

Tumour Markers and Molecular Imaging with FDG PET/CT in Breast Cancer: Their Combination for Improving the Prediction of Disease Relapse

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1. Introduction

The aims of this chapter are to describe:

1. the actual role of tumour markers in the follow-up for breast cancer;
2. the use of tumour markers as an indicator of positron emission tomography (PET) execution and as a predictor of PET positivity;
3. the diagnostic accuracy of tumour markers, PET or PET/computed tomography (CT), and their combination;
4. the clinical and therapeutic impacts of tumour markers and nuclear medicine imaging;
5. the future prospective for breast cancer follow-up.

In this chapter we will bring together various reports on these subjects, and propose the use of tumour markers as a guide for the use of PET/CT, in particular to define the risk categories for breast cancer patients and the correct algorithm for follow-up.

2. Background

The definition of tumour markers is extremely broad, as tumour cells may express certain molecules at different rates from normal cells. These substances are released into the blood stream or other biological fluids. It would be justified to assert that biochemical measurement of the serum marker level in patients with a cancer diagnosis can give dynamic information about the clinical evolution of neoplastic processes and reflect the biological rather than the structural behaviour of the tumour. Even though their use in the follow-up of cancer patients has the advantages of being simple, objective, reproducible and cost-effective, the main problem is the lack of both sensitivity and specificity. In fact, the optimal tumour markers should only increase in the presence of a tumour and in the early phases of tumour growth, but none of the tumour markers currently available completely meet these requirements.

2.1 The role of serum markers in the management of patients with breast cancer

In breast cancer, the role of serum markers has remained unclear. Their potential uses in breast cancer include early diagnosis, determination of the prognosis, prediction of response or resistance to specific therapies, monitoring of the treatment in patients with metastatic disease and follow-up after primary treatment. Cancer antigen 15.3 (CA 15.3) and CA 27.29 are well-characterized assays that allow the detection of circulating MUC-1 antigen in peripheral blood. Carcinoembryogenic antigen (CEA) levels are less commonly elevated than the levels of MUC-1 assays, CA 27.29 or CA 15.3. Only 50% - 60% of patients with metastatic disease will have elevated CEA levels (sensitivity varies from 30 - 70% for visceral and skeletal metastases, with a positive predictive value ranging from 18% - 26%, respectively) compared to 75% - 90% who have elevated levels of the MUC-1 antigens. For this reason CA 15.3 is considered to be more specific than CEA in monitoring breast cancer evolution, and this latter marker is usually considered a poor predictor of breast cancer recurrence.

Unfortunately, aspecific elevation of both CEA and CA 15.3 can also be found in patients with inflammatory disease (e.g. diverticulitis, bronchitis), autoimmune disease (e.g. sarcoidosis) and other benign diseases (e.g. hepatitis, cirrhosis, hypothyroidism) in the presence of lung, gastrointestinal or neuroendocrine tumours, as well as in smokers and the elderly (Lumachi et al., 2004; Duffy et al., 2006).

Many attempts have been made in the past to provide evidence of the ability of CA 15.3 elevation at diagnosis to predict shorter survival rates, both disease-free and overall, but results are conflicting, and statistical significance was often lost at multivariate analysis. CA 15.3 is not therefore an independent prognostic factor in predicting the risk of recurrence, and it has no clinical value in the early detection of local recurrence or second cancer, due to low sensitivity in the presence of localized disease. The importance of detecting locally-recurrent breast cancer at an early stage arises from the fact that an increasing rate of distant metastases and a poor outcome are usually associated with local failure in breast cancer therapy (Fortin et al., 2006).

2.2 Monitoring response to treatment in breast cancer

Traditionally, the response to systemic treatment in patients with metastatic breast cancer is evaluated using criteria from the International Union Against Cancer (UICC). The UICC criteria includes physical examination, measurement of lesions, radiology and isotope scanning (Hayward et al., 1977). Two multi-centre trials, however, have shown that changes in serial concentrations of tumour markers correlate with therapy response based on the UICC criteria (Robertson et al., 1999; Van Dalen et al., 2004). Tampellini et al. (Tampellini et al., 2006) performed a large single institution study with the aim of measuring serum CA 15.3 at baseline, and at three and six months during anthracycline-based first-line chemotherapy in 526 patients with advanced breast cancer who had been prospectively enrolled in five phase II-III trials. A significant relationship between changes in CA 15.3 level and clinical response was found; and at multivariate analysis, CA 15.3 variation at six months was found to be an independent prognostic indicator for time to progression and overall survival. The early detection of disease progression and of resistance to ongoing treatment is considered an important issue in metastatic patients, because the target of therapy in this patient subset is the

palliation. Therefore, tolerability and quality of life are fundamental in therapeutic decisions, and should be balanced against potential gains in disease regression and global survival. A lead time of 1-10 months has been reported when the assessment of treatment response, according to the UICC criteria, was made using blood markers. This finding can be explained by the fact that the international criteria reflect structural change: a metastasis needs to reach a significant size to be detectable by radiological exams; otherwise, blood tumour markers reflect the total tumour burden which is measurable from the summation of numerous sub-clinical metastases (Cheug et al., 2000). Tumour markers can give important information concerning the response of cancer to ongoing treatment, even if they cannot be used alone for monitoring therapy in patients with advanced breast cancer. An increase of tumour markers can be detected even when the tumour has been responding to treatment; this phenomenon is known as a "tumour marker spike" (Yasasever et al., 1997; Hayes et al., 1988) and represents a transient increase in serum CA 15.3 levels following the initiation of effective therapy for metastatic disease. The peak usually occurs 15-30 days after the initiation of treatment, although spikes may last as long as 90 days. The return to a normal value, or to below baseline level, is consistent with response to therapy.

Although the studies available show encouraging data, the American Society of Clinical Oncology (ASCO) panel stated that CA 15.3 and CEA alone cannot be employed to define response to treatment (Harris L et al., 2007). Conversely, both the European Group on Tumour Markers (EGTM) and the National Academy of Clinical Biochemistry (NACB) panels recommend the use of CA 15.3 for monitoring therapy in patients with metastatic breast cancer (Molina et al., 2005; Fleisher et al., 2002).

