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REVIEW ARTICLE

PET and PET/CT with radiolabeled choline in prostate cancer: a critical reappraisal of 20 years of clinical studies

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Abstract We here aim to provide a comprehensive and critical review of the literature concerning the clinical applications of positron emission tomography/computed tomography (PET/CT) with radiolabeled choline in patients with prostate cancer (PCa). We will initially briefly summarize the historical context that brought to the synthesis of [^{11}C]choline, which occurred exactly 20 years ago. We have arbitrarily grouped the clinical studies in three different periods, according to the year in which they were published and according to their relation with their applications in urology, radiotherapy and oncology. Studies at initial staging and, more extensively, studies in patients with biochemical failure, as well as factors predicting positive PET/CT will be reviewed. The capability of PET/CT with radiolabeled choline to provide prognostic information on PCa-specific survival will also be examined. The last sections will be devoted to the use of radiolabeled choline for monitoring the response to androgen deprivation therapy, radiotherapy, and chemotherapy. The accuracy and the limits of the technique will be discussed according to the information available from standard validation processes, including biopsy or histology. The clinical impact of the technique will be discussed on the basis of changes induced in the management of patients and in the evaluation of the response to therapy. Current indications to PET/CT, as officially endorsed by guidelines, or as routinely performed in the clinical practice will be illustrated. Emphasis will be made on methodological factors that might have influenced the results of the studies or their interpretation. Finally, we will briefly highlight the potential role of positron emission tomography/magnetic resonance and of new radiotracers for PCa imaging.

Keywords Prostate cancer · PET/CT · [^{11}C]choline · [^{18}F]fluorocholine · Biochemical recurrence

Introduction

Radiolabeled choline, either as [^{11}C]choline or as [^{18}F]fluoromethylcholine (less commonly [^{18}F]fluoethylcholine) has been extensively used in the last 20 years for imaging prostate cancer (PCa). In this review, we aim to summarize the key steps that brought to the success of this class of PET probes in the urological field. Even though prostate-specific membrane antigen (PSMA) tracers are slowly downsizing the importance of the clinical use of choline-based tracers, the literature available for [^{11}C]choline and [^{18}F]fluorocholine is much more abundant than for recent PSMA tracers, thus a few more comparative studies would be welcome before radiolabeled choline will be substituted in a routine way in every nuclear medicine center. According to this perspective and on the 20-year anniversary of the synthesis of [^{11}C]choline [1], we wish to recapitulate the contribution of choline-based tracers to clinical studies in PCa patients (Figs. 1, 2, and 3).

The birth of a new class of radiopharmaceuticals

One thing that has surprised many of us is that [^{11}C]choline was not first designed and synthesized for PCa evaluation, rather it was for studying brain tumors [1, 3]. These pioneering studies go back to 1997, exactly 20 years ago. At that time, amino acid imaging for brain tumors was still relatively limited and definitely affirmed only for [^{11}C]-methionine. For these reasons, it was felt that there was the need for the

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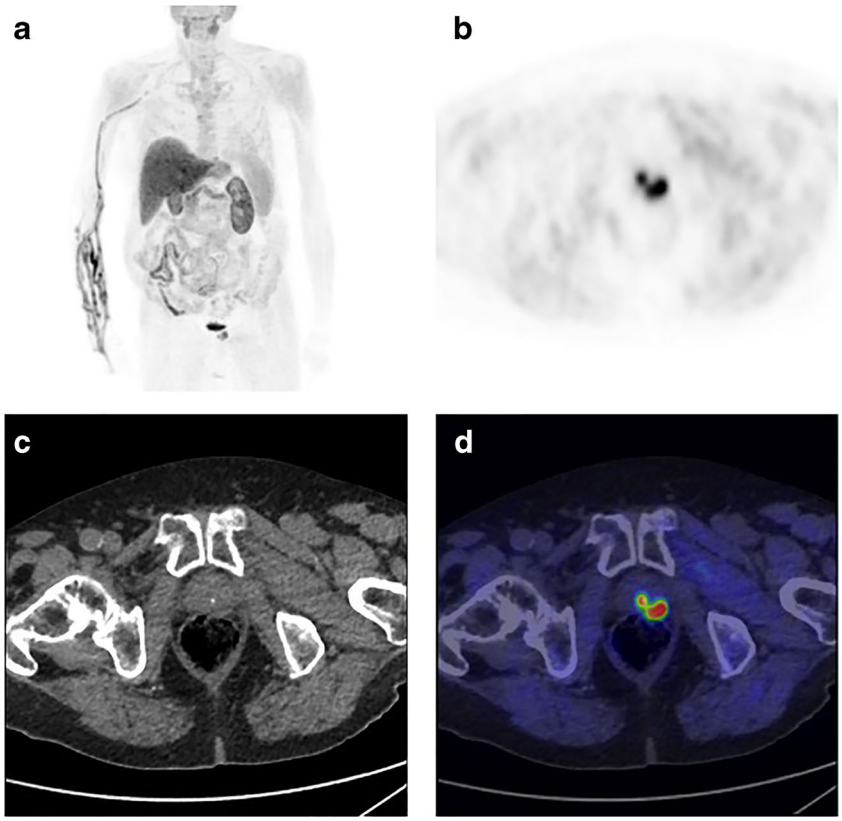

Fig. 1 Maximum intensity projection (MIP) (**a**), PET (**b**), CT (**c**), and fused PET/CT (**d**) axial images of an 81-year-old patient with biochemical recurrence (PSA 4.9 ng/mL) 4 years after RT for PCa (cT3; Gleason score 3 + 4; nadir PSA: 0.1 ng/mL). Images shows two areas of pathologically increased [^{18}F]FCH in the left prostate (SUVmax 14.2 and 9.0, respectively) consistent with local recurrence. Note the intensive flow of the tracer in the right forearm due to a physiological venous variant

discovery of alternative tracers. Research efforts had been directed to the development of low molecular weight chemical entities playing an active role in the biosynthesis of cell constituents, such as proteins, nucleid acids, and lipid derivatives. Monomeric building blocks, such as single natural or synthetic amino acids, nucleotides, and other ubiquitous metabolites, were selected as potential candidates for the design of new imaging probes. Choline, a small molecule involved in many cellular functions, was chosen for its altered homeostasis in different oncological diseases. The rationale behind the use of radiolabeled choline in brain tumors was the same as the one behind the application to PCa, i.e. increased proliferation of membrane lipids, especially of phospholipids, in highly replicating tumor cells. Studies indicated increased choline kinase activity and increased concentration of choline-derivate phospholipids in brain tumors [4–7] and in PCa [8–10].

Much of the work related to the synthesis and early applications of [^{11}C]choline is to be credited to a Japanese group, being Hara probably the most famous single author. Actually, in the Unites States, Friedland et al. had already synthesized radiolabeled choline in the radiochemical species of [^{14}C]choline [11]. However, according to Hara et al., radiochemical details had not been reported, and moreover [^{14}C]choline was not suited to studies in humans owing to the unfavorable emission properties [1]. The radiosynthesis of the positron emitter [^{11}C]choline, suitable for PET imaging, by Hara and his group [1] was, therefore, a milestone for the subsequent clinical applications of this class of tracers. They reported a convenient synthesis with radiochemical yield and purity easily adaptable to nuclear medicine centers supported by a cyclotron facility. The clearance of the tracer was very rapid and allowed early (5–20 min post-injection) imaging of brain tumors. In these patients PET with [^{11}C]choline produced clearly delineated positive images of the tumors with an optimal signal-to-noise ratio [1]. These promising results pointed out that imaging of abnormal choline metabolism could be used to detect a metabolic hallmark related to oncogenesis.

In the following years another major step was achieved at about the same time by the American group of DeGrado et al. [12] and the same group of Hara et al. [13], i.e. the two fluorinated choline analogues, [^{18}F]fluoromethylcholine ([^{18}F]FCH) and [^{18}F]fluoroethylecholine, were also synthesized, which allowed a widespread use of radiolabeled choline in centers devoid of cyclotron. The main advantage of fluorine-18 labeled choline derivatives is represented by the use of a radioisotope with longer half-life (109.7 min), which allows a widespread use of radiolabeled choline in centers devoid of cyclotron. In fact, while [^{11}C]choline has the advantage of being a natural compound, the short half-life of carbon-11 (20 min) mandates an on-site cyclotron.

Future studies did confirm that radioactive choline-based tracers can be used for imaging brain tumors and meningiomas [14–18]. Prospectively, neurooncological applications of radiolabeled choline became however limited, because amino

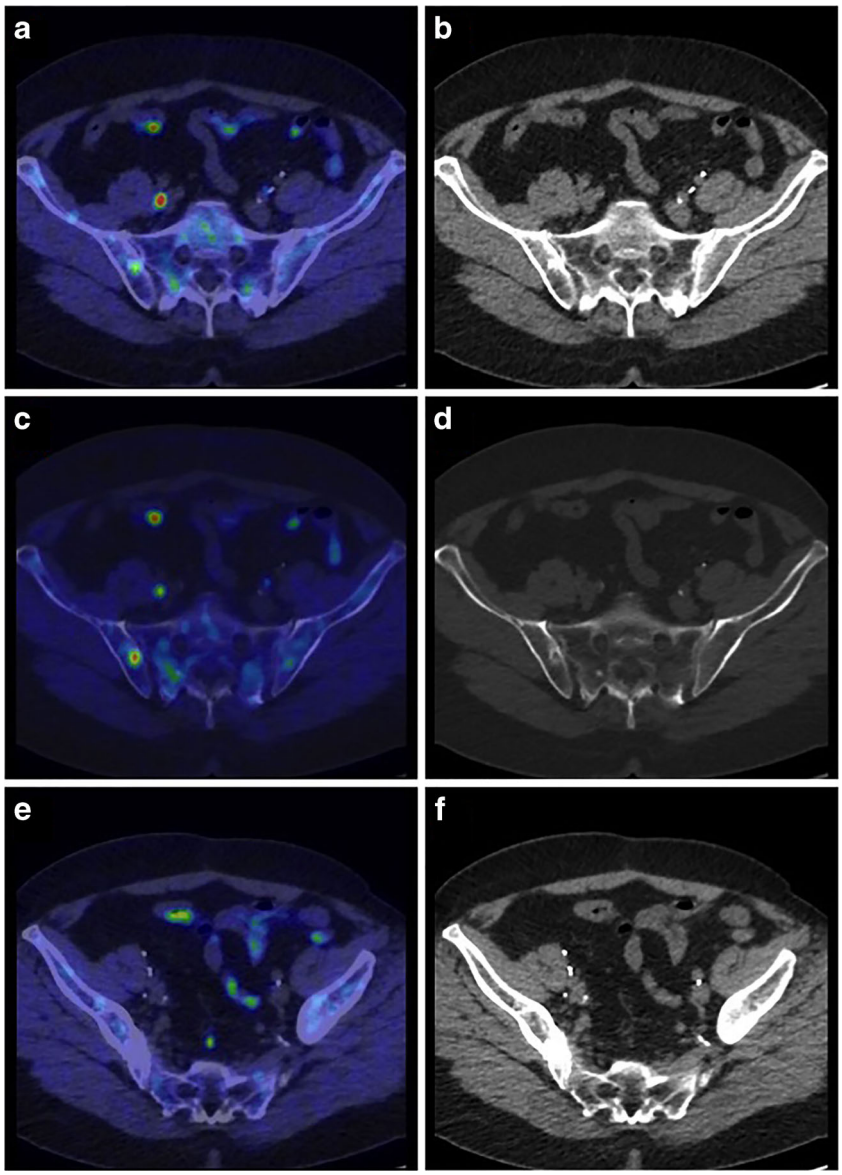

Fig. 2 Fused PET/CT (**a**, **e**), CT (**b**, **f**), fused PET/CT (bone window, **c**), CT (bone window, **d**) axial images of a 66-year-old patient with biochemical recurrence after radical prostatectomy (PSA 2.6 ng/mL) (pT4 pN1; Gleason score 3 + 4). The patient was under therapy with leuprorelin acetate. Images show focal pathologically increased [^{18}F]FCH uptake (SUVmax 12.8) suggesting lymph node disease in the right common iliac region; vascular and muscular structures hinder the clear identification of an eventual pathological lymph node. Focal increased [^{18}F]FCH uptake (SUVmax 8.3) is also found in a relatively small (10 × 17 mm) mainly lytic lesion with sclerotic border in the right iliac bone. Note that images **c**-**d** are one slice caudal to images **a**-**b** to allow better visualization of the bone lesion. Image **e** shows focal pathologically increased [^{18}F]FCH uptake (SUVmax 7.0) in a presacral lymph node that does not present typical CT-criteria of a pathological lymph node. After PET/CT bicalutamide was added. About 15 months later another PET/CT scan with [^{18}F]FCH showed significant reduction of [^{18}F]FCH uptake in all these areas

acid imaging and, to some lesser extent, other tracers such as [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) and 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT), prevailed. Therefore, for studying brain tumors, radiolabeled choline does not represent nowadays a first-line choice.

