

Serum tumor markers and PET/CT imaging for tumor recurrence detection

Vibeke Kruse*, Veronique Cocquyt, Marleen Borms, Alex Maes and Christophe Van de Wiele

Abstract When confronted with a suspicious rise in CA 15.3 in asymptomatic breast cancer patients following primary treatment and negative or equivocal conventional imaging findings, FDG PET/CT allows assessment of the site and extent of the recurring disease with an accuracy of 83 %. Both FDG PET and FDG PET/CT are superior when compared to CT alone for the purpose of recurrence detection in patients suffering from ovarian carcinoma who have completed primary therapy but demonstrate a rising serum CA-125 level. As the global accuracy of CT alone for detection of recurrence of ovarian cancer approximates 80 %, CT scan should be performed upfront to identify the site of recurrence. When confronted with negative or equivocal CT findings, FDG PET alone or FDG PET/CT should be added. In patients with rising serum CEA levels that have undergone primary treatment for a colorectal carcinoma, both FDG PET and FDG PET/CTs allow detection of tumor recurrence with an accuracy of 95 %, well above that of CT and MRI. Available studies further suggest that FDG/PET findings will affect treatment management in 28–50 % of these patients. The detection rate of both ¹¹C-choline and ¹⁸F-choline PET and PET/CT for local, regional, and distant recurrence in prostate carcinoma patients with a biochemical recurrence increases with rising PSA value at the time of imaging and reaches about 75 % in patients with PSA [3 ng/mL. Furthermore, PET and PET/CT with [¹¹C]- and [¹⁸F]-choline derivatives may be helpful in the clinical setting for optimization of individualized treatment.

Keywords Serum tumor markers · PET/CT

V. Kruse (*) · V. Cocquyt
Division of Medical Oncology, Department of Internal
Medicine, University Hospital Ghent, De Pintelaan 185 B, 9000
Ghent, Belgium
e-mail: vibeke.kruse@uzgent.be

M. Borms
Department of Medical Oncology, AZ Groeninge, Kortrijk,
Belgium

A. Maes
Department of Nuclear Medicine, AZ Groeninge, Kortrijk,
Belgium

A. Maes
Department of Morphology and Medical Imaging, University
Hospital Leuven, Leuven, Belgium

C. Van de Wiele
Department of Nuclear Medicine and Radiology, University
Hospital Ghent, Ghent, Belgium

Introduction

Tumor markers are biochemical substances that are produced at a greater rate when compared to normal cells either through upregulation of genes or through activation of genes that are normally quiescent but become transcribed in cancer cells [1–5]. While some tumor markers remain intracellular, others may be exposed at the cell surface from where parts of their extracellular domain are shed into the bloodstream or directly secreted in their entirety into body fluids. The concentration of tumor markers that end up in serum may be quantitatively assessed using, e.g., radioimmunoassays or enzyme-linked immunosorbent assays. Because of their low prevalence in the general population as well as their non-specificity, serum tumor markers are of little use for cancer screening [6–8]. However, in patients with established malignancies

their serum dosage has proven especially useful for recurrence detection; a continuous progressive increase in circulating tumor markers often represents an early sign of tumor relapse. When confronted with a progressive increase in circulating tumor markers in previously treated cancer patients, conventional imaging (echography, CT and MRI) is usually performed to identify the location and extent of the recurring disease, information essential to customise treatment planning. However, conventional imaging has limitations in the accurate detection of recurrent disease because of difficulties associated with the reliable identification of small tumor deposits and the separation of normal tissue structures, e.g., bowel and non-malignant post-treatment tissue modifications, e.g., oedema and fibrosis from adjacent tumor tissue. Accordingly, rising tumor markers and negative or equivocal conventional imaging are a well-known management problem in daily clinical practice. Several studies have demonstrated that positron emission tomography (PET), a functional imaging technique exploiting biochemical differences between normal and malignant tissues for cancer imaging, is capable of detecting and localising tumor recurrence in patients who have an elevated tumor marker level and in whom conventional imaging has proven negative or equivocal.

Available literature on the added value of PET/CT imaging to serum tumor markers and conventional imaging for delineating tumor recurrences following primary curative treatment in patients suffering from breast-, ovarian-, colorectal- and prostate carcinoma is reviewed.