2.3 Tumour markers and surveillance after primary treatment

In breast cancer, not only the use of serum markers, but also the follow-up in general, is not generally established. Two multi-centre randomized prospective trials (The GIVIO Investigators, 1994 and Rosselli et al. 1994), and a systematic review (Collins et al., 2004), compared the outcome in patients followed with clinical visits and mammography, with those followed up with an intensive regime including radiology and traditional laboratory testing. All reports concluded that the use of an intensive follow-up programme failed to improve either the outcome or quality of life. However, in these studies, some limitations with respect to management of patients with breast cancer are reported: 1) the use of old and insensitive biochemical tests and/or radiological exams, and 2) the unavailability of new treatments such as taxanes, aromatase inhibitors and trastuzumab for recurrence treatment (Duffy et al., 2006). The current ASCO guidelines recommend only careful history taking, physical examination and a regular mammography for appropriate detection of breast cancer recurrence (Khatcheressian et al., 2006). The purpose of an intensive follow-up with radiological exams and serial tumour markers determination is the early detection of recurrent or metastatic disease, which can enhance the chances of appropriate treatment and survival. Although serial CA 15.3 concentrations can anticipate the diagnosis of recurrent/metastatic disease with a lead time of between 2 - 9 months (Safi et al., 1989; Colomer et al., 1989; Nicolini et al., 1991; Repetto et al., 1993; al-Jarallah et al., 1993; Sölétormos et al., 1993), it is unclear whether the introduction of early treatment based on this lead time actually improves disease-free survival, overall survival, or quality of life for patients. In an attempt to address these issues, several small-scale studies have been carried out. In one of the first of these, Jager et al. (Jager et al.,

1995) randomized patients who had no evidence of metastatic disease, with increasing concentrations of tumour markers (CA 15-3 or CEA) to receive (n = 21) or not receive (n = 26) medroxyprogesterone acetate, reporting that for the untreated patients, the median time interval between increase in marker concentration and detectable metastasis was four months, while for the treated patients it was >36 months. Kovner et al. (Kovner et al., 1994) randomized asymptomatic patients with increasing mammary cancer antigen concentrations to receive (n = 23) or not receive tamoxifen (n = 26). After an average follow-up of 11 months, 7 out of 29 patients (24%) in the control group had relapsed, whereas none of the 23 patients who had received treatment developed a recurrence (p= 0.012). Nicolini et al. (Nicolini et al., 1997; 2004) compared the outcomes in 36 asymptomatic patients who received salvage treatment based on tumour marker increases (CA 15-3, CEA, or TPA) with 32 patients who were given treatment only after radiologic confirmation of metastasis. Survival from both the time of mastectomy and salvage treatment was significantly improved in the group with tumour marker-guided treatment than in those treated conservatively. These studies suggested that an early treatment of recurrent or metastatic disease based exclusively on an increase of tumour markers can improve the outcome, but the numbers of patients in the studies are too small to recommend this approach. In fact, the ASCO (Harris et al. 2007), the European Society of Clinical Oncology (Kataja et al., 2009) and the National Comprehensive Cancer Network (NCCN 2010) do not recommend their use. Furthermore, in some studies the value of tumour markers resulted positive in two thirds of patients with a recurrence of disease, while for the remaining third it either did not become positive or became positive late, thus showing both low sensitivity and positive predictive value (PPV) (Duffy et al., 2006; Anonymous et al., 1996). Therefore, in patients suspected of having a breast cancer relapse, low levels of markers do not exclude the presence of malignancy; whereas, high levels of markers almost certainly indicate the presence of metastatic disease (Soletormos et al., 2004; Given et al., 2000).

Sutterlin et al. (Sutterlin et al., 1999) evaluated 1228 serum samples from 664 women with a history of breast cancer, with accuracy and predictive values of CEA and CA 15.3. Seventy-six of the 664 women had had a relapse; the diagnostic accuracies of CEA and CA 15.3 were 83% and 88%, with a PPV of 27% and 47% and a negative predictive value (NPV) of 91% and 93%, respectively. The low PPV and sensitivity of CEA and CA 15.3 clearly limit their clinical utility. The effectiveness of routine determinations during the follow-up seems questionable, and the choice of the best marker is also unclear. Given et al. compared the diagnostic accuracy of CA 15.3, CEA and tissue polypeptide antigen (TPS) in the detection of breast cancer recurrences in 1448 patients (Given M et al., 2000). The results are summarized in **Table 1**:

	Sensitivity			Specificity			PPV			NPV		
	Vis	Bone	Loc	Vis	Bone	Loc	Vis	Bone	Loc	Vis	Bone	Loc
CA 15.3	68%	69%	23%	92%	92%	86%	47%	54%	22%	94%	96%	86%
TPS	64%	51%	17%	88%	88%	79%	25%	21%	16%	91%	93%	78%
CEA	27%	46%	11%	92%	92%	76%	18%	26%	13%	90%	92%	84%

Vis: visceral recurrence; Bone: bone recurrence; Loc: loco-regional recurrence; PPV: positive predictive value; NPV: negative predictive value

Table 1. A summary of results based on lesion sites

As shown in **Table 1**, the role of CA 15.3 as the tumour marker remains the better choice as it is useful as a predictor of recurrence in breast cancer, although it has low sensitivity and PPV for loco-regional recurrence, and neither TPS nor CEA complemented its sensitivity or PPV. In conclusion, even if expert panels have different positions on the matter, the actual main utility of CEA and CA 15.3 is in monitoring patients with advanced breast cancer, especially in women with non-valuable disease. Insufficient data has been published to suggest that the use of tumour markers during follow-up can change the course of breast cancer patients. Prospective randomized trials are needed to answer this question definitively.

3. Why is PET associated with tumour markers?

Multiple metastatic disease and a large tumour burden correlate with high marker values (Bast et al., 2001; Berruti et al., 1994). Metastatic disease, especially in the liver, bones and lungs, and metastatic pleural effusions, can give rise to pathological CA 15.3 values (Tampellini et al., 1997). Imaging modalities are important not only for seeing tumour lesions in the case of cancer, but also in evaluating the size of the tumour for staging and restaging assessment, in monitoring the therapy responses, and during follow-up (Ugrinska et al., 2002). The link between imaging and CA 15.3 can be found in the report by Tampellini et al. (Tampellini et al., 1997). The authors demonstrate that the supranormal value of CA 15.3 was positive more frequently in patients with liver metastases (74.6%), pleural effusion (75.7%), and oestrogen receptor (ER)-positive tumours, and in patients with a larger extent of the disease than in patient subgroups with recurrence in the bones (65%), lungs (61.8%) or soft tissue (47.1%). At multivariable logistic regression, the pleural effusion, ER status and disease extent were confirmed as independent variables in determining CA 15.3 positivity. Considering overall survival as the end-point, the multivariable survival analysis calculated with the COX regression model showed that ER status, disease extent and liver metastases were independent variables, and when the disease extent variable was removed, the CA 15.3 values became an independent variable associated with poor prognosis (Tampellini et al., 1997). Thus the extent of the disease represents a marker of poor prognosis, and the use of an imaging tool allows it to be assessed; however if this is not possible, tumour marker values can be used. An asymptomatic patient with elevated tumour markers is quite common in daily practice. Elevated tumour marker levels (both CEA and CA 15.3) are associated with an increased risk of recurrence (Nakamura et al., 2005), but localization of metastases or recurrent disease remains a challenge, which often requires an extensive diagnostic workup. The management of cancer patients has improved in the last few decades with the introduction of 18F-FDG PET (Zangheri et al., 2004). Tumour cells have an increased metabolism of glucose (Warburg et al. 1931), which has been shown to be true for breast cancer cells (Adler et al., 1993; Wahl et al., 1991; Nieweg et al., 1993; Avril et al., 2001). Glucose metabolism can be imaged by metabolic diagnostic modality, such as FDG PET. The imaging tool permits a complete tumour staging with a single whole-body investigation, even allowing the diagnosis of a significant number of metastases, which would be missed or incorrectly diagnosed by computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy. This indicates that a whole-body PET can be fundamental in the search for metastasis, especially when recurrences are suspected due to a progressive increase in circulating tumour markers (Hoh et al., 1999). Circulating tumour markers are biochemical products of the same alterations imaged by nuclear medicine (such as the

overexpression and production of tumour-associated antigens on the membrane surface and in the bloodstream), or, alternatively, resulting from completely different pathways.

