any TN1M0	16 (22)	–	8 (16)	–
Metastases	2 (2)	–	0	–
AnyTNxM0	17 (23)	–	16 (31)	–
Unknown	9 (12)	–	4 (8)	–
Initial Treatment Before Referral for RT and Cho-PET/CT				
None (biopsy only)	9 (12)	–	–	–
Prostatectomy	10 (13)	–	10 (20)	–
Prostatectomy and lymph node dissection	16 (22)	–	16 (31)	–
Prostatectomy + ADT	11 (15)	–	11 (21)	–
Prostatectomy and lymph node dissection + ADT	12 (16)	–	12 (24)	–
Prostatectomy + ADT + CHT	1 (1)	–	1 (2)	–
Prostatectomy and lymph node dissection + ADT + CHT	1 (1)	–	1 (2)	–
ADT	13 (18)	–	–	–
ADT + CHT	1 (1)	–	–	–
Interval Between Diagnosis of Prostate Cancer and Cho-PET/CT				
Mean (range) in months	42 (0-166)	–	51 (2-166)	–
PSA (ng/mL) Before Cho-PET/CT				
Median (range)	–	1.6 (0.1-166)	–	1.1 (0.2-16.2)
Proposed Treatment Before Cho-PET/CT Findings				
Curative RT	–	6 (7)	–	1 (2)
Curative RT + ADT	–	10 (12)	–	2 (4)
ADT	–	11 (13)	–	9 (16)
Salvage RT	–	17 (21)	–	17 (31)
Salvage RT + ADT	–	15 (18)	–	15 (27)
Curative surgery ± RT ± ADT	–	7 (9)	–	0
None	–	12 (15)	–	7 (13)
Other	–	4 (5)	–	4 (7)
Cho-PET/CT Findings				
Positive	–	49 (60)	–	28 (51)
Negative	–	33 (40)	–	27 (49)
Proposed Treatment Based on Cho-PET/CT Findings				
Curative RT		5 (6)	–	1 (2)
Curative RT + ADT		9 (11)	–	2 (4)

Table 1 Continued

Series Characteristics	All Patients N = 74 (%)	All Cho-PET/CT N = 82 (%)	Post-prostatectomy Patients* N = 51 (%)	All Cho-PET/CT in Post-prostatectomy Patients* N = 55 (%)
Curative RT + ADT + RT for cho-PET/CT−positive lesions		2 (2)	–	0
ADT	–	7 (9)	–	5 (9)
Salvage RT	–	14 (17)	–	14 (25)
Salvage RT + ADT + RT for cho-PET/CT−positive lesions	–	8 (10)	–	8 (14)
Salvage RT + ADT	–	6 (7)	–	6 (11)
Salvage RT + RT for cho-PET/CT−positive lesions	–	2 (2)		2 (4)
Curative surgery ± adjuvant RT ± ADT	–	6 (7)	–	1 (2)
Curative surgery	–	2 (2)	–	5 (9)
ADT + RT for cho-PET/CT−positive lesions	–	5 (6)	–	0
None	–	12 (15)	–	7 (13)
Other	–	4 (5)	–	4 (7)

Abbreviations: ADT = androgen deprivation therapy; cho-PET/CT = [11C]choline positron−emission tomography/computed tomography; CHT = chemotherapy; PSA = prostate-specific antigen; RT = radiotherapy.
*Analysis limited to 51 patients who had undergone prostatectomy and underwent cho-PET/CT (55 cho-PET/CT examinations).

13.7 ng/mL (range, 3.2-139 ng/mL). In the negative cho-PET/CT studies, the median pre−cho-PET/CT PSA value was 0.51 ng/mL.

The retrospective analysis revealed that in 22 cases (27%), cho-PET/CT evaluation altered the treatment approach with respect to the treatment that would have been applied in the absence of the cho-PET/CT imaging dataset; in 58 studies (71%), the therapeutic approach remained unchanged; for 2 studies the outcome was unknown (2%). By restricting the analysis on the 49 positive cho-PET/CT studies, the cho-PET/CT evaluation changed the therapeutic approach in 22 cases (45%). In none of the 33 negative cho-PET/CT studies was the therapeutic approach altered.

Treatment indications after the cho-PET/CT evaluation in the 49 positive cases included radiotherapy with or without androgen deprivation (29 patients), surgery with or without radiotherapy (6 patients), androgen deprivation only (8 patients), and other treatment (6 patients). Treatment indications for the 33 patients with negative cho-PET/CT evaluations included radiotherapy with or without androgen deprivation (21 patients), surgery (1 patient), androgen deprivation only (4 patients), and other treatment (7 patients).