The first study with PET and [^{11}C]choline in PCa patients was carried out by Hara et al. and was published in 1998 [19]. The clinical and radiopharmaceutical settings for the application of radiolabeled choline to PCa were very different from those existing for brain tumors; this justifies the different success of the tracer in the two fields. While for studying brain tumors there was a mixture of consolidated and emerging tracers, imaging of PCa has always been disappointing.

Abdominal-pelvic CT with contrast media is sometimes used to detect pelvic or retroperitoneal pathological lymph nodes. However, this technique is gifted with only poor sensitivity for the staging of lymph node disease. This finding is related to the fact that lymph node metastases can be detected only in a minority of patients, especially at initial staging, and the size of the lymph node does not always correlate with the presence of metastasis; on the other side, reactive hyperplasia may induce false positives [20, 21].

Bone scintigraphy has a positive detection rate that is dependent on PSA levels, both at staging and at restaging. Initial studies showed that the probability of a positive scintigraphy increases considerably for PSA > 20 ng/mL [22, 23]. Referral only on the basis of PSA is, however, limited because Gleason score and PSA kinetics, either as PSA doubling time (PSADT) or PSA velocity (PSAV), influence the likelihood of a positive bone scan [24]. Bone scintigraphy has been blamed for decades owing to its poor specificity due to the moderate discriminative power between metastasis and degenerative bone disease. The poor specificity of bone scans can be increased nowadays by the use of hybrid single

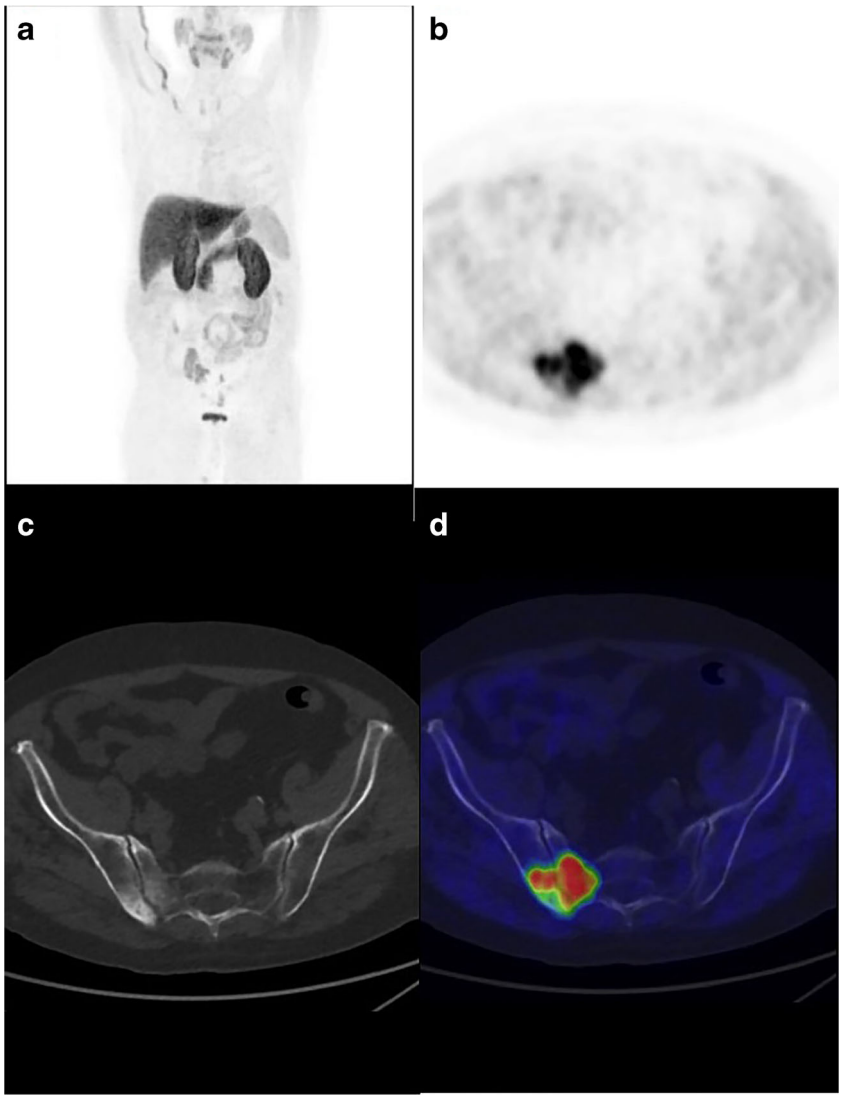

Fig. 3 MIP image (**a**), PET (**b**), CT (**c**), and fused PET/CT (**d**) axial images of a 77-year-old patient with biochemical recurrence (PSA 10.0 ng/mL) 11 years after radical prostatectomy for PCa (pT3b pN1; Gleason score 4 + 4). The patient had been subsequently treated with leuprorelin acetate and bicalutamide. Images show pathologically increased [^{18}F]FCH uptake in the right iliac bone and in the adjacent right sacral wing (SUVmax 13.9). Consistent with the results reported by Beheshti et al. in a large cohort [2], in this patient [^{18}F]FCH uptake is less pronounced in the portion of the bone that displays more sclerosis

photon emission tomography (SPECT)/CT tomographs, which are able to show bone degenerative changes at high spatial resolution with the CT component [25, 26]. Therefore, the specificity of bone scintigraphy in tomographic hybrid SPECT/CT devices has nowadays dramatically increased. Most importantly, this technique can only detect recurrence in a late phase of disease when, owing to bone metastases, a curative attempt is no longer feasible.

[^{18}F]FDG also did not provide for PCa the successful results that it had achieved for other tumors [27, 28]. The main problem is that most PCa phenotypes are slowly growing and feature low glucose consumption. This is because the majority of PCa tumors are well differentiated. As the tumor progresses and becomes resistant to antiandrogenic therapy or chemotherapy dedifferentiation, increased glucose metabolism and distant metastases become more frequent [29]. However, at this stage, skeletal metastases can be detected by bone scintigraphy in most cases and the use of a complex, expensive technique, such as PET/CT, gives little advantages, and it is difficult to justify from an economical point of view.

Keeping in mind this background it is easy to understand why the use of [^{11}C]choline was switched from brain tumors, for which several competitive radiopharmaceuticals were available, to PCa where identification of the best radiopharmaceutical represented the major scientific and clinical challenge.

Hints on physiology and physiopathology

Some considerations on the modality of intracellular accumulation of the tracer and on its physiological interpretation are worthwhile.

In PCa the cellular uptake of choline is regulated both by an active transporter-mediated and by a passive diffusion-like component [30]. In the cytoplasm, choline is phosphorylated to phosphocholine by the enzyme choline kinase, the first enzyme that is involved in the synthesis of phospholipids.

Synthesis of choline-derived membrane phospholipids, however, requires action of additional enzymes. Phosphocholine can also be obtained by lytic action of phospholipase D on membrane phosphatidylcholine [31]. The definite mechanism leading to the intracellular mapping of choline is yet unknown. Increased synthesis of membrane phosphocholine in tumor cells with high turnover was initially believed as the most important modality [19]. However, studies in breast cancer MCF7 cells that were incubated with [methyl-^{3}H]choline showed that the vast majority of radioactivity (about 95%) was found in the non-lipid fraction of the cell, suggesting that in this experimental setting only a small fraction of radiolabeled choline was transformed into phospholipids [31, 32]. Whether tracer uptake is related to cellular proliferation has also been investigated with inconclusive results. In various tumor cell lines, it was found a significant correlation between tracer uptake and cell proliferation, as expressed by the incorporation rate of [^{3}H]methyl-thymidine into DNA [33]. However, in humans, the extent of uptake of [^{11}C]choline in the prostate tumor in vivo does not correlate with the cell proliferation rate, as estimated by Ki67, in postoperative tissue specimens [34].

PET and PET/CT studies at initial staging

Initial staging of PCa patients with PET/CT is primarily aimed at defining the presence of distant metastases. The surgical gold standard is represented by the standard pelvic lymph node dissection, which consists of removal of obturator and external iliac lymph nodes. Some surgeons, in Europe more commonly than in USA, use an extended pelvic lymph node dissection, which implies the additional removal of internal and common iliac lymph nodes [35, 36]. Morbidity and complications of the standard pelvic lymph node dissection are about 5% and these values are much higher for the extended pelvic lymph node dissection. The added value of the extended pelvic lymph node dissection over the standard pelvic lymph node dissection has been subject of extensive discussions for many years [35, 36]. Proper staging is critical for defining the surgical strategy and for accurate risk stratification. Most of PCa patients at initial staging will not display bone metastases, so that the N staging ultimately represents the one associated with greatest prognostic value at this time.

Preoperative nomograms estimating the risk of lymph nodes disease are often used by some institutions and eventually lymph node dissection can be spared in low risk patients [37, 38]. In fact, CT and magnetic resonance (MR) have overall low accuracy at initial staging because lymph node metastases are in most cases in the form of micrometastases and, therefore, they are not always associated with a significant change in the morphology or in the size of lymph nodes [23, 39]. This background motivated the use of PET and, in recent years, of PET/CT with radiolabeled choline for detection of lymph node disease at initial staging. Thorough information on this theme can be found in the systematic review and meta-analysis performed by Evangelista et al. [40]. These authors collected 441 patients from ten studies performed between January 2000 and January 2012. The meta-analysis provided the following results: pooled sensitivity 49.2% (95% confidence interval, CI: 39.9%–58.4%) and pooled specificity 95.0% (95% CI: 92.0%–97.1%). For a detailed presentation of all results we refer to the original publication [40]. Here we would like to stress that the high heterogeneity of the results among the various centers could probably be explained by different inclusion criteria and therefore by differences in the incidence of the risk factors among the various studies. The authors concluded that PET and PET/CT with radioactive choline have low sensitivity for the detection of lymph node metastases prior to surgery in (unscreened) PCa patients. The most favorable characteristic of the technique is represented by the high specificity [40], even though this has to be balanced against the expensive price of negative PET/CT scans in patients that, if not previously selected for their risk, have low possibility of distant macroscopic disease.

Most studies that reported a useful application of PET/CT with radioactive choline at initial staging were carried out in patients at high or intermediate risk [41–50]. Generally, PET/CT was not considered useful in studies that did not select PCa patients on the basis of their risk [51], but occasionally also in studies including intermediate or high-risk patients [49, 50]. One feature that can make PET/CT useful in the preoperative assessment of lymph node disease is the capability of detecting metabolically active lymph nodes outside the field of a standard pelvic lymph node dissection, especially in presacral and common iliac lymph nodes [43, 45, 46]. Such findings imply, when not already planned, a switch from a standard to an extended lymphadenectomy [35]. Moreover, PET/CT is always performed with a whole body acquisition, while MR is confined in most cases to the pelvis and does not always cover retroperitoneal lymph nodes [49, 52].