Recent data suggests that FDG PET is a useful technique for detecting recurrent breast cancer suspected on the basis of an asymptotically elevated tumour marker level and negative conventional imaging results (Siggenkolw et al., 2004; Liu et al., 2002). In the last few years, PET/CT, as an integrated instrument for the evaluation of suspected disease relapse for various tumours (e.g. lymphomas), has become routinely used, showing to be superior to PET alone in re-staging the disease in patients who have been previously treated, particularly when the only indicator of recurrence is a rise in serum tumour markers (such as CA 15.3) (Suarez et al., 2002; Flamen et al., 2001). At present, as described by Siggelkow et al. (Siggelkow et al., 2004), PET should only be performed in cases where tumour marker is increasing and conventional imaging is unclear. In **Figure 1** are shown two examples of PET and PET/CT scan in breast cancer patients.

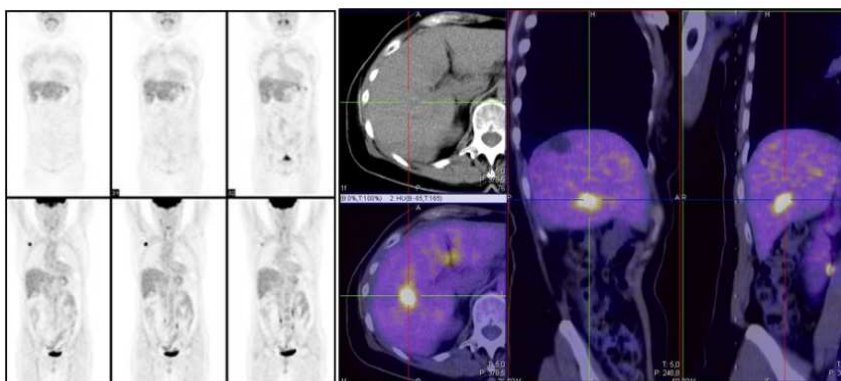


Fig. 1. Left: coronal images of PET scan. Right: PET/CT images on the three planes (transverse, sagittal and coronal)

4. A summary of articles concerning PET and PET/CT in patients with rising tumour markers

Elevated levels of tumour markers are frequently registered in the follow-up of breast cancer patients. This presents a diagnostic challenge, often requiring some conventional diagnostic tests to localize the metastases or recurrent disease. Cases of asymptomatic patients with elevated tumour marker levels have demonstrated a high rate of false-negatives with conventional morphological imaging modalities (Haug et al., 2007). In a review by Lamy et al. (Lamy et al., 2005), the authors summarized the results of a set of some studies in colorectal, breast and ovarian cancer. They stressed that one of the major indications of tumour marker is the detection of occult disease; less than 20% of tumour marker elevations are associated with clinical and radiological findings. Such elevations have led the medical community to doubt the value of tumour marker-based follow-up, such as CA 15.3 in breast cancer. PET with FDG using metabolic parameters of malignant cells allows tumour recurrences to be seen at the early stages of development, before any morphologic changes can be seen by radiological examinations. The authors underlined

that, given the early positives they find, and that they are non-invasive and cost-effective, tumour markers have become an invaluable guide to the prescription of 18F-FDG PET in oncology, giving a 'map' of widespread disease. Suarez et al (Suarez et al., 2002) reported that values of CA 15.3 above 60 UI/ml were always associated with positive PET results and values below 50 UI/ml were accompanied by negative PET results. In the interval from 50 to 60 UI/ml the PET could be either positive or negative. Symptomatic patients, or those with suspected disease relapse, despite negative markers or both negative markers and CT, can nevertheless present with disease recurrence. Some authors have proposed that whole-body PET may become the method of choice for the assessment of asymptomatic patients with elevated tumour marker levels (Ugrinska et al., 2002; Siggelkow et al., 2004; Trampal et al., 2000). Shen et al. (Shen et al., 2003) screened 1283 patients who underwent whole-body FDG PET studies with the additional help of the serum levels of tumour markers. The final diagnoses were obtained by other imaging modalities of pathological findings. The authors concluded that the whole-body FDG PET, with the additional help of tumour markers, could reduce false negative and false positive results of FDG PET in all types of cancer.

In detail, we will consider an accurate description of various reports published concerning the employment of PET or PET/CT in the detection of breast cancer recurrence based on tumour marker levels, making some observations.

4.1 Tumour markers and PET alone

Lonneaux et al. (Lonneaux et al., 2000) were the first authors to evaluate the place of whole-body FDG PET in women presenting symptoms of recurrence, with a special focus on patients with an isolated increase in tumour markers. They studied 39 patients, 34 of whom were selected due to their increase in tumour markers. They found an overall sensitivity of 94%, specificity of 50%, NPV of 60%, PPV of 91% and accuracy of 87%. The high accuracy was related to the discovery of recurrence in 37 out of 39 patients (two false negative diseases were due to lymphedema of the arm and carcinomatosis that developed after some months). They demonstrated that FDG PET is useful in the evaluation of women suspected of a distant recurrence of breast cancer. PET allows for an earlier diagnosis of recurrence, which can lead to earlier therapy. As far as patient management is concerned, their results suggest that, as it is a non-invasive and highly sensitive imaging procedure, whole-body PET FDG should be performed as first line imaging when a recurrence of breast cancer is suspected on the basis of clinical symptoms or biological signs. In the second place, and only when patient management could be affected, dedicated and oriented CT or MRI could confirm precisely the anatomical localization of the sites with increased FDG uptake. Indeed there is no need for additional imaging procedures if PET shows disseminated bone disease or multiple lymph node metastases. On the contrary, the cases of equivocal PET findings should be checked by appropriate procedures.

Trampal et al. (Trampal et al., 2000) studied 72 patients with different types of cancer, 23 of whom had breast cancer. FDG PET detected lesions in 85% of the patients, and at the end of the study this was confirmed for 33 of the patients. PET sensitivity and specificity were 96.4% and 75.6%, respectively. They concluded that PET was an accurate tool in the diagnosis of recurrent tumoural disease in patients with rising tumour marker levels and negative conventional imaging, which could change the form of therapeutic management.