A similar change rate (31%) was observed when the analysis was restricted to only patients who had undergone prostatectomy (51 patients, 55 cho-PET/CT examinations). Twenty-eight cho-PET/CT examinations were positive (51%), and in 17 cases (61% of all cho-PET/CT−positive cases and 31% of all cases), therapeutic strategy was modified.

Discussion

This study shows that cho-PET/CT imaging supports the definition of the extent of prostate disease and provides valuable assistance in the selection of the best therapy option for patients with cancer. According to our findings, therapeutic indications were influenced by the cho-PET/CT assessment in about one third of the patients included in this retrospective study. In almost half of the 49 positive cho-PET/CT studies, a different therapeutic strategy was selected after cho-PET/CT evaluation. As a consequence, cho-PET/CT turned out to represent a specific steering factor in the therapeutic management of patients with cancer, contributing to the avoidance of unnecessary invasive treatments and orienting the therapeutic decision toward a localized high-precision radiation treatment targeted to the cho-PET/CT−positive lesion.

Currently, cho-PET/CT is a widely used and important imaging tool, and its usefulness in prostate cancer has previously been demonstrated in the literature.[5-7] In recent years, many studies have investigated the impact of this imaging modality on patient management.[9] Although cho-PET/CT should not be routinely used for initial diagnosis and staging, it is useful in detecting recurrence in patients with biochemical relapse. Indeed, our study confirms the increased probability of positive cho-PET/CT findings with increasing PSA values (median PSA values in negative, T-positive, and N/M-positive cho-PET/CT studies were 0.51, 7.4, and 13.7 ng/mL, respectively).

The majority of our patients were referred for salvage radiotherapy because of an increase in PSA levels after prostatectomy. Demonstration of recurrent disease in the prostate bed by cho-PET/CT confirms that prostate bed salvage radiotherapy is indicated and may be helpful in the dose escalation approach. When cho-PET/CT reveals the presence of the disease beyond the prostate bed, unnecessary irradiation to the prostate bed can be avoided and alternative therapeutic options can be explored. In the presence of oligometastatic disease, a local approach such as stereotactic body irradiation represents one of these options.[16-21] The technical development of imaging techniques combined with state-of-the-art high-precision radiotherapy machines has changed the prognosis of patients with cancer with limited metastatic disease. For example, in a phase II study from Belgium, stereotactic body irradiation to

a dose of 50 Gy in 10 fractions in patients with up to 3 synchronous metastases (bone or lymph nodes, or both) diagnosed on PET resulted in 2-year local control and clinical progression-free survival rates of 100% and 42%, respectively.[21] Importantly, the median androgen deprivation-free interval was 38 months. The increasing evidence on the role of limited and local treatment in oligometastatic prostate cancer may soon change the standard therapeutic approach in this patient population. Lifelong androgen deprivation remains routinely proposed at present, but it has high costs both for the patient (in terms of multiorgan toxicity and deterioration in quality of life) and for the healthcare system and society in general. Therefore, alternative approaches based on local treatments capable of combining improved disease control with higher quality of life standards for cancer patients deserve specific attention to define the most appropriate management of recurrent prostate cancer.

Conclusion

The impact of PET on disease management has been demonstrated in numerous malignancies, including lung, esophageal, and head and neck cancers.[22-24] PET imaging in prostate cancer has so far been limited to the evaluation of recurrent disease and, more recently, to radiotherapy planning.[25,26]

We are aware that our series has several limitations, including heterogeneity of the patient population, lack of routine confirmation of cho-PET/CT findings (by biopsy procedure or surgical data) and the low number of cases. Patients with different stages of prostate cancer who were treated with various modalities were analyzed, giving rise to some difficulties in the interpretation of results. Nevertheless, the reported outcomes are put forward to support the important role of cho-PET/CT as a steering factor in the therapeutic approach for the management of prostate cancer. A modification of the therapeutic indication in light of the cho-PET/CT assessment was found retrospectively in approximately 30% of the patients in our study. This result appears significant and worth further prospective investigations.

Clinical Practice Points

- Cho-PET/CT has proved useful in detecting recurrences of prostate cancer in patients with biochemical relapse after various primary treatments. Furthermore, several studies have reported an increase in the probability of positive cho-PET/CT findings with increasing PSA values.
- The aim of the present retrospective study was to analyze the role of cho-PET/CT in the management of patients with cancer referred for radiotherapy. In particular, the study focused on the impact of cho-PET/CT on the definition of the specific therapeutic approach.
- The reported outcomes are put forward here to support the important role of cho-PET/CT as a steering factor in the therapeutic approach for the management of prostate cancer. A modification of the therapeutic indication in light of the cho-PET/CT assessment was found retrospectively in approximately 30% of the patients in our study. This result appears significant and worth further prospective investigations on larger series of patients.

Disclosure

The authors have stated that they have no conflicts of interest.

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