Bone involvement at initial staging is generally rare, but it depends on several biochemical and pathological variables. Some nomograms are available to estimate bone involvement [53, 54], even though the use of nomograms in this context is much less frequent than for lymph node disease. Data from the previously cited studies confirm that the detection of bone metastases at initial staging is unusual [22, 23, 55]. Some reviews emphasize the relevant role of PET/CT with radioactive choline for detection of bone metastases [56]. While this is well proven in the restaging setting, as we will see in later sections, the same does not always hold at initial staging. Few studies mixed patients at initial staging and patients with biochemical failure [57, 58], possibly introducing some bias. In a study performed by Beheshti et al., which included exclusively patients at initial staging with either intermediate or high risk, bone metastases were

detected in 13/132 patients, corresponding to approximately 10% of the whole sample. In this population mean PSA was 27 ng/mL (range: 0.25–462 ng/mL) [59].

PET and PET/CT studies in patients with biochemical failure: the early years

Considering the high prevalence of PCa especially in the western society [60] and the potential clinical outcome related to the use of choline-based tracers, shortly after the synthesis of the new radiopharmaceuticals numerous preliminary studies were carried out to assess their potentiality.

We have arbitrarily divided the clinical studies into three time intervals: 1) the early studies (approximately between 1998 and 2003); 2) the studies that witnessed the boom of the clinical applications of PET and PET/CT with radiolabeled choline (approximately between 2003 and 2012); 3) the studies that proved the feasibility to use PET/CT with radiolabeled choline for new applications, mainly in radiotherapy (RT) and in monitoring the response in the oncological setting (approximately from 2012 until now).

Clinical studies of the "early years" can be classified as of two different types: 1) proof-of-concept studies; 2) comparative studies.

In proof-of-concept studies bone scintigraphy or CT served as gold standard and the capability of PET with radiolabeled choline to detect distant disease, most frequently bone metastases, was evaluated. We should not forget that by those years most nuclear medicine facilities were equipped with stand-alone PET devices, as the systematic diffusion of hybrid PET/CT devices came only some years later. Because of the study design, many patients had high PSA levels and diffuse metastatic involvement so that the capability to detect early recurrence of disease could not be ascertained [61–65]. Studies often included both patients at initial staging and patients with biochemical failure; in the latter case, patients with different primary and salvage treatments were often mixed. Other authors used an opposite design to support the accuracy of [^{11}C]choline PET, i.e. they recruited PCa patients with no evidence of biochemical failure and compared the positive detection rate in this group to the one obtained in PCa patients with biochemical failure; as expected, higher positive detection rate was found in the latter group. For example, de Jong et al., reported that all PCa patients without biochemical failure had negative PET scan; on the contrary, 55% of PCa patients with biochemical failure had a positive [^{11}C]choline PET [64]. Few years beyond our arbitrary interval, Reske et al. reported that in patients with biochemical failure after radical prostatectomy [^{11}C]choline PET/CT was true positive in 70% of PCa patients and true negative in 92% of controls [66].

All the above cited studies were conducted using [^{11}C]choline and in Europe underlying the extreme importance of the development of a competing radiopharmacy for research. Because of the heterogeneity of the sample population recruited by different authors, the positive detection rate ranged substantially between 30 and 80% of patients [61, 62, 64, 67]. [^{11}C]choline PET/CT was shown to detect all or most metastases that were known from bone scintigraphy or CT scans and often to provide additional information in a sizeable number of patients [61, 65]. In general, all authors agreed that [^{11}C]choline PET was a promising new tool for staging and restaging PCa, having the ability to detect in a single examination local recurrence, lymph node and bone metastases and demonstrating high signal-to-noise ratio. It was also speculated that [^{11}C]choline PET/CT could have prognostic value and influence the therapeutic management of PCa patients [61], a hypothesis that indeed was formally confirmed some years later [68–73].

Comparative studies were done vs. [^{18}F]FDG, which was considered the gold standard tracer for oncology. The group of Price et al. performed an important head-to-head comparison between [^{18}F]FCH and [^{18}F]FDG in human patients as well as in cultured PCa cells [74]. In vitro studies showed greater [^{18}F]FCH than [^{18}F]FDG uptake in androgen independent and in androgen dependent PCa cells. PET studies were also carried out, but in a very limited (n = 8), mixed group of patients at restaging and initial staging. Results indicated that [^{18}F]FCH was more accurate than [^{18}F]FDG for detection of local tumor and of distant metastases. The results of this preliminary study appeared very promising; at the same time, because of the small sample size, further confirmation was advocated [74]. One year later, Picchio et al. compared [^{11}C]choline and [^{18}F]FDG in 100 patients that had experienced biochemical failure after radical prostatectomy [67]. The positive detection rate of [^{11}C]choline PET was 47%, while [^{18}F]FDG PET was positive only in 27% of cases. The additional number of anatomical sites with pathological [^{11}C]choline uptake was detected in all major sites of tumor recurrence, i.e. in the skeleton, in pelvic and retroperitoneal lymph nodes and in the post-surgical prostate bed. Moreover, across lesions the mean maximum standardized uptake value (SUVmax) for [^{11}C]choline was higher than for [^{18}F]FDG. The study unequivocally showed the superiority of [^{11}C]choline vs. [^{18}F]FDG for restaging PCa and these results [67] severely limited the further use of [^{18}F]FDG from clinical imaging of PCa [75], especially from the context of initial staging and early restaging.

The boom of the clinical studies

In the decade between approximately 2003 and 2012 there was a boom in the clinical studies performed in PCa patients with radiolabeled choline. Most frequent studies were performed in patients with biochemical failure occurring after radical prostatectomy or, less frequently, after radiotherapy; other studies were performed in patients at initial staging.

Many studies were performed using [^{18}F]FCH and most studies were performed using PET/CT. Finally, during this period the first studies were also published addressing the role of PET with radiolabeled choline to guide radiotherapy or to monitor chemotherapy. However, since most of these studies have been published in very recent years, we will illustrate them in the next section.

Studies in patients with biochemical failure

The definition of biochemical failure differs according to the primary treatment. In patients treated with radical prostatectomy, PSA levels greater than 0.2 ng/mL and rising on at least two consecutive measurements performed 3 months apart, are taken to signify biochemical failure [76]. In patients treated with RT, with or without adjuvant androgen deprivation therapy (ADT), a PSA value 2 ng/mL higher than the lowest (nadir) post-therapeutic PSA value represents biochemical failure [77].

After the feasibility studies of the early period, subsequent studies were performed with multiple aims, including: 1) relating the positive detection rate of PET and PET/CT with radiolabeled choline to the known risk factors of PCa; 2) addressing the issue of early diagnosis of recurrence; 3) assessing the role of antiandrogenic drugs on the uptake of radiolabeled choline; 4) assessing independent validation of the PET/CT findings; 5) assessing whether PET/CT with radiolabeled choline can be used to change the clinical management of the patient; 6) investigating the optimum PET/CT protocol.

Correlation with risk factors

PSA levels Correlation with PSA levels has been, as expected, the most frequently targeted question addressed in these years. There is nowadays consensus that the positive detection rate is somehow linearly related to PSA levels. The reason we intentionally used the word "somehow" is that linearity is not exactly respected for two reasons: 1) saturation occurs and for PSA higher than about 10 ng/mL a plateau best describes the relationship between the two variables; 2) other factors (see later) significantly affects the positive detection rate of the technique and therefore the relationship between PSA and the positive detection rate is also affected by the inclusion criteria, i.e. by other characteristics of the sample. Having outlined these general premises, we will only illustrate in detail few studies and refer the reader to further recent reviews [78–81].

The first study with a reasonably large sample size ($n = 63$) was performed by Krause et al. in 2008 [82]. At that time, centers performing PET/CT with radiolabeled choline were somehow limited, PET/CT with radiolabeled choline still had limited acceptance and obtaining large sample sizes was much more difficult than nowadays. The group of Munich reported positive detection rates of: 36% for PSA <1 ng/mL, 43% for PSA between 1 and 2 ng/mL, 62% for PSA between 2 and 3 ng/mL, and 73% for PSA ≥3 ng/mL [82].

Some years later Giovacchini et al. published a study with a larger sample size ($n = 356$) [83]. They reported an overall detection rate of [^{11}C]choline PET/CT of 45% [83]. PSA was the single, most powerful predictor of positive PET/CT, a finding that confirmed the results obtained by Krause et al. [82] and that has been consistently reproduced over time [67, 82–90]. Overall, positive detection rates lower than 30% were reported either in samples recruited according to particularly restrictive inclusion criteria, for example, absence of disease on conventional imaging [85] or with low PSA for early detection of tumor recurrence [91, 92] and, therefore, that differed from most studies that included consecutive patients without a priori selection.

From a statistical point of view, the relationship between PSA and PET/CT positive detection rate has been shown either by plotting percent values as a function of PSA intervals or by assessing the predictive power in univariate or in multivariate analysis. The latter approach, even if statistically more complex, has the advantage of providing a formal comparison of the predictive power of PSA over the remaining risk factors. However, review of numerous articles regarding this issue shows how, independently of the methodology used, some sort of significant relation between PET/CT positive detection rate and PSA value was always detected [79]. This does not apply to other risk factors, being some risk factors not significant in this or that study depending on the characteristics of the sample and on the methodology used. In the cited study by Giovacchini et al. a progressive increase in the positive detection rate of [^{11}C]choline PET/CT was observed for increasing PSA values. The positive detection rate was as low as 7% for PSA between 0.2 and 0.4 ng/mL and increased up to 80% for PSA between 3 and 5 ng/mL. The detection rate reached a plateau for higher PSA values (84% for PSA > 10 ng/mL) suggesting that 85–90% might represent the upper edge of the detection rate of the technique [83]. In the interval between 1 and 2 ng/mL, which is the interval for which the European Association of Urology endorses the use of PET/CT with radiolabeled choline [93], the positive detection rate was 45.9%. In the receiver operating characteristic (ROC) curves 1.37 ng/mL represented the best PSA value to distinguish patients with positive [^{11}C]choline PET/CT from patients with negative [^{11}C]choline PET/CT; as expected, this value was similar to the median PSA (1.34 ng/mL) [83].

Graziani et al. very recently published a [^{11}C]choline PET/CT study in PCa patients with biochemical failure with the largest sample size [94]. Even though they combined patients treated with radical prostatectomy and patients treated with primary external beam radiotherapy, their sample size ($n = 4426$) surpasses by far the sample size of any other study performed so far and will probably remain for a significant time the reference article when calculating [^{11}C]choline PET/

CT positive detection rate in a unscreened, mixed PCa population. Another very important merit of this study lies in the fact that the authors performed additional analyses in the previously cited interval of interest between 1 and 2 ng/mL. They found with ROC analysis an optimal cut-off of PSA equal to 1.16 ng/mL. Oligometastatic disease (one to three lesions) was found in 22.7% of patients with PSA < 1.16 ng/mL and in 37% of patients with PSA > 1.16 ng/mL. In the whole interval 1–2 ng/mL oligometastic disease was found in 19.2% of patients [94]. The only potential limit that might be attributed to this study is that the authors did not perform a separate analysis for the two groups of patients treated with different types of therapy. Since definition of PSA failure is different for the two groups and a therapy effect cannot be excluded, some bias might have occurred. The difference in the cut-off derived from the ROC analysis between the study of Giovacchini et al. [83] and of Graziani et al. [94] (1.37 ng/mL vs. 1.16 ng/mL, respectively) corresponds to about 15%, which is not unexpected given the potential bias introduced by the summation of 2 ng/mL to the nadir in the definition of failure for patients treated with radiotherapy. On the contrary, the positive detection rates of PET/CT (45.9% and 44.7%, respectively) agree possibly beyond any optimism und further stresses the need of studies with large sample sizes to obtain stable, reproducible results.

PSA kinetics Other factors may predict a positive [^{11}C]choline PET/CT scan, including measurements of PSA kinetics, expressed as either PSADT or PSAV, advanced pathological stage, Gleason score, older age, and previous biochemical failure (i.e., development of biochemical after salvage radiotherapy) [83, 87, 95, 96].

For an appropriate treatment of PCa patients with biochemical failure is critical to distinguish whether only local recurrence occurred or whether distant disease is present. Patients with local recurrence or, in some cases, with oligometastatic lymph node are preferentially treated with salvage radiotherapy; if only lymph node disease can be detected macroscopically, salvage lymphadenectomy is offered by some surgeons [97, 98]. On the contrary, if disease is generalized ADT or chemotherapy represent the preferred choices [98]. PSA kinetics, primarily PSADT and PSAV, may predict the site of recurrence: long PSADT and low PSAV are usually associated with local recurrence, while short PSADT or high PSAV are usually associated with distant disease [24, 99]. However, this association cannot be always demonstrated in the single patient.