Pecking et al. (Pecking et al., 2000) reported that 1) blood tumour marker are widely used in the follow-up of patients treated for a malignant tumour and 2) in many cases where the tumour associated marker increases, the clinical and radiological evaluations remain normal. FDG PET and CT-scan have proven to be powerful tools in oncology, and their use in such situations may give a new appraisal on the development of the disease. They tested 70 patients with isolated increasing in tumour markers (CEA, CA 19.9, CA 15.3, CA 125). Focusing on breast cancer and CA 15.3, as well as ovarian cancers and CA 125, the sensitivity and predictive value reached 100%. Patients exhibiting a tumour target associated with an increase in blood tumour markers can be treated earlier with dedicated protocols. They concluded that where occult metastasis is detected by blood marker measurements, the tumour volume is smaller than when the patient presents overt symptoms; the treatment should therefore be more effective, and the use of imaging is advised. The same authors, after one year, (Pecking et al., 2001) evaluated the efficacy of PET in clinically disease-free breast cancer patients in whom occult disease was suspected on the basis of increased blood tumour markers. They studied 132 patients who had received a totally negative follow-up evaluation, but who had a persistent increase in blood CA 15.3 confirmed by serial measurements. The confirmation of disease relapse was given by fine needle biopsy or surgical biopsy no later than two months later, or by imaging follow-up performed 6-12 months later. Ninety-two out of 119 eligible patients had a recurrence of disease after two months, while 102 out of 119 had a recurrence after 12 months, thus the sensitivity of PET/CT was 92.9% and 93.6%, respectively. The increase between the early and delayed recurrence of disease was more evident for specificity and PPV (30 vs. 60% and 86.8 vs. 96.2%) than accuracy (83.2 vs. 90.7%) and NPV (46.1 vs. 46.1%). Moreover, PPVs of PET increased with the serum CA 15.3 levels (diagnostic accuracy after 12 mo. was CA 15.3 <30 and ≤ 50 U/ml = 84.0% vs. serum CA 15.3 > 75 U/ml = 90.3%). They concluded that when rising serum CA 15.3 is confirmed, positive FDG imaging can be significantly associated with recurrence, becoming significantly associated to recurrence or metastatic disease within one year ($p=0.036$ for 12 mo. vs. 0.046 for 2 mo.). Moreover, they suggested designing new therapeutic protocols based on positive FDG imaging in disease-free patients with an elevated serum CA 15.3 marker.

Spanish authors (Suarez et al., 2002) retrospectively studied 45 women with a histological diagnosis of breast cancer who had undergone a tumour marker-guided whole-body FDG PET. All patients were in remission, and without any other clinical symptoms or instrumental signs of relapse, except for the progressive elevation of CA 15.3 and/or CEA, tested during follow-up. FDG PET was obtained in 38 out of 45 patients, with 24 true-positives and 3 false positives. In total, 54 sites of FDG accumulation were revealed and 48 out of 54 patients were confirmed as metastases. The performances of tumour marker-guided FDG PET per patient were as follows: sensitivity = 92%, specificity = 78%, PPV = 89%, NPV = 82%, accuracy = 89%. They concluded that tumour marker-guided PET in the follow-up of breast cancer patients is of clinical utility. PET/CT was also able to identify three new neoplasms (ovary, contralateral breast and endometrium cancers). The inclusion of PET in the diagnostic algorithm allowed the clinical management to be modified (the change was shown in 24 out of 38 patients, or 63%) in those patients in whom a tumour relapse or unexpected primary neoplasm was discovered. It should be noted that tumour marker-guided PET led oncologists to adequate therapeutic decisions - performing different treatments - when three unknown primary cancers were detected.

Liu et al. (Liu et al., 2002) studied 30 patients with recurrent breast cancer after primary treatment. They evaluated both CA 15.3 and CEA, dosing the same day as FDG PET. They used the threshold of 32 UI/mL and 5 UI/mL respectively for CA 15.3 and CEA, useful to address PET. Employing this cut-off value, they found that PET had a high sensitivity and specificity (96 and 90%, respectively), identifying the presence of disease in 25 out of 28 recurrent patients, with only one false-negative result and two false positives. Their conclusion was that FDG PET is a useful technique for detecting recurrent breast cancer suspected from asymptotically elevated tumour marker levels and negative or equivocal other imaging modality results.

Galloswitch et al. (Gallonswitch et al., 2003) studied 62 patients with breast cancer who were evaluated with both conventional imaging and FDG PET for disease relapse. A patient-based and lesion-based analysis was performed. The concordance of the conventional imaging and FDG PET were computed. Furthermore, patients were divided in two groups (with negative and positive tumour markers; CA 15.3 and CEA). PET in both subsets of patients showed a higher diagnostic accuracy than conventional imaging (87 vs. 90.3% and 61.5 vs. 90.3% respectively in patients with pathologic and normal tumour markers). They concluded that 18F-FDG PET demonstrates apparent advantages in the diagnosis of metastases in patients with breast cancer compared with conventional imaging on a patient base. On a lesion base, significantly more lymph nodes and fewer bone metastases can be detected using 18F-FDG PET compared with conventional imaging, including bone scan. Concerning bone metastases, sclerotic lesions are predominantly detected by bone scan. On the other hand, there are several patients with more FDG positive bone lesions and also mixed FDG positive/Tc-99m MDP negative and FDG negative/Tc-99m MDP positive metastases. In patients with clinically-suspicious, but negative, tumour marker profiles, FDG PET seems to be a reliable imaging tool for the detection of tumour recurrence or metastases.

Kamel et al. (Kamel et al., 2003) studied 43 breast cancer patients with suspected disease relapse. Twenty-five of those patients had available value of tumour markers that had been collected within two weeks of their PET scan. Among the 25 patients, 19 were proven to have disease relapse, while six patients were categorized as being free from any tumour-related manifestation. Eight patients with local recurrence (n=3), distant metastases (n=1), or both (n=4) did not show elevated values (an average of 12.4 U/ml) despite the true positive PET findings. However, in 11 patients both PET findings and tumour marker status (median 42 U/ml) indicated disease recurrence. Three of these 11 patients had characteristically increased value of CA 15.3 (1394 U/ml, 666 U/ml, 185 U/ml), and PET revealed extensive disease relapse, while four had normal tumour markers (an average of 16.6) and two had slightly elevated values (an average of 21.5 U/ml). FDG PET was more sensitive than serum marker CA 15.3 in detecting relapsed breast cancer, CA 15.3 levels were normal in eight out 19 (42%) patients with true positive PET findings.

Siggelkow et al. (Siggelkow et al., 2003) studied 35 patients suspected of having recurrent disease or elevated tumour markers. Depending on the region of suspicion, conventional imaging included chest X-ray, MRI, CT and US. All patients had had at least 12 months of follow-up treatment. In the patients who were examined due to elevated CA 15.3, PET was able to detect recurrence or metastatic disease in six of the eight patients (sensitivity = 75%). PET missed three tumour sites in three patients: two supraclavicular lymph node metastases

and one lung metastasis. The overall sensitivity and specificity for PET for the whole series of patients was 80.6% and 97.6%, respectively. The same authors (Siggelkow et al. 2004) declared in a review that few studies have gathered sufficient data on the value of FDG PET in a patient with asymptotically elevated tumour marker levels during follow-up for breast cancer.