Breast cancer

Up to 30 % of breast cancer patients will develop a recurrence within 10 years of initial treatment, the characterization of which (location, isolated or multiple, bone or visceral etc.) is critical for the further therapeutic management of the patient [9, 10]. Breast cancer follow-up for the purpose of early detection of local or metastatic recurrence is predominantly based on clinical examination and bilateral mammography [10]. Though controversial, serum markers are also routinely used by many physicians for this purpose [11, 12]. The serum marker that is most strongly associated with local or metastatic recurrent disease in patients suffering from breast cancer is CA15-3. CA15-3 is derived from proteolytic shedding of the extracellular domain of the mucin 1 (MUC1) glycoprotein that is over-expressed on breast cancer cells [13, 14]. An increase in CA15-3 level is most commonly observed in hormone receptor positive breast cancer (HR+) whereas the incidence of CA15-3 elevation is lowest in the HER2-enriched type of disease [15–17]. In addition, elevation of CA15-3 proved more common and pronounced in breast

cancer with three or more metastatic sites, when compared to breast cancer with single metastasis and in patients with pleural metastasis at the time of diagnosis. Importantly, in asymptomatic patients that have undergone curative treatment for breast cancer, regular serum measurements of CA15-3 were shown to provide a lead-time of 2–9 months for the early detection of local or metastatic recurrent breast cancer [18, 19]. Accordingly, many centres world-wide perform serial CA15-3 measurements in the routine follow-up of these patients as for some women it provides the earliest evidence of recurrent disease, for which multiple forms of treatment are available, and intuitively it might be hoped that the earlier treatment is initiated, the better the outcome. Firm evidence demonstrating that early initiation of treatment based on this lead-time improves patient outcome or quality of life is lacking although a small number of papers do suggest a benefit in outcome adopting this approach [20–22].

As CA15-3 serum measurements lack specificity and progressive increases in their levels are not always related to recurrence nor do they predict the number and location of recurrent disease sites, imaging modalities that exclude or confirm tumor recurrence and accurately assess the extent of the recurrent disease are of major scientific interest [10]. Conventional morphological imaging often yields equivocal or negative findings when trying to identify sites of breast cancer recurrence. However, various studies originating from centres that perform serial CA15-3 measurements as part of routine surveillance in breast carcinoma patients have shown that FDG PET/CT imaging can complement information provided by morphological imaging techniques, increasing both sensitivity and specificity for recurrence detection of breast cancer [23–31]. These studies have been recently the subject of a meta-analysis. In this meta-analysis, including 13 studies, a pooled specificity and sensitivity of 69.3 and 87.8 %, respectively, for the detection of breast cancer recurrence was found using histology and long-term follow-up as gold standard [32]. Overall pooled accuracy was 83 %. FDG PET/CT imaging proved especially useful for assessing spread to axillary-, supraclavicular-, internal mammary- and mediastinal lymph nodes. The meta-analysis further indicated that FDG PET/CT proved similarly accurate for the detection of occult soft tissue local recurrences as well as for the detection of distant metastases in the presence of a progressive increase of serum tumor markers. Importantly, for CA15-3 driven prescription of FDG/PET/CT imaging, a CA15-3 cut-off level, either of a single value or of a percentage increase over time, allowing identification of those patients likely to present with FDG PET/CT positive findings would be of great clinical interest. However, while in breast cancer patients suspected to suffer from disease recurrence CA15-3 levels as well as increases

of CA15-3 levels over time have proven systematically higher in PET positive patients when compared to PET negative patients, no single cut-off value yielding an acceptable sensitivity and specificity has been identified for either variable [23–32]. Rather the combination of increases in CA15-3 over time and the clinical suspicion of progression should prompt clinicians to perform PET/CT imaging. Finally, limited available data further suggest that FDG PET/CT imaging performed in breast cancer patients with rising CA15-3 affects treatment management in up to 50 % of patients [25, 28–30, 32].

Ovarian cancer

Carcinoma of the ovary is the third most common tumor of the female genital tract after the cervix and endometrium and accounts for half of all deaths caused by these tumors [33]. Following effective primary therapy, 60–70 % of patients will relapse within 2 years following primary treatment [34]. While currently available salvage therapy does not seem to prolong survival, it is hoped that treatment with newly developed targeted drugs may eventually lead to prolonged remission and sustained quality of life. With this goal in mind, accurate, non-invasive detection of ovarian carcinoma recurrence is of clinical interest.