Castellucci et al. first demonstrated that PSA kinetics predicts [^{11}C]choline PET/CT findings [96]. In their study, 190 patients with median PSA of 2.1 ng/mL were enrolled. [^{11}C]choline PET/CT was positive in about 39% of patients and the positive detection rate increased for increasingly higher PSA values. In this study, however, PSADT and PSAV were available only in 56% of patients, which implies that the final multivariate analysis was performed with slightly more than a half of the initial sample. PSAV was higher, while PSADT was shorter in patients with positive PET/CT in comparison to patients with negative PET/CT. At multivariate analysis PSA and PSAV were found to be independent predictive factors for positive PET/CT, while PSADT was significant only in the subgroup of patients with PSA lower than 2 ng/mL. However, by comparing *P* values, it was evident that PSA was still the factor with strongest statistical power. It was concluded that indices of PSA kinetics could be used by clinicians to select patients at higher risk and to reduce the number of false negative scans [96].

In the following years, the predictive role of PSA kinetics has been confirmed by many studies [87, 90, 95, 100–103]. Giovacchini et al. performed a similar study in 170 patients; PSADT and PSAV were available for all patients [95]. Possibly owing to the larger number of patients with available information on PSA kinetics, the statistical power of PSADT was very similar to that of PSA also at the multivariate analysis. Another difference in respect to the study of Castellucci et al. [96] was that in the mentioned study PSADT was used as categorical variable (using as cutoffs 3 and 6 months) rather as continuous variable, a procedure that also might have affected the results. Additionally, a region-based analysis was performed. Results showed that the percentage of patients that displayed pathological [^{11}C]choline uptake in the skeleton significantly increased from 3% for PSADT >6 months to 52% for PSADT <3 months. Conversely, patients that displayed pathological [^{11}C]choline uptake in the prostatectomy bed were 0% for PSADT <3 months and 17% for PSADT >6 months. Using the results of the multivariate analysis, nomograms were developed to predict the probability of a positive [^{11}C]choline PET/CT in PCa patients [95]. As previously said, many other studies assessing the relationship between PSA kinetics and radiolabeled choline PET/CT were performed [87, 90, 100–103]. The main merit of these studies was to confirm in independent samples the results previously obtained. Attempts were made to find, using ROC analysis, PSADT or PSAV values to best differentiate patients with positive and patients with negative PET/CT [90, 101]. While ROC analysis is an established procedure, it is noteworthy to remind that results are influenced by the characteristics of the sample and therefore generalizations of results obtained in single studies should be taken cautiously. In a study that included 41 patients with mean PSA of 4.1 ng/mL, Schillaci et al. concluded that [^{18}F]FCH PET/CT was recommended in patients with PSA >2 ng/mL, PSADT ≤6 months and PSAV >2 ng/mL/year [101]. Graute reported an optimal PSA cut-off of 1.74 ng/mL and an optimal PSAV cut-off of 1.27 ng/mL/year [90].

Pathological stage We now address the role of the TNM system, which plays a critical role in virtually all tumors and

it was expected to have some relevance also in the prediction of PET/CT with radioactive choline in PCa patients. The San Raffaele Milan group [83] and the S. Orsola Bologna group [91] addressed this issue at about the same time in two studies that presented only minor differences. Giovacchini et al. distinguished four groups focused on T and N staging, namely pT2 pN0, pT3a pN0, pT3b pN0, and pT4 pN0 (combined together), any T pN1. This classification was based on the wish to distinguish patients with extracapsular extension from those that also displayed macroscopic seminal vesicles invasion, and patients with and without lymph node metastases, distinctions that were expected to have some prognostic relevance. Results showed a significant difference vs. the baseline reference category virtually for every group (a statistical trend was found for pT3a pN0) [83]. In the study by Castellucci et al. pT and pN were entered as two independent variables. Regarding the pT variable, pT2 patients were contrasted to pT3 and pT4 patients (joined together to increase the statistical power). Results for pT stage were not significant. On the contrary, the pN analysis (positive vs. negative) provided highly significant results [91]. The negative findings in the pT analysis could have the following explanation: the greater pN effect, which is not controlled for in the pT analysis, might have counterbalanced and masked the pT effect (i.e., patients might have had, for example, low pT, but positive lymph nodes and the opposite). The difference in the statistical power between the two studies (n = 356 vs. n = 102) might represent an alternative or concurrent cause.

Gleason score With surprise in many studies the Gleason score did not significantly predict PET/CT. In the cited studies by Castellucci et al. [91] and by Giovacchini et al. [83] patients were divided according to a Gleason score ≤ 7 and >7. Patients with Gleason score higher than 7 were only 11% and 28%, respectively. At univariate and multivariate analysis, Gleason score did not predict PET/CT [83, 91]. No significant association between PET/CT positive detection rate and Gleason score was reported also in many other studies [34, 68, 104, 105].

The predictive role of the Gleason score was demonstrated by Cimitan et al. in an extremely large sample of 1000 patients [106]. In this sample, 40% of patients had Gleason score higher than 7. The Gleason score was stratified in three categories (<7, =7, >7). Results showed that Gleason scores equal to 7 and greater than 7 were predictive of a positive PET/CT in comparison to the reference category (<7) [106]. Different factors could account for the positive results of this study and the negative results of previous studies. First, it was postulated that as disease progresses dedifferentiation may occur and Gleason score in metastatic lesions may be different from the Gleason score in the primary tumor [107, 108]: this factor might have accounted for the negative findings of many studies. However, methodological factors might also have played a role. For example, data suggested that the binary stratification of the Gleason score, which was done in many studies, would have not been the most appropriate one. These data derive from studies assessing the relationship between the Gleason score and prognosis of PCa patients [109–111]. For example, previous studies had observed not only that Gleason score = 7 should be distinguished from Gleason score <7 and Gleason score >7, but also that Gleason score equal to 7 is a heterogeneous entity [109–111]. Sakr et al. in a large study including 534 patients reported that PCa patients with Gleason score 3 + 4 had lower rates of PSA recurrence than patients with Gleason score 4 + 3 [110]. Alenda et al. reported that 3- and 5-year biochemical biochemical-free survival in patients with Gleason score 3 + 4 was higher (84.6% and 76.4%) than in patients with Gleason score 4 + 3 (69.9% and 61.1%) [109]. Very similar results were obtained by Tollefson et al., who reported more aggressive disease and higher rates of biochemical failure, systemic recurrence and PCa-specific survival in patients with Gleason score 4 + 3 [111].

Two other factors that are likely to have facilitated the positive results of the study by Cimitan et al. are represented by the extremely large sample size (n = 1000) and the high number (40%) of patients with Gleason score higher than 7 that represent the subgroup of patients at higher risk [106].

This example illustrates well possible caveats that are easy to introduce or to be hidden in the statistical analysis and, at the same time, the constant need for a critical interpretation of methodology used and obtained results.

Early diagnosis

Clinicians would wish to have available imaging techniques that have high positive detection rates for low PSA levels, ideally lower than 1 ng/mL, since in this interval the disease is more probably locally confined and salvage therapy is expected to be more efficacious [93, 112].

In the early studies, the possibility of an early diagnosis through PET and radiolabeled choline seemed unlikely. We will remember for example that De Jong et al. carried out a study including 16 PCa patients that had been treated with external radiotherapy and 20 PCa patients that had been treated with radical prostatectomy [64]. In the whole group, 22 patients had experienced biochemical failure. No positive scans were detected for PSA levels lower than 5 ng/mL, questioning the utility of PET for early diagnosis [64]. It is difficult to speculate nowadays on the possible reasons for this finding. The contrast with other series performed several years later with hybrid PET/CT devices and larger populations, where the positive detection rate for PSA between 2 and 3 ng/mL ranges about between 40 and 50% [83, 96], is remarkable. Most likely several factors played a role, including the lower image quality of older stand-alone PET scanners, the absence of anatomical references from CT, and possibly chance, i.e. the small sample size. Few years later Heinisch

et al. using PET/CT and [^{18}F]FCH reported in 8 of 17 patients (47%) with PSA < 5 ng/mL, at least one site of pathological tracer uptake suggesting recurrent disease. Follow-up confirmed PET/CT findings in 88% of these patients. Even though generalization of results was limited by the small sample size, Heinisch et al. concluded that PET/CT with radiolabeled choline should not be restricted to patients with PSA > 5 ng/mL [84].

The first study that addressed the issue of early diagnosis of PCa recurrence was carried out by Vees et al. [113]. These authors studied 11 patients with a very low PSA (median PSA = 0.33 ng/mL) with [^{18}F]FCH. Vees et al. reported a positive detection rate of 45%. Although this value appears relatively high in comparison to what obtained over comparable PSA intervals by subsequent studies [85, 91], the merit of this study lies in the fact that it first clearly demonstrated the possibility to use PET/CT with radiolabeled choline for early detection of disease [113].

Castellucci et al. tested the feasibility of early diagnosis of PCa recurrence through the use of [^{11}C]choline PET/CT in a group of 102 patients with PSA < 1.5 ng/mL [91]. They reported a positive detection rate of 28%. Interestingly, [^{11}C]choline PET/CT detected unexpected distant metastases in 21% of patients. At multivariate statistical analysis, only PSADT and lymph node status were independent predictive factors for positive [^{11}C]choline PET/CT. The authors concluded that [^{11}C]choline PET/CT could be used early during initial biochemical relapse in patients with fast PSA kinetics. The early detection of the site of recurrence could lead to prompt instauration of the most appropriate treatment. An additional advantage offered by the technique is represented by the avoidance of unnecessary local radiotherapy in those patients showing at [^{11}C]choline PET/CT previously unknown distant metastases [91].

The traditional approach to early restaging is based on selection of patients with low PSA values. In an alternative approach Giovacchini et al. selected 109 PCa patients that had no evidence of disease on conventional imaging and assessed in this group the additional information provided by [^{11}C]choline PET/CT [85]. This approach corresponds to the selection of patients that the Prostate Cancer Clinical Trial Group defines as “rising PSA status”, i.e. in whom despite rising PSA no evidence of macroscopic disease is detected on conventional nuclear medicine and radiological imaging [114]. This criterion, therefore, identified patients that were most likely to profit from [^{11}C]choline PET/CT and in whom this technique might have been used for early diagnosis. Median PSA in the whole sample was 0.81 ng/mL and PET/CT scans were positive in a very small fraction of patients (11%) in comparison to other studies, reflecting the very selective inclusion criteria. Of interest, pathological uptake areas of [^{11}C]choline were detected only in the post-surgical prostate bed and in pelvic lymph nodes. There was no pathological uptake site in extra-pelvic lymph nodes or in the skeleton, indicating that in very selected patients PET/CT with radiolabeled choline could be used for early identification of disease relapse [85]. Note, however, that using this approach early diagnosis would be accomplished to the expenses of a high number of negative PET/CT scans. Moreover, since PET/CT with radiolabeled choline is since many years used in most centers as first imaging test for restaging, selecting patients on the basis of negative conventional imaging is now obsolete. Therefore, this study should now be considered more like an updated proof-of-concept study verifying the superiority of [^{11}C]choline PET/CT [85]. It was shown that, in a population similar to this, the positive detection rate can be increased from 21 to 50% if PSADT is used to select patients [92].

On the basis of these results, many authors proposed that identification of risk factors predicting positive [^{11}C]choline PET/CT scans should be used to select patients that are at greater risk to increase the positive detection rate of the technique [63, 85, 91]. On the basis of the positive detection rate, PSA > 1 ng/mL is generally accepted as a clear indication to PET/CT with radiolabeled choline [63, 80], even though early diagnosis requires much earlier imaging (i.e., for lower PSA values). As previously stated, the European Association of Urology endorses the use of PET/CT with radiolabeled choline for PSA between 1 and 2 ng/mL as a compromise between the possibility to begin an early therapy and the risk of avoiding an excessive number of negative PET/CT scans [93]. For patients with PSA lower than 1 ng/mL, the indication to PET/CT with radiolabeled choline should be critically discussed on a personal basis among the patient, the nuclear medicine physician and the referring physician or in the context of multidisciplinary tumor boards.