Eubank et al. (Eubank et al., 2004) retrospectively analysed 125 consecutive patients with breast cancer with the aim of 1) evaluating the impact of FDG PET on defining the extent of disease and 2) evaluating the impact of FDG PET on patient management. The patients were referred for FDG PET for the following reasons: evaluation of disease response or viability after therapy (n=43; 35%), local recurrence with intent of aggressive local treatment (n=39; 31%), equivocal findings on conventional imaging (n=25; 20%), evaluation of the extent of the disease in patients with known metastases (n=13; 10%) and elevated tumour markers with unknown disease site (n=5; 4%). In this latter subset of patients, the authors found that PET enabled the therapeutic management to be changed in three out of five patients (60%); in particular, one patient received systemic therapy other than surgery (intermodality change) and two patients were treated with systemic chemotherapy (intramodality change). For the whole group, the overall sensitivity, specificity, and accuracy of FDG PET was 94%, 91% and 92%, respectively. The final conclusions of the study were: 1) FDG PET helped to define the extent of disease and determine the treatment plan in a significant number of patients with advanced breast cancer; 2) the treatment plan was altered by FDG PET findings most frequently in patients who had loco-regional recurrence and an increase in tumour markers.

The findings of the articles mentioned above are summarized in **Table 2**:

Study	No. of patients/ proven recurrence	Sensitivity (%)	Specificity (%)
Lonneux et al., 2000	33/31	-	-
Pecking et al., 2000	132/92	93.6	-
Liu et al., 2002	30/28	96	90
Suarez et al., 2002	38/27	92	75
Kamel et al., 2003	25/19	-	-

Table 2. A summary of current studies on the impact of FDGPET in patients with elevated tumour marker levels

Current reports univocally indicate that the use of FDG PET is rational in patients with asymptotically elevated tumour marker levels and equivocal findings on conventional imaging. Both FDG PET and tumour marker status are biological tools that characterize the functional state of existing tumour tissue, but the tumour marker status was previously reported to be too insensitive to identify the existence of tumour tissue with a relatively smaller burden (Kokko et al., 2002). However, FDG PET is not sensitive enough for the detection of micrometastases, yet it remains the most accurate imaging device for early breast cancer recurrence detection. In fact, although FDG PET cannot rule out microscopic disease, it nevertheless has particular value in providing a reliable assessment of the true extent of the disease in a single examination (Vranjesevic et al., 2002; Haug et al., 2007).

4.2 PET vs. PET/CT and tumour markers

A PET scan alone has certain limitations, for example the exact localization of pathologically-increased focal glucose metabolism can be crucial, and physiological accumulation of FDG without precise anatomical localization can be misinterpreted as pathological. Conversely, CT permits exact anatomical localization of small physiological and pathological foci, but does not provide any information with regard to tissue metabolism. Combining both morphological and functional imaging technologies in a single scanner can be expected to overcome the respective limitations of CT, MRI, and PET, and provide the additional advantage of simultaneous data acquisition, obviating the need for patient repositioning, and so on. Haug et al. (Haug et al., 2007) studied patients with an isolated increase of tumour markers, who were asymptomatic but with suspected disease recurrence. Thirty-four patients were studied, five of whom were symptomatic and 29 asymptomatic. The authors compared PET, CT and PET/CT in a subset of patients with high levels of tumour markers (both CEA and CA 15.3), showing that the combined modality is associated with a higher diagnostic accuracy than when considered alone. PET/CT was able to identify 149 malignant foci in 24 patients (71%); CT identified 96 foci and PET 124 foci, in 18 and 17 patients respectively. The PET results were no different to the CT results, but both were significantly different from the PET/CT results (all $p < 0.01$) (see Table 3).

	Sensitivity (%)	Specificity (%)
PET	88	78
CT	96	78
PET/CT	96	89

Table 3. Diagnostic accuracy of PET alone, CT alone and PET/CT

The authors concluded that PET/CT is a valuable modality for the follow-up of patients with suspected breast cancer relapse and elevated levels of tumour markers.

4.3 PET/CT and tumour markers

Fueger et al. (Fueger et al., 2005) made a comparison between PET and PET/CT for diagnostic accuracy and the advantages for patients with a recurrence of breast cancer. They studied 58 patients with suspected disease recurrence, including the elevation of tumour marker levels (21/58 patients). They suggested that integrated PET/CT restages breast cancer patients with a higher accuracy than PET alone, but only marginally ($p = 0.059$). This observation emphasizes the need for a careful evaluation of the entire CT data set for an appropriate interpretation of PET/CT studies.

Saad et al. (Saad et al., 2005) in their retrospective study evaluated 35 patients with metastatic breast cancer. The results of PET/CT were compared with CA 27.29 and circulating tumour cells (CTC). A correlation between the results of PET/CT scans, CA 27.29 and CTC was found. CA 27.29 and CTC had poor sensitivity (59 and 55%, respectively) and NPV (24 and 33%, respectively) to detect metastatic disease observed on PET/CT scan, therefore PET remains the most sensitive test in detecting metastatic disease.

Radan et al. (Radan et al., 2006) retrospectively evaluated 47 patients with elevated tumour markers, 1 - 21 years from diagnosis. Thirty patients had had a recurrence of disease and 16 had not. Sensitivity, specificity and accuracy were 90%, 71% and 83%, respectively. PET/CT was compared to contrast enhancement CT demonstrating a higher sensitivity (85 vs. 70%), specificity (76 vs. 47%) and accuracy (81 vs. 59%). The impact of PET/CT on management was found in 51% of the patients. In conclusion, PET/CT had high performance indices and was superior to CT for the diagnosis of tumour recurrence in patients with breast cancer and rising tumour markers.

An Italian group (Grassetto et al., 2010) retrospectively studied 89 breast cancer patients with high values of CA 15.3 and inconclusive or negative PET/CT findings. Forty out of 89 patients (45%) had evidence of disease at FDG PET/CT, 23 had a solitary FDG-positive small lesion multiple cancer deposits were found in 14 of the 23 patients, and three patients were negative. The authors found that PET/CT may be able to detect occult metastatic and recurrent disease in post-therapy breast cancer patients with rising CA 15.3 levels and negative conventional imaging. They suggested that it could be reasonable to use tumour markers for guiding the performance of PET with the purpose of identifying the site of relapse in order to choose the most appropriate treatment.

Filippi et al. (Filippi et al., 2011) evaluated the role of FDG PET/CT in recurrent breast cancer detection in the presence of high levels of tumour markers and equivocal or negative conventional imaging. They studied 46 patients without any other clinical or laboratorial sign of disease; conventional imaging was negative in 29 patients and inconclusive in 17. FDG PET/CT resulted positive in 34 out of 46 patients. True-positive findings were found in 33 out of 46 patients (sensitivity = 86.8%, PPV = 97.1%) while false-positive and false-negative results were shown in six patients (specificity = 87.5%, NPV = 58.3%). The global diagnostic accuracy of PET/CT for disease detection was 86.9%. Change in clinical management was obtained in 50% of cases (23 out of 46), performing selective therapy in a number of patients. They concluded that the FDG PET/CT scan plays an important role in restaging breast cancer patients with rising tumour markers and negative or equivocal findings in conventional imaging techniques, with a consequent significant clinical impact on further management in these patients.