The reference method for the detection of ovarian carcinoma recurrences with a positive predictive value close to 100 % is CA-125 serum measurement [35, 36]. CA-125 is a high-molecular weight glycoprotein that is expressed at the cell-surface of epithelial cells from where it is actively secreted into the lumen and subsequently drained into the bloodstream [37, 38]. Immunohistochemical analyses have shown that 80 % of serous ovarian cancers will express CA-125, while fewer than 30 % of mucinous-, clear-cell-, and endometrioid cancers are positive for this surface antigen [39]. Recurrence as well as progression based on sequential CA-125 measurements has been defined as follows by the Gynaecologic Cancer Intergroup (GCI): evidence of a CA-125 concentration greater than, or equal to, two times the upper normal limit or nadir value on two occasions at least 1 week apart, respectively, in patients with normal post primary-treatment CA-125 values or patients with increased pre-treatment CA-125 concentrations [40]. When confronted with a significant increase in CA-125 measurement over time, usually a CT scan is performed to identify the site of recurrence. Based on a recent meta-analysis, the pooled sensitivity and specificity of CT for detection of recurrence of ovarian cancer are 79 and 84 % [41]. In case the CT scan shows new or progressive disease, early reintroduction of treatment follows. Of interest, in the same meta-analysis referred to above, the pooled sensitivity and specificity of FDG PET alone and

FDG PET/CT for detection of recurrence of ovarian cancer were respectively 88 and 89 % for PET alone versus 91 and 88 % for PET/CT. Accordingly, FDG PET either alone or in combination with CT might be a useful supplement in those patients that present with a significant increase in CA-125 levels but negative or equivocal CT findings. CT sensitivity is reported to be especially low for detection of peritoneal carcinosis and lymphatic metastases which is not so for FDG PET. In this regard, in a series by Murakami et al. including 90 patients, FDG PET had a sensitivity for the detection of intraperitoneal and retroperitoneal metastases of ovarian cancer of 93.9 and 92.9 %, respectively [42]. Furthermore, FDG PET imaging was able to detect metastases in normal-sized lymph nodes. Overall, FDG PET had an 87.5 % positive rate for recurrence detection in patients with an asymptomatic rise of CA-125 who had no sign of recurrence by conventional imaging methods.

Colorectal cancer

Following initial treatment of colorectal cancer, within the first 2 years of treatment approximately 30–40 % of patients will develop recurrent disease [43, 44]. As in some of these patients, cure is feasible, exact restaging is mandatory in order to achieve an optimal individualized treatment benefit [45, 46]. The most frequently used method to detect asymptomatic recurrences is serial blood monitoring of CEA, an oncofetal glycoprotein that is over-expressed in adenocarcinoma and especially in colorectal cancer. While both the sensitivity and specificity of this approach are low, respectively 59 and 84 %, in those patients who present with elevated CEA levels after surgery, it is estimated that tumor has recurred in approximately 90 % [47]. Given the confirmed reduction in mortality associated with an intensive surveillance by means of sequential CEA measurements post-primary treatment of colorectal carcinoma, the revised American Society of Clinical Oncology guidelines on the use of tumor markers advocate three monthly measurements of CEA in patients with stage II or III disease for at least 3 years after surgery for primary CRC, provided the patient is candidate for surgery or systemic therapy [48].

When confronted with an elevated CEA level following surgery for a primary colorectal carcinoma, identification of the site of recurrence is essential for treatment planning. For this purpose, CT has both a low sensitivity and specificity [49]. While MRI performs better in differentiating local recurrence from scar tissue when compared to CT, limitations still exist in terms of specificity and in the size of tumor detectability [50]. As opposed to morphological imaging, FDG PET has proven to be a valuable imaging tool in patients who have rising CEA levels after colorectal surgery. In a meta-analysis by Huebner et al. [51],