Role of ADT

Antiandrogenic therapy is frequently used in PCa patients in multiple clinical contexts, before surgical therapy (neoadjuvant ADT), concurrent to RT or shortly after surgery (adjuvant ADT), or in the late phases of disease when the disease has spread to a systemic level. ADT exerts an inhibitory effect on PSA concentration and prostate metabolism [115, 116], so that it was felt the need to assess whether ADT could reduce the sensitivity or the positive detection rate of PET/CT scans with radioactive choline.

To the best of our knowledge, the first description of an inhibitory effect of ADT on the uptake of radiolabeled choline in vivo was reported by DeGrado et al. in their initial evaluation of [^{18}F]FCH [12]. They reported about a 59-year-old patient with untreated locally advanced PCa with increased [^{18}F]FCH uptake in the primary tumor and in bone metastases. Two months after ADT, uptake of the tracer decreased by more than 60% [12]. De Waele et al. described a similar case of a 57-year-old PCa patient that underwent PET/CT with

[^{11}C]choline for initial staging of disease. PET/CT showed focal tracer uptake in multiple iliac lymph nodes and in the prostate bed. After 6 months of therapy with flutamide and leuprorelin [^{11}C]choline uptake was no longer visible [117].

Still in the context of initial staging Giovacchini et al. reported an average 45% reduction of SUVmax of [^{11}C]choline in the whole prostate in PCa patients after neoadjuvant treatment with bicalutamide (median treatment: 4 months). The limit of this study is represented by the very small sample size (n = 6). However, owing to the paired design and the robust effect of bicalutamide, statistical significance was achieved [118]. Very recently, Evangelista et al., in an unpaired designed study, showed that PCa patients with neoadjuvant ADT had lower median SUVmax and lower metabolic tumor volume than drug-naïve patients [119].

Mechanisms underlying the decrease in uptake of radiolabeled choline after ADT were previously discussed [120]. Briefly, they include atrophy of glandular cells with loss of prostatic choline metabolites, reduction of prostatic volume (i.e., partial volume effect), down-regulation of the expression of genes involved in phospholipid metabolism, such as the choline transporter or choline kinase, and reduced cell proliferation rate [34, 115, 118, 121–123].

Results are different when we move to the clinical stage of the biochemical failure, i.e. if we consider those patients that develop biochemical failure during ADT treatment itself. Krause et al. reported in 2008 no significant differences in the positive detection rate of [^{11}C]choline PET/CT between PCa patients with biochemical failure treated with ADT and patients not treated with ADT [82]. Even though the statistical approach was not ideal, because t-test does not correct for differences in other variables of the two groups, this was a very important study because it first brought to the attention and gave some formal solution to a theme that would have been extensively discussed until recently.

In a subsequent study in patients with biochemical failure it was found that [^{11}C]choline PET/CT scans were significantly more frequently positive in the group experiencing biochemical failure during ADT (i.e., hormone resistant patients) than in drug naïve patients and in drug free patients that develop biochemical failure (i.e., hormone sensitive patients) (56% vs. 44%, respectively) [83]. At univariate analysis, hormone resistance was a significant predictor of positive [^{11}C]choline PET/CT. This finding could be attributed to the greater prevalence of other predictive factors (i.e., more advanced pathological stage, higher PSA levels at the time of PET/CT, etc.) in the group of hormone resistant PCa patients in comparison to hormone sensitive patients [83]. The ad-hoc study design, where a large sample size was recruited to enter at multivariate analysis the desired number of variables and to allow convergence, demonstrated that the significance of treatment with ADT was lost when all variables were taken together. This showed that the positive association between [^{11}C]choline PET/CT positive detection rate and ADT was spurious and related to the higher incidence of other predictive factors, which ultimately resulted in a greater aggressiveness of the disease.

In later years until now, further studies were performed to address this issue. All studies consistently reported that the positive detection rate in patients who developed biochemical failure during ADT was higher or equal to that observed in hormone sensitive patients experiencing biochemical failure [51, 82, 83, 88, 95, 103, 124, 125]. Therefore, authors now agree that in patients with biochemical failure during ADT, ADT itself does not significantly affect the uptake of radioactive choline. This finding is not in contrast with that obtained in patients studied at initial staging under neoadjuvant ADT [118], in whom PCa is still in the androgen-dependent stage and tumor cell growth and uptake of radiolabeled choline are sensitive to androgen regulation.

We would like again to emphasize that the lack of a significant inhibitory effect of ADT on radioactive choline holds in the restaging setting only if patients develop biochemical failure during ADT. If biochemical failure occurs in patients that are drug-naïve or drug-free (after termination of adjuvant therapy) an inhibitory effect is to be expected. This is well exemplified by the study by Fuccio et al. who studied 14 drug-naïve PCa patients twice with PET/CT and [^{11}C]choline. Patients were studied first during biochemical failure and those with positive findings were studied a second time after at least 6 months of ADT. At the first PET/CT, 13 out of 14 patients had positive [^{11}C]choline PET/CT. After ADT, PET/CT was positive only in five out of 14 patients [126].

Based on cumulative data from the last ten years, ADT are now generally not withdrawn before PET/CT with radiolabeled choline if biochemical failure occurs under ADT. On the contrary, in the setting of initial staging PET/CT with radiolabeled choline should be performed before begin of the neoadjuvant ADT [120, 127].

Validation of PET and PET/CT findings

False positives and false negatives As every technique, PET/CT with radiolabeled choline has intrinsic limitations. False positives are encountered; in fact, increased [^{11}C]choline uptake is not specific for carcinogenesis, as focal tracer uptake may occur in animal models of inflammation [128]. In humans, false positives have been reported in retroperitoneal lymph nodes of PCa patients and have been attributed to reactive hyperplasia [113, 129, 130]. False positives were also reported in the skeleton, such as in Paget's disease [131] even though in this case the associated structural abnormalities and diffuse, rather than focal, uptake make the differential diagnosis visually possible.

It is sometimes remarked that, among the various anatomical regions, false negatives are more frequent in the post-

prostatectomy bed and this is probably related to small tumor volume [63, 79, 132]. Reske et al. studied 36 patients with biochemical failure and in whom 30 patients had histological evidence of local recurrence [66]. Mean PSA 2.0 ng/mL (0.3–12.1). [^{11}C]choline PET/CT had a positive detection rate of 67%. Mean lesion size was 1.7 cm (0.9–3.7 cm). The authors concluded that focally increased [^{11}C]choline uptake in the prostatic bed reliably predicted local low volume occult relapse after radical prostatectomy [66]. In another study by Vees et al., [^{18}F]FCH PET/CT identified local recurrent disease in about 50% of patients with PSA < 1 ng/mL after radical prostatectomy [113]. The allegedly low sensitivity of PET/CT with radiolabeled choline to the detection of local recurrence requires one consideration. Giovacchini et al. reported a [^{11}C]choline PET/CT detection rate of 51% for PSA between 1.5 and 2 ng/mL [83]. Krause et al. reported an overall detection rate of about 52% for PSA between 1 and 3 ng/mL [82]. In the largest study by Graziani et al. the overall positive detection rate of [^{11}C]choline PET/CT was about 55% with a median PSA of 2.1 ng/mL and a mean PSA of 4.9 ng/mL [94]. Therefore, this selective choice of literature does not seem to show a lower sensitivity of PET/CT in the post-surgical prostate bed in comparison to the other anatomical regions. This apparent discrepancy is related to the fact that biopsy is preferably performed for very low PSA values (PSA < 0.5 ng/mL or PSA < 1 ng/mL) and for such PSA levels the general detection rate of PET/CT, which is dependent on a critical mass of the recurrence, is intrinsically low and it is not comparable to the sensitivity offered by the histological analysis of the biopsy.

False negatives or weak activities were also reported in metastatic sclerotic lesions, in which uptake of [^{18}F]FCH inversely correlated with the density of sclerotic lesions by Hounsfield units [2].

The most annoying weak point of PET/CT with radiolabeled choline is the low positive detection rate for low PSA levels, especially in the interval between 0.2 and 1.0 ng/mL (for patients treated with prostatectomy), which prevents a successful use of the technique in the interval where salvage radiotherapy is expected to be more efficacious.

The occurrence of false positives and false negatives mandates the need for some form of validation of PET/CT findings.

Pattern of spreading The pattern of anatomical uptake sites of [^{11}C]choline or [^{18}F]FCH found in PCa patients is consistent with the natural spread of the disease as known from autopsy and previous imaging studies and, therefore, it can be considered an indirect index of the accuracy of the technique. Retroperitoneal lymph nodes were the most frequent anatomical sites of [^{11}C]choline uptake (66% of patients), followed by the post-surgical prostate bed (34%), and by the skeleton (29%). Pelvic lymph nodes were more frequently involved than retroperitoneal lymph nodes. In the skeleton, the pelvis and the spine were most frequently affected. Local recurrence in the prostatectomy bed was present in the majority of cases as an isolated finding (58%) and somehow less frequently in concurrence to either lymph node or bone metastasis (42%) [83]. Unfortunately, these data inferred from clinical studies do not provide direct information on tracer uptake observed in the single subject.

Validation of PET/CT findings in the single patient is a major issue in restaging PCa-patients because only a minority of patients will undergo biopsy due to medical, ethical, and logistical considerations. For example, one study reported validation of PET/CT findings with biopsy of either prostate bed or retroperitoneal lymph nodes was performed only in 11% of patients [85]. In an attempt to overcome these difficulties imaging, pathological and biochemical criteria were developed [82, 83, 91, 100]. In many studies validation of PET/CT findings was performed in comparison with other techniques even though information about the validation process remained scant. Moreover, in some studies a variable fraction of patients was validated using only clinical and biochemical follow-up. On top of this, since most studies were retrospective, patients received different combination of conventional imaging examinations at different times.

According to our opinion, the process of validation of PET/CT findings vs. conventional imaging has two main problems: 1) with increasing experience most if not all of us realized that PET/CT is more sensitive than many conventional imaging examinations, including CT with contrast media and bone scintigraphy. 2) only CT with contrast media could cover all structures from the pelvis (middle thigh) to the neck, but generally only the pelvis and the abdomen are included in the field of view in PCa protocols. This applies to MR as well. Bone scintigraphy does allow whole body acquisitions, but comparisons cannot be extended to the prostate loge and to lymph nodes. Therefore, a battery of imaging studies, all performed at about the same time, would indeed be necessary if such systematic comparisons were wished. This contrasts clearly with the current, patient-oriented, good clinical practice.

In a very well designed perspective study performed few years ago, [^{18}F]FCH PET/CT was compared to bone scintigraphy and contrast-enhanced abdominopelvic CT in 26 patients with castration-resistant PCa. Results showed that PET/CT with [^{18}F]FCH had high (81%) concordance with bone scintigraphy and CT in the detection of metastatic PCa. Follow-up of discordant cases showed that PET/CT had provided the accurate information in 79% of lesions [133]. The main limit of this study lies in the fact that patients with advanced disease were selected. These are the patients for whom early diagnosis of recurrent disease is no longer an issue and in whom, because of the extensive tumor load, PET/CT is of less additive value in comparison to conventional imaging.

In summary, we personally agree with a recent editorial by Fanti and Lalumera concluding that sensitivity, specificity and

accuracy values should be taken cautiously [134], because these statistical parameters are heavily affected by the characteristics of the recruited sample and by number, type, and timing of examinations used for the validation process, as well as by the phase of the disease (early phase with low tumor load vs. late phase with high tumor load).