Champion et al. (Champion et al., 2011) studied 368 patients, 228 of whom had increased CA 15.3 and/or CEA. The cut-off value of CA 15.3 serum level was 60 UI/mL, as previously defined by various studies (Suarez et al., 2002; and Aide et al., 2007; Molina et al., 2005). The average CA 15.3 serum level was significantly higher in the true positive group than in the false negative one (166±115 vs. 77±52 UI/mL; $p < 0.001$) and the true-negative one (166±115 vs. 65±56 UI/mL; $p < 0.001$) (**Figure 2**). In asymptomatic patients with rising tumour markers, FDG PET/CT imaging is an accurate modality to screen for breast cancer recurrence. It is more sensitive than a conventional imaging workup; showing the extent of disease, it enables further treatment to be adjusted, proving a general picture in a high performance “one stop-shop” procedure.

In a study performed at our Nuclear Medicine Unit (Evangelista et al., 2011), we assessed the role of tumour markers, CT and 18F-FDG PET/CT in identifying disease relapse in patients with breast cancer which had already been treated, and the impact of PET/CT findings on patient management. We studied 111 patients with breast cancer with clinical-

biochemical signs of loco-regional and distant recurrence of disease. Within three months, all patients performed CA 15.3, CT and PET/CT imaging for the evaluation of the extent of the disease. Recurrence was found in 32 out of the 111 patients, and PET/CT recognized the majority of patients with disease relapse, irrespective of the value of CA 15.3 and CT findings, identifying 81% of cancer recurrence and missing only 19%, with a gain of 30% toward tumour markers and 10% toward CT (see **Table 3**). The change in management was significantly important after PET/CT evaluation (change in 56% vs. 34%, respectively for PET/CT and CA 15.3). Furthermore, no advantage was obtained by reducing the value of the abnormal cut-off point of CA 15.3 from 31.0 to 19.1 U/mL, increasing the detection of recurrence by only 6%.

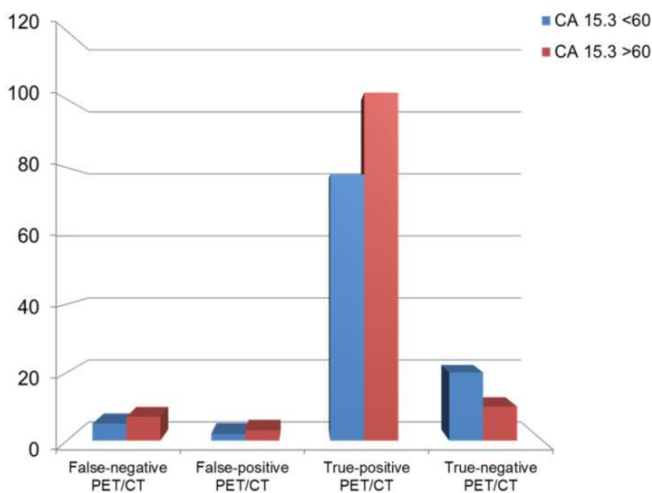


Fig. 2. A histogram showing the different groups of PET/CT results expressed as the number of patients against the CA 15-3 blood level (cut-off, 60 UI/mL) (from Champion et al., 2011).

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Tumour markers	50	69	40	77	64
CT	72	37	32	76	47
PET/CT	81	62	41	87	60
Elevated tumour markers					
CT	69	93	50	72	60
PET/CT	88	33	47	80	55
Normal tumour markers					
CT	75	29	24	80	39
PET/CT	75	60	35	89	63

PPV, positive predictive value; NPV, negative predictive value

Table 3. Diagnostic accuracy of tumour marker (CA 15.3), CT and PET/CT in detecting relapse of disease

There is a general consensus in literature that steadily rising levels of CEA and CA 15.3 value must be regarded as a significant sign of change in tumour cell growth; this means that tumour marker determination during follow-up in breast cancer patients who have been radically operated on could anticipate the clinical diagnosis of cancer relapse. In our opinion, the use of PET/CT in patients with breast cancer could improve accuracy in the determination of the extent of the disease in case of an increase of tumour markers, but it is important to evaluate the trend of the increase in tumour marker rather than its single value. In fact, several non-cancerous conditions (benign breast or ovarian disease, endometriosis, pelvic inflammatory disease and hepatitis) can raise levels of CA 15.3, thus reducing the specificity of biochemical relapse; on the contrary, PET/CT can identify the disease before it becomes clinically manifested, even when the value of tumour markers is in a normal range.

5. Doubling timing and serial determinations

A discrepancy exists between the high positivity rate of serological markers in metastatic disease *vs.* the low positivity rate of serological markers in metastatic disease and the low positivity rate related to early relapse, when the results of tumour marker assays are interpreted by means of a dichotomous positive/negative cut-off point. This latter criteria, although easy to use and well accepted in clinical practice, is not powerful enough for the detection of early biological relapse: *a relevant quantity of tumour tissue is necessary to produce a sufficient quantity of tumour markers to exceed the cut-off point.* Dynamic interpretation based on serial samples might provide earlier diagnostic information, so a significant increase could be detected before exceeding the cut-off level, i.e. the difference between the values in three consecutive determinations should be at least two fold the inter-assay coefficient of variation (20%). The interval between the serial tests should be at least one month.

Mariani et al. (Mariani et al., 2009) recommended that the tumour markers should be considered as an indicator of disease presence, not only a tumour marker value above the normal limit (dichotomic criteria) but also a difference between two consecutive measurements greater than a critical value (dynamic criteria). Serial CA 15.3 measurements may be an efficient and cost-effective method of monitoring disease progression, and this is a potentially powerful means of obtaining information about breast cancer whilst causing minimal morbidity, inconvenience and cost (Buffaz et al., 1999). Both CA 15.3 and PET are based on metabolic changes due to tumour activity; they provide information on disease progression in a different way to conventional imaging. The advantage of adding PET or PET/CT in combination with constant elevation of CA 15.3 (15) could be translated into a more valuable method of identifying earlier metabolic changes (which is the basis of the PET principle) even before the morphological changes (noticeable with ultrasound and CT) occur.

Aide et al. (Aide et al., 2007) retrospectively evaluated 35 FDG PET examinations in 32 patients with CA 15.3 blood level above the normal range, and negative conventional imaging within three months before a PET exam. CA 15.3 assays were performed prior to the PET examinations and, all using the same techniques, were collected and used for doubling time calculation if 1) no therapeutic modification occurred in the meantime, and 2) the delay between assays was less than six months. Median CA 15.3 blood levels were higher in the positive PET group (100 U/ml) than in the negative group (65 U/ml) ($p=0.04$).

The likelihood of depicting recurrence was higher in patients with a short doubling time (<180 days) ($p=0.05$), a CA 15.3 blood level >60 U/ml ($p=0.05$), and when a short doubling time was associated with a CA 15.3 blood level >60 U/ml ($p=0.03$). The authors concluded that the likelihood of recurrence was influenced by CA 15.3 blood level and doubling time.