performed on 11 series, dating from 2000, an overall sensitivity of 97 % and specificity of 76 % was reported for FDG PET detection of colorectal cancer recurrence. In these studies, stand-alone PET machines were used. When using PET/CT machines, lesion characterization in the CT portion of a PET/CT study increases the specificity of PET/CT reporting, especially for lesions with moderate and marked FDG uptake. Accordingly, using combined FDG PET/CT imaging for the purpose of tumor recurrence detection in CRC patients with rising CEA levels, specificity proved significantly better when compared to stand-alone FDG PET imaging with reported figures varying from 92 to 96 % as evidenced by a more recent meta-analysis [49]. Overall, PET/CT allows detection of tumor recurrence in CRC patients with rising CEA levels with an overall sensitivity and specificity of 95 %. Finally, available studies suggest that FDG/PET findings affect treatment management in 28–50 % of these patients [52, 53].

Prostate carcinoma

One out of every ten men will become affected by prostate carcinoma during his lifetime. Treatment options with curative intent for localized prostate cancer include prostatectomy, brachytherapy, and external beam radiation therapy [54]. While many patients will be cured with definitive local therapy, approximately 15–40 % of men will experience a recurrence within 10 years from the primary treatment. Salvage therapeutic options following radical prostatectomy or radiotherapy for patients with local relapse of prostate cancer include radical prostatectomy, radiotherapy, brachytherapy or cryotherapy, whereas for distant relapse, hormone/chemotherapy is available [55]. The mainstay for the detection of prostate carcinoma recurrence following “first-line” treatment with curative intent is regular monitoring of serum PSA (prostate specific antigen), a protein normally made in the prostate gland in ductal cells that helps to keep the semen liquid. PSA threshold levels suggesting recurrence depend on the initial primary treatment [56, 57]. According to the American Urological Association guidelines, a PSA recurrence after radical prostatectomy is defined as having a PSA level greater than 0.2 ng/mL and rising [58]. Following primary radiotherapy for prostate carcinoma, according to guidelines set by the American Society for Therapeutic Radiology and Oncology, a rise of 2 ng/mL above the nadir PSA value reached following treatment is considered to be a biochemical recurrence [59]. When confronted with a PSA-relapse, most often CT, MRI and/or bone scintigraphy are performed in order to detect the site (local failure or distant failure) and determine the extent of the recurrence in order to establish a correct and tailored therapeutic strategy.

Unfortunately, neither of these imaging modalities has proven useful when PSA values are lower than 5 ng/mL and PSA doubling time is greater than 10 months. Furthermore, even at more pronounced mean PSA levels of on average 20 ng/mL, this approach has proven suboptimal, resulting in a large number of negative or inconclusive investigations leaving the sites of local and distant recurrence, mainly lymph-nodes or bone lesions, undetected [60, 61]. Accordingly, the attention of several authors has been directed towards functional imaging techniques, including PET/CT imaging using [(11)C]- and [(18)F]-labeled choline derivatives; FDG PET–CT is not suitable for diagnosing prostate cancer in general because of the generally low glycolysis of prostate cancer cells [62, 63]. Choline, as a component of phospholipids, makes up the cell membrane. Prostate carcinoma and other malignancies, display an increased uptake of choline when compared to normal tissue as a result of an increased demand as well as alterations in uptake and retention [63]. When labeled with 11C and 18F, the resulting radiopharmaceuticals, respectively ¹¹C-choline and ¹⁸F-choline, may be used for imaging prostate carcinoma using PET/CT.

The diagnostic value of PET- and PET/CT with [¹¹C]- and [¹⁸F]-labeled choline derivatives for detection of the site of recurrence as well as of its extent when confronted with a biochemical recurrence of prostate cancer has been assessed by several authors.