Meta-analysis Meta-analyses also represent a way to approximate statistical measures of sensitivity and specificity. A certain number of studies satisfying methodological rigorous inclusion criteria are selected. Summing patients of several studies increases substantially the final sample size and, therefore, the reliability of statistical measurements. Since studies in different centers are likely to differ somehow in some methodological aspects, a random-effects model is generally used in meta-analyses to account for inter-center variability [102]. Some meta-analyses have been written in recent years to assess sensitivity and specificity of PET and PET/CT with radioactive choline [40, 79, 81, 135], to assess the relationship between the positive detection rate and PSA kinetics [102] or to assess the change on treatment [135], testifying the huge interest in the application of this technique. It is impossible to cite all the single works that have been selected for the meta-analyses, thus we remind the reader about the results obtained by Fanti et al. that appropriately distinguished between the three most common anatomical sites of recurrence in an analysis limited to [^{11}C]choline PET and PET/CT in patients with biochemical failure after radical prostatectomy or curative radiotherapy [81]. Statistical values were derived from 12 studies with a total of 1270 participants. The pooled overall positive detection rate was 62% (95% CI: 53%–71%). Pooled overall sensitivity was 89% (95% CI: 83%–93%) and pooled overall specificity was 89% (95% CI: 73%–96%). In the post-surgical prostate bed pooled detection rate was 27% (95% CI: 16%–38%) (n = 993); pooled sensitivity was 61% (95% CI: 40–80%) and pooled specificity was 97% (95% CI: 87–99%) (n = 491). For lymph node disease pooled rate was 36% (95% CI: 22%–50%) (n = 752). For bone metastases pooled rate was 25% (95% CI: 16–34%) (n = 775). For lymph node and bone disease data on sensitivity and specificity were not pooled because of a very high heterogeneity of the data. The authors concluded that despite some inter-center variability convincing evidence could be provided to further support the role of PET/CT with radioactive choline in PCa patients with biochemical failure [81].

Impact on survival It is our opinion that, given these premises, a reliable way to provide indirect evidence of accuracy is to measure the impact of PET/CT findings on survival. If in our medical report what we call positive is really something related to tumor and what we call negative is really free of tumor, then patients with positive and negative PET/CT must differ in their survival rates. If so, then the technique must be accurate.

There have been few studies on PET/CT with radioactive choline and PCa. The first was performed by Giovacchini et al. [71]. The authors performed a retrospective study in 195 PCa patients treated with radical prostatectomy and experiencing biochemical failure during ADT. The median PCa-specific survival was significantly shorter in patients with positive [^{11}C]choline PET/CT (median: 11.2 years, 95% CI, 9.8–12.6 years) than in patients with negative [^{11}C]choline PET/CT (median: 16.4 years, 95% CI, 14.0–18.8 years). At multivariate analysis, statistical significance was obtained for [^{11}C]choline PET/CT, PSA, and Gleason score. Patients with pathologic [^{11}C]choline uptake in the skeleton had shorter survival (median: 9.9 years, 95% CI, 6.8–13.1 years) than patients with pathological tracer uptake in the prostatic bed or in pelvic or retroperitoneal lymph nodes (median: 12.1 years, 95% CI, 10.5–13.7 years). The authors also developed two internally validated nomograms predicting 10- and 15-year PCa-specific survival probability with an accuracy of 76% and 74%, respectively [71].

In the following year, the same group performed a very similar study, the only difference being that drug-naïve and drug-free patients, rather than hormone-resistant patients, were recruited [70]. Median PCa-specific survival after prostatectomy was 14.9 years (95% CI, 9.7–20.1 years) in patients with positive [^{11}C]choline PET/CT, while median survival was not achieved in patients with negative [^{11}C]choline PET/CT owing to the very low prevalence of fatal events in this group. The 15-year PCa-specific survival probability was significantly shorter in patients with positive [^{11}C]choline PET/CT than in patients with negative [^{11}C]choline PET/CT (median: 42.4% vs. 95.5%). In multivariate analysis, [^{11}C]choline PET/CT and Gleason score > 7 predicted PCa-specific survival [70].

In the same years, also Kwee et al. performed a study addressing the issue of PET/CT with [^{18}F]FCH and survival [73]. There are some differences in the design of this study compared to the two studies performed by the San Raffaele group in Milan. Kwee et al. enrolled metastatic castration resistant PCa (mCRPC) patients; all of them had positive PET/CT and had been treated with first- or second-line ADT, as well as with chemotherapy. Several semiquantitative measurements were used for the data analysis [73]. On the contrary, in the studies performed by Giovacchini et al. in either hormone-sensitive patients [70] or in hormone-resistant patients [71], only a fraction of patients had positive PET/CT, this being lower in hormone-sensitive patients [70], and visual analysis was adopted. Kwee et al. interesting showed that all defined semiquantitative indices (i.e. SUVmax, metabolically active tumor volume, and total lesion activity), as well as PSA predicted overall survival. Moreover, using median values of the semiquantitative indices,

significant differences were detected between the derived subgroups [73].

Other studies assessing prediction of survival were done in the context of prediction of response to ADT and chemotherapy [136–138] or chemotherapy [139, 140] and they will be discussed in a following section.

Impact on clinical management

Even though the change of the therapeutic management cannot be related exclusively to the accuracy of the technique (false positive and false negative findings might also induce changes in management), this parameter is interesting because it reflects on one side the performance of the technique and on the other side the extent to which clinicians rely on the final medical report.

Few studies addressed this issue, generally with similar results and conclusions, supporting a significant effect of PET/CT with radiolabeled choline on patient management. Some possible confounding variables, however, should be discussed, namely the baseline for assessing changes, the criteria used for the classification of the change of management and the design of the study.

The first study on the impact on clinical management was performed by Soyka et al. from the group of the Zurich University Hospital [69]. Questionnaires for each PET/CT examination were sent to the referring physicians 14–64 months after PET/CT of 156 PCa patients treated with different modalities. In 48% of patients the treatment plan was changed due to the [^{18}F]FCH PET/CT findings. The most frequent change was represented by a change from palliative treatment to treatment with curative intent (22%). In 11% of patients the treatment plan was adapted and in 10% of patients the treatment plan was changed from curative to palliative. Remaining changes followed other strategies. This study first showed that PET/CT with radioactive choline has an important impact on the therapeutic strategy in patients with PCa patients and it can help to determine the appropriate treatment [69]. It is important to remark that, given the retrospective design, no comparison with other imaging modalities was performed. Indeed referring physicians were first asked to indicate the therapeutic strategy as defined on the basis of the results of [^{18}F]FCH PET/CT; then they were asked to define a hypothetical therapeutic strategy, assuming the results of [^{18}F]FCH PET/CT (and of no other imaging technique) had not been available [69].

Ceci et al. performed a retrospective study in 150 patients addressing the same issue [68]. The main two remarkable features of this study are its bicentric design (Bologna and Wurzburg) and in the distinction regarding the effective clinical impact between major changes (change in therapeutic approach) and minor changes (same treatment, but modified therapeutic strategy). This distinction appears to us particularly important because based on a clinical rather than on a merely imaging perspective. Changes in therapy after [^{11}C]choline PET/CT were done in 47% of patients. A major clinical impact was observed in 18% of patients and a minor clinical impact in 29% of patients [68]. Even though the total number of patients in whom PET/CT introduced a change of management was virtually identical to that reported by Soyka et al. (48%) [69], the results of Ceci et al. [68] indicate that changes with major clinical consequences are largely overestimated if appropriate design is not adopted. In either case, both authors [68, 69] advocated the need for further evaluation in perspective studies.

Protocol optimization

Choice of the radiotracer Centers that are equipped with a cyclotron and, therefore, that could have access to both [^{11}C]choline and [^{18}F]FCH, might have to decide whether to invest or continue investing on one or the other tracer. The main kinetic difference between carbon-11 and fluorine-18 labeled tracers is that fluoride-18 labeled compounds have some more urinary excretion starting as early as 3 to 5 min after injection [13, 141]. Some issues were initially raised about the possibility to detect local recurrence because of some concurrent bladder activity [12, 13, 141]; however, subsequent studies later revealed this not to be a major issue in most cases also for fluorinated compounds [142–144]. In vitro studies revealed that cellular uptake and phosphorylation by choline kinase for [^{18}F]FCH are very similar to those for natural choline, while [^{18}F]fluoroethylecholine displays lower values for both uptake and phosphorylation. Thus, [^{18}F]FCH has been adopted in almost every center using fluorinated choline derivatives for PCa imaging [12, 141].

There is general agreement that there are no major differences in the positive detection rate between [^{11}C]choline and [^{18}F]FCH [142–144]. von Eyben et al. performed a systematic review and a meta-analysis to evaluate eventual differences in the positive detection rate of [^{11}C]choline and [^{18}F]FCH PET/CT in patients with biochemical recurrence [144]. PSA levels of 1–10 ng/mL, which was considered a clinically relevant interval, represented a selection criterion. Six articles with [^{11}C]choline and 12 articles with [^{18}F]FCH were selected. Detection rates of metastatic sites were 30 ± 5% in [^{11}C]choline PET/CT studies and 39 ± 5% in [^{18}F]FCH PET/CT studies; the difference was far from the statistical significance ($P = 0.26$).

There are, however, other reasons that might support the choice of the radiotracer. For example, most historical groups have used [^{11}C]choline because [^{11}C]choline was the first synthesized radiotracer and because at that time emphasis was made on possible advantages of the natural compound. Most of these centers have continued to use [^{11}C]choline. On the other hand, use and large production of [^{18}F]FCH could allow,

if legislation applies, the possibility to sell this radiotracer to some peripheral centers.

Dynamic imaging In many centers, current protocols include an early dynamic acquisition (typically 3–5 frames shortly after tracer injection) before the standard whole body acquisition [61, 88]. The use of an early dynamic acquisition stems from the occasional difficulty of differentiating tracer uptake related to local recurrence from urine activity encountered especially in the early studies performed with stand alone PET tomographs. There is, however, insufficient information in most papers to understand how many local recurrences detected by early dynamic imaging could not be detected or remained doubtful with only static pelvic imaging. Steiner et al. used PET/CT with [^{18}F]FCH in 47 PCa patients with biochemical relapse and performed early dynamic pelvic acquisition, whole body as well as and delayed static pelvic acquisition [87]. They found a total of 15 local recurrences in which average SUVmax increased during dynamic acquisition and marginally decreased in delayed scanning. The authors claimed an added value of three-phase PET/CT in 10 of 47 (21%) patients [87]. Other groups have used static, rather than dynamic, early images. For example, Chondrogiannis et al. reported that findings in the prostate bed were better visualized during a static acquisition immediately after injection and therefore early static acquisition was associated with a higher confidence of the nuclear medicine physician in the diagnosis of local recurrence. However, early static acquisition was not associated with a significant increase in the detection rate of local recurrences [145, 146].

Delayed imaging In many oncological fields, delayed imaging results in an increase in the signal-to-noise ratio, owing to the fact that with increasing post-injection interval tracer uptake increases or does not change in tumor lesions while the tracer washes out from benign lesions [147]. The relevance of this approach for PCa has been insufficiently explored, partially because many studies have been performed with [^{11}C]choline. Cimitan et al. using PET/CT and [^{18}F]FCH examined 100 PCa patients treated with different primary therapy with an early static scan (< 15 min, post-injection) and a delayed scan (> 60 min, post-injection) [148]. They reported a significant increase of about 60% in [^{18}F]FCH SUVmax in bone lesions in the delayed acquisition in comparison to the early scan, while SUVmax did not significantly change in lymph nodes and in the prostate bed. The authors, however, failed to report whether delayed imaging reduced the number of false negative scans, i.e. if there were patients with negative early scan but positive delayed scan, which represent the key information before routine application of additional imaging.

At the moment, there is some variability in the acquisition protocols among centers [145, 146]. However, given the fact that a late acquisition is always performed and that the advantage conveyed by additional acquisitions is questionable, the clinical significance of this variability is also uncertain.

The late years: PET/CT with radiolabeled choline to guide or to assess therapy response

Assessment of therapy response in mCRPC patients

In recent years, there have been some studies assessing the role of PET/CT with radiolabeled choline in the response to either second-line ADT [136–138] or chemotherapy [139, 140]. All these studies share the common feature of being carried out in mCRPC patients that are typically affected by diffuse bone metastases.