In our recent report (Evangelista et al., 2011) we assessed the relationship between serial measures of CA 15.3 and FDG PET/CT findings in the follow-up of patients who had already been treated for breast cancer. In sixty patients, three serial measures of CA 15.3 were collected within one year of the PET/CT examination. Coefficient of variation of the CA 15.3 serial determinations was significantly higher in patients with positive than negative PET/CT (39 vs. 24%, $p < 0.05$). ROC analyses showed that an increase of CA 15.3 between the second and third measures have better individuated positive PET/CT and disease relapse (AUC 0.65 and 0.64, respectively; $p < 0.05$). We concluded that an increase of CA 15.3 could be considered optimal in addressing FDG PET/CT examination during breast cancer patients' follow-up. PET/CT performed just on time might allow disease relapse in breast cancer patients to be detected earlier and with higher diagnostic accuracy.

6. The current recommendations according to the American and European societies

Approximately 30-50% of breast cancer patients have a recurrence of disease within ten years after diagnosis. Several international guidelines help physicians using tumour markers to give practical recommendations for the appropriate interpretation of circulating tumour markers. Due to low levels of evidence; the ASCO recommendations for the use of tumour markers do not support the determination of CA 15.3 during the follow-up of patients who have been treated for breast cancer, for monitoring the recurrence of disease (Harris et al., 2007). In clinical practice, disease relapse is suspected if there is positive clinical findings, the appearance of new lesions on imaging examinations, and/or unclear and persistent elevation of tumour markers. The "biochemical evidence" of a possible cancer relapse suggested by increased tumour markers leads oncologists to discover or exclude the sites of the cancer lesions through conventional radiological imaging techniques or nuclear medicine modalities (Strauss et al., 1991; Brown et al., 1996). The early individuation of disease relapse could improve the prognosis and allow for better management, through starting a new treatment or changing the ongoing therapy. Currently, according to ASCO guidelines (Khatcheressian et al., 2006), the follow-up of breast cancer patients should involve only physical examination and conventional mammography; whereas in the presence of new symptoms oncologists recommend performing conventional imaging, such as a chest-X ray, CT or MRI and PET scan. The European Group on Tumour Marker (EGTM) (Molina et al., 2005) panel suggests the following approach during the follow-up of asymptomatic women: tumour markers should be determined every two - four months (according to the risk of recurrence) during the initial five years after diagnosis, and at yearly intervals thereafter. This practice could be considered to be the most useful for monitoring disease development and reducing the lead time.

PET is a rapidly evolving field at both national and international level, with sometimes striking differences between its use in individual countries (Boellaard et al., 2009). The

indications for PET and PET/CT are constantly changing, and require updating over time. Based on the current recommendations by the European Association of Nuclear Medicine (EANM guidelines), other than staging and restaging by PET/CT, establishing and localizing disease sites as a cause for elevated serum markers in some tumours (e.g. colorectal, thyroid, ovarian, cervix, melanoma, breast and germ-cell tumour) are also considered important aims.

7. Discussion

There are several patients in whom tumour marker levels are either high or progressively increasing, and neither physical examination nor diagnostic imaging are able to detect the tumour. In these cases the level of tumour markers (biochemical occult disease) serves as a guide to studying the patient with more powerful instruments (tumour marker-guided imaging) (Figure 3).

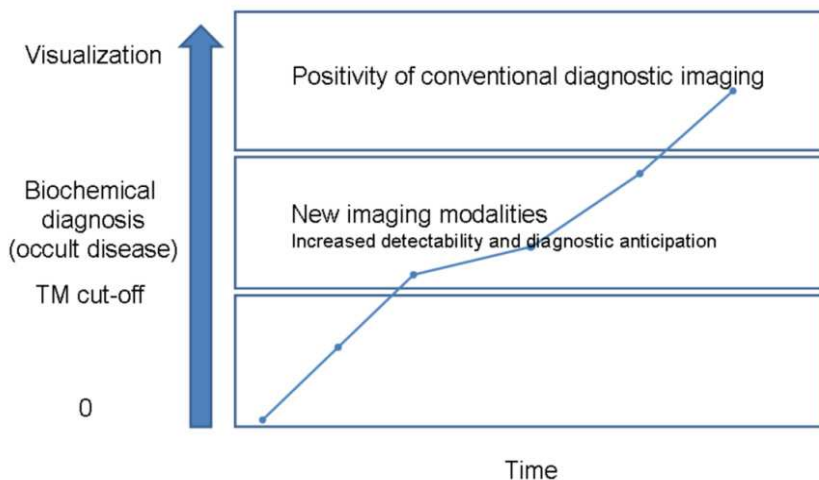


Fig. 3. The impact of technical implementation of diagnostic imaging (from Prof. Bombardieri Emilio, 1stImmunometry Congress ; 27 March 2009, Bari, Italy)

As previously mentioned, PET and PET/CT have proven to be useful imaging devices for earlier detection of disease recurrence, especially when tumour markers are increasing.

The main question is: when is the association of tumour markers and PET or PET/CT (tumour marker-guided imaging) useful? It is undoubtedly useful at early presentation for patients at high risk of metastases, in the diagnosis of tumour relapse/restaging, and for monitoring tumour response (Prof. Bombardieri Emilio, 1st Immunometry Congress ; 27 March 2009, Bari, Italy). In **Table 4** the advantages and limitations of tumour markers as a guide for PET/CT imaging are summarized:

	Added value	Limitations
Diagnosis of metastases at tumour presentation	PET seems more accurate than conventional imaging in the diagnosis of metastases at cancer presentation (in particular for internal chain lymph nodes).	PET usefulness is related to the stage of disease, being more accurate for stage II-III. The sensitivity of tumour markers is very low at early stages. tumour markers tests are not recommended at tumour presentation in low-risk patients.
Detection of recurrent Disease	Limited sensitivity of PET and tumour markers in depiction of loco-regional recurrences High accuracy (~90%) for the detection of metastatic disease.	Inadequate detection by PET of anatomical details. PET/CT overcomes this problem and increases the diagnostic accuracy (with a gain of ~ 10% in diagnostic accuracy, Haug et al., 2007).
Unclear elevation of tumour markers in asymptomatic patients during follow-up	High sensitivity (> 90%) for the detection of occult recurrence in asymptomatic patients with a progressive increase of tumour markers levels.	Some false negative results in breast cancer with low metabolism (lobular carcinoma). Additional conventional imaging is sometimes necessary.

Table 4. A summary of the advantages and limitations of tumour markers as a guide for PET/CT imaging (from Prof. Bombardieri Emilio, 1st Immunometry Congress ; 27 March 2009, Bari, Italy)

Tumour marker tests are a metabolic measure of tumour growth and tumour activity, and well integrate the metabolic imaging information. The association of tumour marker with PET/CT appears to be perfect giving qualitative and quantitative metabolic information, in particular tumour marker concentrations express the blood measure of the tumour products, and the pixel content of morphologic images is related to tumour uptake.