¹¹C-choline PET/CT

Krause et al. [64] performed ¹¹C-choline PET/CT in a series of 63 prostate carcinoma patients presenting with a biochemical relapse after primary treatment with a mean PSA value of 5.9 ng/mL. The recurrence detection rate was 36 % for a PSA value <1 ng/mL, 43 % for a PSA value 1 to <2 ng/mL, 62 % for a PSA value 2 to <3 ng/mL and 73 % for a PSA value ≥ 3 ng/mL. The overall detection rate for PET was 59 %. A similar relationship between PSA levels and ¹¹C-choline PET/CT positivity was put to evidence by Rinnab et al. [65] in a series of 50 patients. Castellucci et al. [66] studied the relationship between ¹¹C-choline PET/CT detection rate and other PSA derivatives in particular PSA kinetics (PSA velocity, PSA vel; PSA doubling time, PSA_{dt}) in a series of 190 prostate carcinoma patients following radical prostatectomy (RP) who presented with a biochemical recurrence (mean 4.2 ng/mL; median 2.1 ng/mL). Their study put to evidence an overall detection rate of 38.9 %. PSA values, PSA_{dt} and PSA vel values proved statistically significantly different in patients with PET-positive findings when compared to patients with PET-negative findings. The authors concluded that PSA kinetics should be taken into consideration prior to performing a ¹¹C-choline PET/CT in

patients with biochemical failure. The authors also assessed whether ^{11}C -choline PET/CT was useful for recurrence detection in a series of 102 patients with PSA values <1.5 ng/mL early after biochemical recurrence [67]. ^{11}C -choline PET/CT proved positive in 29 (28 %) patients, the majority of which had a short PSAdt (mean PSAdt in PET-positive patients was 4.34 months versus 13.30 months in PET-negative patients ($p = 0.0001$)). Similar findings were reported by Giovacchini et al. [68] in a retrospective series of 170 patients studied with ^{11}C -choline PET/CT that had undergone radical prostatectomy and subsequently presented with a biochemical failure. The study showed an overall detection rate of 44 % and high PSA values as well as short PSAdt proved the only significant predictors of a positive ^{11}C -choline PET/CT scan following multivariate analysis. Using criteria based on histological analysis, clinical follow-up and imaging data and binary logistic analysis in a series of 358 patients referred for ^{11}C -choline PET/CT that had previously undergone radical prostatectomy and presented with a biochemical failure, the same authors also showed that in addition to PSA levels, advanced pathological stage, previous biochemical failure and older age portend an increased risk of positive ^{11}C -choline PET/CT findings [69]. In a series of 42 patients Rybalov et al. [70] further showed that ^{11}C -choline PET/CT proved feasible for detection of intra-prostatic recurrent prostate carcinoma following external beam radiation therapy, the concordance with routine trans-rectal prostate biopsies was moderate and the accuracy too low for routine clinical use. Finally, in a series of 37 patients by Souvatzoglou et al. [71], that were referred to salvage radiotherapy following radical prostatectomy, ^{11}C -choline PET/CT detected abnormalities in 13 % of patients outside the prostatic fossa thereby affecting the extent of the planning target volume.

^{18}F -choline PET/CT

Schillaci et al. [72] performed ^{18}F -choline PET/CT in 49 patients with rising PSA (mean 4.13 ng/mL). Results obtained were related to the initial PSA level. ^{18}F -choline PET/CT detected relapse in 33 patients. The detection rates were, respectively, 20, 55, 80 and 87 % in the PSA groups ≤ 1 , 1 to ≤ 2 , 2 to ≤ 4 and > 4 ng/mL, respectively. ^{18}F -choline PET/CT proved positive in 21/25 patients with PSAdt ≤ 6 months and in 12/24 patients with PSAdt ≥ 6 months. Of interest, CT proved useful for detecting bone metastases that were not ^{18}F -choline avid. Comparable results were obtained by Pelosi et al. and Graute et al. [73, 74]. In a series by Pelosi et al. [73], including 56 patients with increased serum PSA levels after radical prostatectomy using different PSA sub-classifications, respectively ≤ 1 , 1 to ≤ 5 and > 5 ng/mL. The sensitivity for

recurrence detection of ^{18}F -choline PET/CT in these three different subgroups was 20, 44 and 80 %, respectively. Graute et al. [74] studied 82 patients in the same clinical setting. PSA levels measured at the time of imaging were correlated with ^{18}F -choline PET/CT detection rates in the entire group, with PSA velocity in 48 patients, with PSA doubling time in 47 patients and with PSA progression in 29 patients. Overall detection rate was 62 % (51/82 patients) with an optimal PSA threshold of 1.74 ng/mL based on ROC curve analysis (82 % sensitivity and 72 % specificity). Median PSA velocity and PSA progression proved significantly higher in PET-positive patients when compared to PET-negative patients. Finally, Soyka et al. [75] studied the impact of ^{18}F -choline PET/CT on the therapeutic strategy in 156 patients with recurrent prostate carcinoma. In their series, ^{18}F -choline PET/CT resulted in a switch from palliative treatment to treatment with curative intent in 33 patients, from treatment with curative intent to palliative treatment in 15 patients, from one curative strategy to another in 8 patients and from one palliative strategy to another in 2 patients. Furthermore, the treatment plan was adapted in another 17 patients resulting in an overall modification of therapeutic strategy of 75 patients (48 %).