Overall, results have been relatively disappointing. Response Evaluation Criteria in Solid Tumors (RECIST) were used by Schwarzenbock et al. in a very well-designed prospective study that assessed changes in [^{11}C]choline SUVmax, PSA, Hounsfield units and volumes of bone, lung, lymph node metastases and local recurrences after chemotherapy with docetaxel in mCRPC patients [139]. Quantitative changes were measured the first time as early as one week after start of treatment and a second later assessment was at done at a variable time depending on the lost at follow-up due either to side effects of the therapy or to death. There was no relationship between any of the cited measurement with either RECIST criteria or usual clinical criteria neither at the early nor at the late response assessment. Follow-up was too short and the study group was too small to obtain any prognostic information. The authors concluded that [^{11}C]choline PET/CT seems to be of limited use in therapy response assessment in standardized first-line chemotherapy in mCRPC patients [139].

A major issue regarding the use of PET/CT with radioactive choline in the assessment of the response to therapy is the comparison with the inexpensive PSA measurement or with bone scan.

De Giorgi et al. had performed a study with a similar design in 43 mCRPC patients [137]. At multivariate analysis, only positive [^{18}F]FCH PET/CT significantly predicted progression-free survival and overall survival after abiraterone therapy. The authors, consistently with their results, concluded that [^{18}F]FCH PET/CT can predict the clinical outcome in mCRPC beyond PSA response and that [^{18}F]FCH PET/CT could be used to monitor therapy with abiraterone and to predict outcome in patients with mCRPC. Similarly to what observed for bone scintigraphy, bone flare, defined as combination of progression disease on [^{18}F]FCH PET/CT and PSA decrease, was reported in 10% of patients [137].

One year later, De Giorgi et al. studied 36 mCRPC patients with PET/CT and [^{18}F]FCH at baseline and after 3–6 weeks of docetaxel therapy [138]. A decrease in PSA level of more than

50% was used to distinguish PSA responders from non-responders. In an elegant design, the authors showed that progression at [^{18}F]FCH PET/CT predicted CT progression 3 months in advance. At multivariate analysis, only PSA decrease and [^{18}F]FCH PET/CT were significant predictors of progression free survival, whereas PSA decrease alone was predictive of overall survival. They concluded that PSA remains the single most important prognostic factor, while [^{18}F]FCH PET/CT does not add more information on overall survival beyond that obtained from PSA [138]. To the best of our knowledge, no explanation was offered to the discrepant results obtained in the two studies [137, 138]. We argue that many factors might have contributed to the different results, such as some slight differences in the timing of the PET/CT scans, different tumor burden of recruited patients, different previous treatment with antiandrogenic drugs or chemotherapy regimens, and the occurrence of the bone flare. The statistical design appears very similar in both studies.

Ceci et al. carried out a study with PET/CT and [^{11}C]choline in 61 mCRPC patients before and after docetaxel [140]. Using binary logistic analysis, they tested several variables, including baseline PSA and SUVmax, changes in PSA after therapy, PSA response, PET response, number of positive lymph nodes and number of bone lesions on baseline PET. They found that the only factor predictor of progression at PET/CT after docetaxel therapy was represented by an extended (>10) number of bone lesions. They reported a disagreement between PSA and PET/CT response in 52% of patients that most frequently occurred in patients with decreasing PSA and with PET/CT progression after therapy. The loose relationship between PSA and [^{11}C]choline PET/CT response was supported by the logistic analysis where PSA changes did not predict PET/CT progressions after therapy [140].

Caffo et al. [136] reported a reduction of [^{18}F]FCH SUVmax in the prostate and a reduction of prostate volume in advanced mCRPC patients in response to enzalutamide, the latter finding contrasting with the negative findings obtained by Schwarzenbock et al. [139]. In the study by Caffo et al. the comparison between PET/CT and PSA was not addressed [136].

Small animal PET with [^{11}C]choline was used in human PCa models in athymic nude mice to assess sensitivity to photodynamic therapy, a promising therapy based on photon absorption and generation of toxic reactive oxygen species [149]. In treated tumors, [^{11}C]choline uptake significantly decreased 24 and 48 h after photodynamic therapy. On the contrary, in control tumors, [^{11}C]choline uptake significantly increased. Levels of PSA paralleled changes in [^{11}C]choline uptake while viability was longer in treated animals [149].

In summary, the limited number of studies indicates that PET/CT with radiolabeled choline could be used to monitor second line ADT or chemotherapy in PCa patients with advanced disease. However, it remains to be solved for which type of patients and therapeutic regimens PET/CT provides additional information to that provided by the inexpensive measurement of PSA.

Applications in radiotherapy

The use of PET/CT with radiolabeled choline to direct RT has been one of the major new clinical applications in the most recent years: several studies were performed and some reviews have already been published on this topic [80, 150–152]. The use of PET/CT to direct RT covers multiple aspects: 1) to assess whether, on the basis of PET/CT findings, PCa patients can be treated with primary RT and eventually whether PET/CT can be used to direct a local boost to the prostate or to include pelvic lymph nodes in the RT plan; 2) in the setting of salvage RT, i.e. in patients with biochemical failure, to assess the eligibility to local RT (i.e., exclude distant metastases), to adapt the extension and the modulation of the treatment plan, to select oligometastatic patients for advanced forms of RT (i.e., helical tomotherapy). Some studies will be briefly exposed to illustrate these applications.

Use of PET/CT to direct primary RT

Pinkawa et al. performed two of the first studies assessing the possibility to use PET/CT with [^{18}F]FCH to perform a boost on the prostate of PCa patients undergoing primary RT [153, 154]. In their study published in 2010 they recruited a relatively large sample (n = 66) of PCa patients [154]. Owing to the possibility of concurrent, non-malignant uptake of radiolabeled choline, malignant tissue was distinguished from non-malignant tissue on the basis of an arbitrary threshold of SUVmax >2: pixels with value above this threshold were used to define the PET-based gross tumor volume receiving the boost. This threshold was similar to that obtained in a previous study where uptake of [^{11}C]choline PET/CT in the prostate was correlated on a sextant-by-sextant basis to histological results: in this study a SUVmax of 2.5 was the best cutoff to differentiate between malignant and benign histopathology [131]. Even though the exact SUVmax distinguishing benign from malignant tissue is dependent on several factors, the study by Pinkawa et al. indicates how PET/CT could be used for identification of the boost volume. In the study by Pinkawa et al. [154] a dose of 76 Gy was prescribed to the prostate in 2-Gy fractions, with a simultaneous integrated boost up to 80 Gy on voxels with SUVmax >2. The authors concluded that treatment planning with [^{18}F]FCH PET/CT allows the definition of an integrated boost in nearly all PCa patients and that therefore this technique can be useful in the planning of RT in these patients [153, 154].

Use of PET/CT to direct salvage or palliative RT

In patients treated with radical prostatectomy experiencing biochemical failure, especially in patients with low PSA values and

in whom imaging fails to detect macroscopic evidence of disease, RT of the prostate loge is a frequent empirical treatment.

In the scenario of restaging, Souvatzoglou et al. recruited 37 PCa patients treated with radical prostatectomy referred to salvage RT after biochemical failure [155]. Thirty percent of patients had a positive finding at [^{11}C]choline PET/CT, and in 13% of patients the positive finding was located outside of the prostatic fossa (in iliac lymph nodes), implicating an extension of the planned target volume. After a median follow-up of 51.2 months, 56% of the sample had plasma PSA ≤ 0.2 ng/mL. The authors summarized the main results of their study underlying that PET/CT affected the extent of the RT plan in 13% of patients. At the same time, since a control group of patients studied with PET/CT was not available, the implication of the change in the planned target volume induced by PET/CT on biochemical control and on survival could not be determined [155].

Picchio et al. used PET/CT with [^{11}C]choline to evaluate the therapeutic role of salvage helical tomotherapy in treating patients that displayed evidence of pathological tracer uptake only at lymph node level [156]. They enrolled 88 patients with biochemical failure after primary radical treatment, either radical prostatectomy or RT. Mean PSA was 7.61 ng/mL (range: 0.37–187 ng/mL). At a variable distance after the end of helical tomotherapy (range 16–365 days; mean: 83 days), PSA was measured in all patients. Complete biochemical response, defined as percent PSA decrease higher than 50%, occurred in 70% of helical tomotherapy treatments, a partial response occurred after 12% of treatments, stable disease occurred after 2% of treatments, and progression of disease occurred after 16% of treatments. Helical tomotherapy with simultaneous integrated boost was well tolerated in all patients. [^{11}C]choline PET/CT revealed as a valuable tool for planning and monitoring radiotherapy in case of biochemical failure with evidence of lymph node disease. However, in this study, as in the study performed by Souvatzoglou et al. [155], no control group was available and the implications on biochemical control and survival could not be obtained [156].

This important issue was tackled by the same Italian group in a study performed in the following year [157]. Incerti et al. assessed the role of [^{11}C]choline PET/CT on several survival outcomes, including overall survival, locoregional relapse-free survival, clinical relapse-free survival, and biochemical relapse-free survival in PCa patients treated with helical tomotherapy for lymph node recurrence. Several PET-derived semiquantitative parameters were explored, including SUVmax, SUVmean, and metabolic tumor volume. The 2-year overall survival, locoregional relapse-free survival, clinical and biochemical relapse-free survival were 87%, 91%, 51%, and 40%, respectively. The metabolic tumor volume, calculated using a 60% threshold as resulted from a ROC-analysis, was shown to be the most powerful independent predictor and significantly correlated to biochemical and clinical relapse-free survival [157].

In the general practice, patients treated with RT are often additionally given ADT in different preparation and for variable length of time to consolidate the RT effect. Considering that the previously cited studies were retrospective, it is possible that this might have occurred. Information about eventual additional ADT is generally scanty. Further, prospective studies will be needed to assess to which extent ADT, if indeed used, might influence the biochemical control in patients already treated with RT.

Use of PET/CT with radiolabeled choline to direct salvage lymph node dissection

Detection of lymph node or bone disease through imaging devices in patients that experience biochemical failure indicates systemic disease. In this clinical context systemic antiandrogenic therapy is generally preferred; if a single site or limited sites of disease with tumor burden is identified, this site can also be targeted with RT. ADT does not represent a potential curative treatment and many of these patients ultimately develop castration-resistant disease [158].

In patients in whom PET/CT shows only evidence of lymph node disease, salvage lymph node dissection is an emerging alternative to RT. This procedure is technically demanding and it is performed only in selected centers [72, 159]. In the study by Suardi et al. [72], which represents the prosecution of the study by Rigatti et al. [159] with longer follow-up, 59 PCa patients were enrolled. This study included patients who had biochemical recurrence after radical prostatectomy, evidence at [^{11}C]choline PET/CT of lymph node disease, and absence of both local recurrence and bone metastases. Patients were treated with pelvic and/or retroperitoneal salvage lymph node dissection. Median follow-up after salvage lymph node dissection was 81 months. Overall, 59% of patients achieved biochemical response. The 8-year biochemical recurrence free survival rate in patients with complete biochemical relapse was 23%. Overall, the 8-year clinical response- and cancer-specific mortality free survival rates were 38% and 81%, respectively. In multivariate analysis high PSA at salvage lymph node dissection and the presence of retroperitoneal lymph node metastases, as shown by [^{11}C]choline PET/CT, were significantly associated with an increased risk of recurrence. The main limit of the study is represented by the lack of a control group. The authors concluded that [^{11}C]choline PET/CT-based salvage lymph node dissection may represent a therapeutic option for selected patients with nodal recurrence after radical prostatectomy. Roughly 40% of men did not show any further clinical recurrence at long-term follow-up after surgery [72, 159].

The contribution of PET/MR tomographs

In recent years, PET/MR hybrid scanners were developed. Owing to the limited accuracy of visualizing primary PCa through CT and ultrasound, PCa has been considered a field

of potential successful application of PET/MR. It is beyond the aim of this paper to review the hardware and software components of such devices, as well as to provide extensive overview of artifacts, primarily attenuation artifacts, and for further reading we refer to some recent papers [160–162]. However, initial hopes and enthusiasms did not have correspondence in the results of the first clinical studies. The first pilot study in a mixed population at initial staging and restaging indicated no significant difference in the detection rate between PET/CT and PET/MR with images of poorer quality been generated by the PET/MR scanner owing to the difficulties in the attenuation correction. The only advantage of PET/MR was that it provided better anatomical allocation of lesions, especially in the bone and in the pelvis [163].

