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Review – Prostate Cancer

The Role of Choline Positron Emission Tomography/Computed Tomography in the Management of Patients with Prostate-Specific Antigen Progression After Radical Treatment of Prostate Cancer

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Abstract

Context: Choline positron emission tomography (PET)/computed tomography (CT) is a currently used diagnostic tool in restaging prostate cancer (PCa) patients with increasing prostate-specific antigen (PSA) after either radical prostatectomy (RP) or external-beam radiation therapy (EBRT). However, no final recommendations have been made on the use of this modality for patient management.

Objective: To critically analyse the current evidence for the use of choline PET/CT scanning in the management of patients with a progressive increase in PSA after radical treatment for PCa, evaluating its diagnostic accuracy in the detection of recurrences, the clinical predictors of positive PET/CT examinations, and the modalities' role as a guide for tailored therapeutic strategies.

Evidence acquisition: Data on recently published (2003–2010) original articles, review articles, and editorials concerning the role of choline PET/CT in this scenario were analysed.

Evidence synthesis: The diagnostic accuracy of choline PET in detecting sites of PCa relapse has been investigated by several authors, and the overall reported sensitivity ranges between 38% and 98%. It has been demonstrated that choline PET technology's positive detection rate improves with increasing PSA values. The routine use of choline PET/CT cannot be recommended for PSA values <1 ng/ml. However, in addition to PSA serum value, PSA doubling time (PSA DT), and other clinical and pathologic features—including locally advanced tumour (pT3b–T4) or lymph node involvement at initial staging—should be considered to refer patients to choline PET/CT study. Choline PET/CT may be also proposed as a image guide either for experimental surgical or radiation therapy treatments.

Conclusions: According to the current available data, choline PET/CT plays a role in the management of biochemical relapse. Its accuracy is correlated to PSA value, PSA DT, and other pathologic features. Choline PET/CT may be proposed as a guide for individualised treatment of recurrence.

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1. Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer among men and the second cause of cancer mortality after lung cancer. The lifetime risk of developing PCa in the United States and in Western Europe is 1 in 6, and the lifetime risk of death caused by metastatic PCa is 1 in 30 [1].

In patients with PCa, the recurrence after radical treatment is frequent, occurring—within 10 yr—in 20–50% of patients after radical prostatectomy (RP) [2,3] and in 30–40% of patients after external-beam radiation therapy (EBRT) [4,5]. Tumour recurrence is commonly assessed by a progressive increase of serum prostate-specific antigen (PSA) that typically precedes the clinically detectable recurrence. After RP, a serum PSA level >0.2 ng/ml, confirmed by two consecutive measures, can be associated with either residual or recurrent disease. Conversely, after radiation therapy (RT), a PSA value of 2 ng/ml above the nadir represents persistent/recurrent disease [6,7].

Patient management in case of recurrent PCa depends strongly on whether disease progression is confined to the prostatic fossa or distant spread has occurred [8]. Although the trend of PSA increase has been proposed as a predictive method for discriminating local from distant recurrence, only imaging procedures are capable of demonstrating the two scenarios [9]. Patients with only local failure following RP may be candidates for salvage RT, while in cases of metastatic involvement, local therapy is not recommended except for palliative reasons [7]. Several imaging methods, including computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy (BS), are currently being evaluated, but none of these modalities are as yet of proven, general clinical utility for selecting patients for salvage therapy with curative intent [7–13].

In particular, conventional MRI, although able to provide excellent anatomic detail and soft tissue contrast, is relatively insensitive for detecting pelvic lymph node metastases. Different imaging agents and acquisition techniques, such as the use of lymph node–targeted magnetic nanoparticles, could be helpful in improving its sensitivity [12,14–16].

Positron emission tomography (PET) and the integrated modality PET/CT, which combines the most advanced performance for both techniques, are emerging as primary tools in the restaging of oncologic patients [17,18]. In recent years, both the PET and the CT components of PET/CT technology—including computer hardware and integrated software—have been greatly improved [19]. In addition, it is now possible to perform a contrast-enhanced CT scan in conjunction with PET scanning in the same exam session.

In parallel to technological improvements, a significant development in PET radiopharmaceuticals has occurred. Several radiotracers able to visualise different tumour metabolisms are currently available, including fluorodeoxyglucose (18F-FDG) for glucose metabolism, carbon 11(11C)/fluorine 18 (18F)–labelled choline (choline) and 11C-acetate for lipid metabolism, 11C-methionine for amino acid metabolism, and deoxy-18F-fluorothymidine for imaging cell proliferation. In addition, PET tracers capable of imaging specific biologic aspects of cancer tissue are also accessible, including those for hormonal receptor status (eg, 18F-fluorodihydrotestosterone); for hypoxia (eg, 18F-labelled fluoroazomycin arabinoside) and 64Cu-diacetyl-bis [N4-methylthiosemicarbazone]); and for tumour angiogenesis (eg, 18F-arginine-glycine-aspartic acid peptide).

The leading PET tracer, 18F-FDG, which is widely used for a variety of neoplasms, presents limitations in imaging PCa. Although 18F-FDG may accumulate in aggressive and undifferentiated tumours, PCa often presents with poor avidity for 18F-FDG, probably because of the high incidence of well-differentiated tumours [9,11,20,21]. Furthermore, 18F-FDG is physiologically secreted into the urinary system, possibly interfering with pelvic pathologic findings.

Among the different PET tracers evaluated for PCa imaging, 11C/18F choline has been particularly investigated. The large amount of literature shows that choline PET/CT scanning may not be routinely recommended for detecting and staging primary PCa, mainly because its spatial resolution limits the evaluation of local extension of disease and the identification of small lymph nodal neoplastic deposits [22,23]. Conversely, it is widely used for restaging PCa patients [24]. Choline is an essential component of phospholipids of the cell membrane. Cell proliferation and upregulation of choline kinase are two mechanisms suggested for the increased uptake of this tracer in PCa [9]. The presence of choline transporters also seems to be involved in the process of its uptake in cancer cells [25].

Both 18F- and 11C-labelled choline have been proposed as PET tracers to study PCa patients, presenting similar results. However, some differences between the two analogues occur. 11C-labelled choline is characterised by a short half-life (20 min), which limits its use to centres with an onsite cyclotron. Conversely, the 18F-labeled analogue presents a longer half-life (110 min), allowing transportation to centres without cyclotron, but it is characterised by a higher urinary excretion compared to 11C-choline, which may alter imaging findings in the pelvis [9,10]. PET advantages and limitations for imaging recurrent PCa with 18F-FDG and choline PET tracers are summarised in Table 1. The superiority of choline PET in comparison with 18F-FDG has been largely demonstrated, namely, the two different PET modalities and the conventional imaging diagnostic tools commonly used for restaging PCa (transrectal ultrasound, CT, MRI, and BS) have been compared in a large group of 100 patients. Areas of abnormal focal increases were reported in 47% of patients on choline PET scans and in 27% on 18F-FDG PET scans [11].

The present review is aimed at critically analysing the current evidence for the use of 11C/18F choline PET/CT scanning in the management of patients with increasing PSA after radical treatment of PCa, evaluating its diagnostic accuracy in the detection of recurrences, the clinical predictors of positive PET/CT examinations, and its role as a guide to tailored treatment strategies.