Discussion

While serial measurements of CA15-3 allow the preclinical detection of recurrent breast carcinoma with a lead-time of 2–9 months, large randomized trials showing that early treatment based on this lead-time improves disease-free survival, overall survival or quality of life for patients are currently lacking. Nevertheless, many clinicians worldwide perform serial measurements of CA15-3 in the surveillance of breast carcinoma patients given it might be intuitively expected that earlier treatment improves outcome and given a number of smaller studies suggest that early treatment based exclusively on increasing marker concentrations does indeed improve prognosis. Data on FDG PET/CT imaging originating from centers that perform routine CA15-3 surveillance in breast carcinoma patients illustrate that when confronted with a suspicious rise in CA15-3 in asymptomatic breast cancer patients following primary treatment and negative or equivocal conventional imaging findings, FDG PET/CT allows assessment of the site and extent of the recurring disease with an accuracy of 83 %. Furthermore, in these patients FDG PET/CT imaging proved equally sensitivity and specific for the detection and assessment of loco-regional and distant recurrence. Given its superior accuracy when compared to conventional imaging modalities, FDG PET/CT imaging should enable a more accurate adjustment of treatment planning in these

patients; limited available data suggest FDG PET/CT imaging affects treatment management in 36–56 % of patients. Whether the modification in treatment planning induced by FDG/PET CT treatment in these patients also affects their survival and quality of life should be the subject of well-designed prospective studies. Of interest, in a study by Champion et al., it was suggested that sensitivity of FDG PET/CT imaging might be negatively influenced by adjuvant endocrine therapy; 9 patients receiving adjuvant endocrine therapy at the time of their first scan had a second exam performed after treatment withdrawal, which then switched to a positive result, while the patients remained asymptomatic. As such, it might be useful to interrupt endocrine therapy when considering FDG PET/CT imaging for the purpose of recurrence detection. This finding warrants further exploration by future studies as it may lead to an increase in diagnostic accuracy of FDG PET/CT imaging for recurrence detection in breast cancer patients. Both FDG and FDG PET/CT are superior (with less inter-observer variability) when compared to CT alone for the purpose of recurrence detection in patients suffering from ovarian carcinoma who have completed primary therapy but demonstrate a rising serum CA-125 level; although in a number of patients peritoneal deposits may be missed by FDG PET/CT. FDG PET has shown a high sensitivity for detecting intraperitoneal and retroperitoneal metastases (93.9 and 92.9 %, respectively) (Murakami et al.). However, as the global accuracy of CT alone for detection of recurrence of ovarian cancer approximates 80 %, CT scan should be performed upfront to identify the site of recurrence. When confronted with negative or equivocal CT findings, FDG PET alone or FDG PET/CT should be added.

In patients with rising serum CEA levels that have undergone primary treatment for a colorectal carcinoma, both FDG PET and FDG PET/CT were shown to allow detection of tumor recurrence with an accuracy of 95 %, well above that of other imaging modalities, e.g., CT and MRI. As such, in many centres worldwide it has become the image modality of choice for this indication. Available studies further suggest that FDG/PET findings will affect treatment management in 28–50 % of these patients.

The detection rate of both ^{11}C -choline and ^{18}F -choline PET and PET/CT for local, regional, and distant recurrence in prostate carcinoma patients with a biochemical recurrence increases with rising PSA value at the time of imaging and reaches about 75 % in patients with PSA >3 ng/mL. Even at PSA values below 1 ng/mL, tumor recurrence can be diagnosed with choline PET/CT in approximately one-third of the patients. Furthermore, PET and PET/CT with [^{11}C]- and [^{18}F]-choline derivatives may be helpful in the clinical setting for optimization of

individualized treatment: an early diagnosis of recurrence is crucial to the choice of optimal treatment.

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