More recently, Choi et al. used PET/MR with [^{18}F]FCH in 12 patients with newly diagnosed intermediate- and high-risk PCa patients planned for radical prostatectomy [164]. Tumor SUVmax correlated with PSA and pathologic stage. PI-RADS (Prostate Imaging Reporting and Data System) score correlated with pathologic tumor volume and Gleason score. Both parameters correlated with a postsurgical clinical-pathologic risk score. Combined PET and MR provided enhanced sensitivity (88%) for prediction of pathologic extraprostatic disease extension in comparison to MR (50%) and PET (75%) only [164].

Whether PET/MR can be successfully used with other tracers, such as ligands of the antagonists of the prostate specific membrane antigen, is currently under evaluation [165, 166]. As these initial studies seem to suggest, it is possible that PET/MR might be more useful at initial staging of PCa when clinical T staging, which requires high spatial resolution, may be important for further therapeutic decisions.

Other radiopharmaceuticals for prostate cancer imaging

PSMA Recently, new tracers have emerged as promising probes for imaging PCa. The most promising radiotracer class is represented by the inhibitors of the prostate specific membrane antigen (PSMA) protein [167–170]. PSMA is an enzymatic system physiologically expressed on extern membrane prostate cells that can be detected at higher concentrations in PCa cells. Among the several radiopharmaceuticals that have been synthesized [^{68}Ga]-HBED-CC, better known as [^{68}Ga]-PSMA, represents the radiopharmaceutical with better pharmacokinetic profile [167–170]. Contrary to the other radiopharmaceuticals commonly used for diagnosis and restaging of PCa, [^{68}Ga]-PSMA is a receptor ligand.

Preliminary data suggest that [^{68}Ga]-PSMA PET/CT could be more accurate and sensitive than PET/CT with radiolabeled choline for early detection of PCa recurrence [167, 168, 171, 172]. Contrary to [^{11}C]choline PET/CT and [^{18}F]FCH, which can be produced only in centers equipped with cyclotron, radiopharmaceuticals based on gallium-68, which is a product of the germanium-68/gallium-68 generator, can be prepared in all PET/CT centers equipped with appropriate radiopharmacy. This allows a wide distribution of the diagnostic technique.

Recent studies in PCa patients showed a better contrast in [^{68}Ga]-PSMA PET/CT images and higher positive detection rate in PCa patients in comparison to [^{18}F]FCH [167, 168, 171, 172].

Several studies have already demonstrated a high positive detection rate of [^{68}Ga]-PSMA PET/CT ranging from 50 to 88%, which may vary according to PSA values and presence of other risk factors, such as indices of PSA kinetics [167, 168, 171–174]. High positive detection rates were reached also for low PSA levels, especially for PSA < 1 ng/mL. Particularly interesting are the results of a study reporting that, for PSA < 0.5 ng/mL, the positive detection rate was 50% for [^{68}Ga]-PSMA PET/CT and 12.5% for ^{18}F–FCH PET/CT [167]. One study that used histological analysis as gold standard after extended lymph node resection reported that [^{68}Ga]-PSMA PET/CT had specificity higher than 95% for lymph node staging [174].

Moreover, PSMA-ligands can be labeled with beta-emitters, such as Lu-177, in a chemically stable bound; they have high affinity for the target, high tumor penetration, rapid clearance from the blood, and a favorable lesion-to-background ratio [169, 175–177]. Therefore, PSMA-ligands can be used for radiometabolic purposes in PCa patients that have positive [^{68}Ga]-PSMA PET/CT [169, 175–177]. Results from several studies have shown that radiometabolic therapy with [^{177}Lu]-PSMA-617 is effective and well tolerated and increases overall survival; significant PSA declines ranged occurred from 43 to 75% of patients depending on the number of therapies and the characteristics of the patients [178–180].

Amino acid analogs Another class of promising radiotracers is represented by amino acid analogs [181]. Transport of amino acids is upregulated in carcinomas [182]. The most frequently used tracer is represented by anti-1-amino-3-[^{18}F]-fluorocyclobutane-1-carboxylic acid ([^{18}F]-FACBC or [^{18}F]-fluciclovine). In comparison to naturally occurring amino acids, [^{18}F]-FACBC, a synthetic amino acid, is neither incorporated into proteins nor metabolized [183]. In PCa specific amino acids transporters are overexpressed. Overexpression of the L amino acid transporters 1 system (LAT1) has been correlated to higher Gleason score and with poorer prognosis [184, 185]. Similarly to radiolabeled choline, [^{18}F]-FACBC was shown to be more useful in restaging than at initial staging [181]. In a representative study in PCa with suspected recurrence, the overall positive detection rate was 77%. The detection rate increased with increasing PSA levels: 37% for PSA < 1 ng/mL, 78% for PSA between 1 and 2 ng/mL, 92% at PSA levels of greater than 2–5 ng/mL, and 83% at >5 ng/mL [186].

Nanni et al. carried out a prospective study including 100 consecutive PCa patients with biochemical failure after surgery. [^{11}C]choline PET/CT and [^{18}F]-FACBC had sensitivities of 32% and 37%, specificities of 40% and 67%, and accuracies of 32% and 38%, respectively. For any PSA interval, [^{18}F]-FACBC had detection rates that were higher or similar to those of [^{11}C]choline. For PSA <1 ng/mL the positive detection rate was 14% for [^{11}C]choline and 21% for [^{18}F]-FACBC [187]. In a recent meta-analysis that included six studies and 251 PCa patients with biochemical failure, [^{18}F]-FACBC PET/CT had 87% pooled sensitivity and 66% pooled specificity [188].

In summary, while a sufficient number of studies have convincingly shown that [^{18}F]-FACBC is a very promising radiotracer for imaging PCa recurrence, more comparative studies with either [^{11}C]choline or PSMA-ligands are needed to assess which PET tracer should be used as first line tracer for imaging PCa.

RM2 Another interesting line of research is represented by the further development of radiopharmaceuticals for the gastrin-releasing peptide receptor (GRPr). This receptor is overexpressed in PCa [189]. Many GRPr-tracers, mainly agonists, were synthesized in the past. Even though some tracers had the favorable capability of being suitable both for diagnostic and for therapeutic purposes, clinical applications have always been limited partly due to more available and more efficacious diagnostic and therapeutic compounds [190, 191].

In recent years, interest in GRPr imaging was renovated by the synthesis of the DOTA-conjugated GRP-receptor antagonist 4-amino-1-carboxymethyl-piperi-dine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2 (RM2, BAY 1017858), which can be easily labeled with different radiotracers [192]. RM2 and other GRP-receptor antagonists have shown a more favorable biodistribution than GRP-receptor agonists (such as [^{177}Lu]-AMBA) for imaging of PCa [193, 194]. Dumont et al. showed that [^{68}Ga]-RM2 could be successfully used to assess the response to therapy with rapamycin and [^{177}Lu]-RM2 in PC-3 PCa line [193]. Minamimoto et al. reported about a comparative study in a small (n = 7) group of PCa patients with biochemical recurrence using [^{68}Ga]-PSMA-11 PET/CT and [^{68}Ga]-PSMA-RM2. They found slight differences in the biodistribution and similar pathological findings in sites of disease recurrence [194].

A very recent new trend is represented by the synthesis of dual modality, i.e. nuclear and optical (fluorescence), probes that allow traditional in vivo imaging, as well as intraoperative imaging [195]. Zhang et al. in a proof-of-concept study reported promising results with [^{68}Ga]-HZ220, a dual modality GRPr receptor ligand in PC-3 PCa cells and in PC-3 xenografts [195].

On the basis of these developments it is reasonable to expect that university centers will begin in the near future pilot studies with these newly available radiotracers. [^{68}Ga]-PSMA is undoubtedly the tracer that already offers very consolidated results and it is most likely to be rapidly transferred into the clinical routine. Prerequisite is the availability of the germanium-68/gallium-68 generator that, however, should be financially accessible to many centers. Some specialized radiochemical expertise is also needed, even though instantaneous kits are expected to be released on the market in the very next future. Amino acid and GRPr imaging probably represent a second-line choice in comparison to [^{68}Ga]-PSMA. Preliminary data showing superiority of [^{18}F]-FACBC over [^{11}C]choline are definitely encouraging [187], but independent replication is wished. GRPr imaging might be an interesting option especially for centers that have a special expertise in radiometabolic therapy [193]. However, all these new radiotracers still need formal approval for clinical use in most countries. Therefore, it would be reasonable to expect that at least for some years and especially in peripheral hospitals radiolabeled choline will continue to be successfully used for routine clinical studies.

Conclusions

From 1997, when [^{11}C]choline was synthesized [1], until nowadays we have assisted to the publication of an increasing number of studies. Starting from the feasibility studies in patients with high tumor load and the comparative studies vs. [^{18}F]FDG that were carried out in the early years subsequent to the synthesis of the tracer, the utility of PET and PET/CT with radiolabeled choline in staging and restaging PCa was robustly demonstrated. Radiolabeled choline derivatives were shown to be superior to [^{18}F]FDG, to have an accuracy comparable or superior to conventional imaging, to have a positive detection rate that is influenced by the known risk factors for PCa, primarily PSA and subsequently by indexes of PSA kinetics, pathological stage, and Gleason score. Most of early studies were carried out with [^{11}C]choline, but subsequently the possibility of performing clinical studies was extended to all PET centers by the availability of [^{18}F]FCH. The two most targeted research questions were represented by the quantification of the overall positive detection rate and by the dependency of the detection rate on PSA levels. Given the impossibility to obtain bioptic or histological studies in every patient, attempts to validate PET/CT findings were done with different, often mixed, biochemical and imaging criteria in generally retrospective studies. PET/CT was applied more frequently in patients with biochemical failure, especially after radical prostatectomy, than in patients at initial staging. However, recent studies indicate that PET/CT with radiolabeled choline can be used with profit at initial staging especially in high-risk PCa patients. More recent studies addressed the role of PET/CT with radiolabeled choline in

selected therapeutic applications, such as the impact of PET/CT on patients' management, the use of the technique to assess the eligibility to RT and the capability to affect the RT plan, the identification of lymph nodes oligometastatic sites to use as target of radiotherapy, the identification of patients with exclusively lymph node disease that can be treated with salvage lymph node dissection, the capability to monitor changes in response to systemic ADT or chemotherapy. In patients with biochemical failure, PET/CT with radioactive choline predicts PCa-specific survival and its prognostic power is greater than any other traditional biochemical or pathological risk factor.

There is generally nowadays good agreement among different nuclear medicine centers that PET/CT should be used for PSA levels >1 ng/mL. The European Association of Urology also endorses this position. For patients with lower PSA values the presence of other predictive factors should be considered to increase the likelihood of a positive PET/CT. Generally, in these cases, the indication to PET/CT should be discussed critically on a personal basis among the patient, the referring physician and the nuclear medicine physician or in the context of multidisciplinary tumor boards.

Patients that develop biochemical failure during ADT have a higher likelihood of a positive PET/CT in comparison to patients that develop biochemical failure, but they are drug naïve or drug-free. Therefore, withdrawal of ADT before PET/CT in patients experiencing biochemical failure is not necessary.

Recently PET/MR hybrid devices were developed and applied also for PCa imaging. While PET/MR is gifted with some interesting properties, including reduced ionizing radiation and improved soft-tissue contrast, the technique did not provide substantial advantages over PET/CT in the clinical setting of the biochemical recurrence, which is the main scenario of PCa imaging. However, initial promising data suggest that PET/MR might be more useful in newly diagnosed PCa patients in whom the synergistic information of the two techniques may improve the definition of extra-prostatic disease and better predict histology.

Tracers other than radiolabeled choline might play an important role for PCa imaging in the near future. [^{68}Ga]-PSMA has been independently shown to have a higher positive detection rate than radiolabeled choline and it is undoubtedly the most promising radiotracer that is expected to rapidly enter into the clinical routine as soon as legislative issues (formal approval) and technical prerequisites (germanium-68/gallium-68 generator) will become available. Amino acid and GRPr tracers may represent other valid options for PCa imaging, but more independent validation is needed at this time.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

For this review, no research involving human participants and/or Animals was necessary. Similarly, no informed consent was necessary.

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