7.1 Considerations

1. In the majority of reports analysed, tumour marker-guided PET and PET/CT have shown a high diagnostic accuracy in the early detection of breast cancer recurrence;
2. PET and PET/CT can be considered to be accurate and powerful tools in detecting disease recurrence even when tumour markers are low or in a normal range;

3. The association of tumour markers and PET/CT also has an impact on patient management; many reports have described a change in planned therapy of about 50%. In a review, Yu et al. (Yu et al. 2007) discussed cancer biomarker development, opportunities for PET to elucidate tumour biology, and the potential role of PET in clinical research and practice. They underlined that the practice of oncology has been changing, with novel biologic agents broadening the therapeutic armamentarium. The concept of individualized cancer care, where therapies are selected based on the unique characteristics of the patient's tumour, is gaining favour as an approach to address the heterogeneity of cancer; for this reason they were incited to discover biomarkers with prognostic and predictive value to improve drug selection, alteration and cancer development. For this purpose, the combination of metabolic data and molecular imaging with PET or PET/CT is at the forefront of this critical field.

8. Conclusions

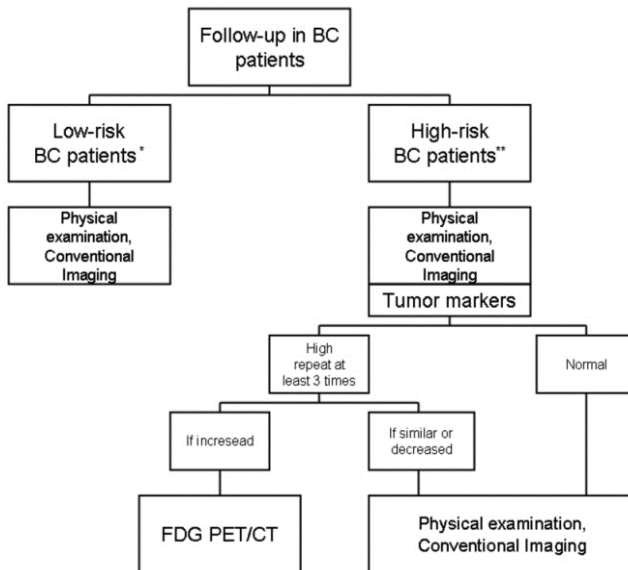
Tumour marker-guided PET during the follow-up of patients who have already been treated for cancer has not yet been investigated sufficiently. The questions to be solved are: 1) Can the combination of tumour markers and PET scans substitute all other conventional modalities currently used in follow-up? 2) Can this approach affect the survival of patients? Considering the need for stricter integration between laboratory tests and metabolic imaging, in particular FDG PET, we will hopefully be able to answer these questions in the near future.

However, the use of CA 15.3 tests in breast cancer follow-up could involve a considerable risk of over-diagnosis and lead time. When the test result is positive but there is no other confirmation of metastatic disease, decision-making is difficult as to whether to treat or not (Kokko et al., 2002).

As documented in the "Recommended Breast Cancer Surveillance Guidelines" adopted by ASCO, the achievement of survival benefit with clinical follow-up is one of the most important documents that did not confirm the necessity of more aggressive follow-up strategies (Levels of evidence). However, the majority of the studies were carried out 10-20 years ago when many of the current drug regimens were not available. The Association of Breast Surgery to The British Association of Surgical Oncology has noted the above report and made a number of recommendations. One of the most important recommendations states that "follow-up should be stratified according to disease risk". The follow-up management of breast cancer patients based on different risk category of recurrence should therefore be appropriately defined. We suggest considering three categories of patients:

1. Low risk of recurrence (ductal carcinoma in situ, DCIS; lobular carcinoma in situ, LCIS)
2. Intermediate risk (hormone receptor positive cancer; invasive ductal cancer, IDC; invasive lobular cancer; HER-2 negative cancer)
3. High risk (triple negative, advanced stage at diagnosis, cancer associated with familial genetic mutations, and any remaining categories)

Figure 4 shows a possible clinical and diagnostic algorithm during follow-up:



BC = breast cancer

Fig. 4. A follow-up algorithm in breast cancer patients based on risk category (*low-risk and **high risk breast cancer patients are referred to the above definitions)

The clinical experience in breast cancer management and different studies support the following concepts: a) a tumour marker test is not useful in the diagnosis of primary breast cancer, due to their very low sensitivity at cancer presentation; b) there is a correlation between CA 15.3 levels and the presence of bone and visceral metastases; c) the combination of tumour markers with diagnostic imaging can improve the diagnostic sensitivity and the PPV; d) tumour markers may be helpful in the interpretation of equivocal bone scans or any other equivocal imaging modality; e) bone scintigraphy cannot be precluded on the basis of normal tumour marker tests in the presence of suspicious skeletal metastases alone; f) some bone metabolic markers might be helpful in the evaluation of “flare phenomenon” and monitoring therapy response; g) even if tumour marker-guided PET still has to be extensively evaluated, the current experience demonstrates the potential of FDG-PET in discovering occult soft and bone metastases in the presence of a progressive increase of serum tumour markers (Ugrinska et al., 2002).

Some limitations of this article should be remembered: 1) many of the revised articles were retrospective; 2) we reported studies which considered both patients who underwent FDG PET alone and PET/CT imaging for increase in tumour markers, 3) the imaged field of view for whole-body PET/CT protocols is not already standardized and varies by institution (Huston et al. 2010), thus the heterogeneity of the analysis could be skewed the conclusions. Some considerations can be enhanced, firstly in literature there are not prospectively randomized studies which compared the standard follow-up procedures with new imaging technologies (e.g. FDG PET) and secondly the worldwide diffusion of hybrid PET/CT is approximately recent, thus reducing the available results.

9. The future prospective in the follow-up for breast cancer

In an editorial, Hortobangyi et al. (Hortobangyi et al., 2002) hypothesized that a multimodality therapy administered to a group of patients (1-3%) with limited metastatic breast cancer could produce long-term disease-free survival or cure. He concluded that, in this patient subset, the approach should be curative and not palliative. Consequently, intensive postoperative monitoring should be revisited, and large prospective trials are needed to identify the optimal candidates. Nevertheless, the subsequent ASCO guidelines (Khatcheressian et al., 2006) did not take in these indications. As previously mentioned, it is currently recommended that the follow-up of breast cancer patients involves only physical examination and conventional mammography; other examinations are recommended only in the presence of new symptoms. In the last few years we have seen great developments in the biological characterization of breast cancer and in diagnostic technology. These last improvements have profoundly changed breast cancer treatment but whether they can modify the follow-up for breast cancer treatment in the near future is still unclear. Breast cancer is a heterogeneous disease, showing many biological subtypes with different clinical features. For example, the positivity to hormone receptors requires different therapeutic management to the expression of human epidermal growth factor receptor 2 (HER2)-positive or a triple negative breast cancer; furthermore, the prognosis is differs widely from one case to another. Could the future strategy for breast cancer follow-up be adapted to biological characterization? Esserman et al. (Esserman et al., 2011) retrospectively evaluated the hormone receptor, the HER2-receptor and the grade from archival blocks of 23 years minimum follow-up breast cancer to establish if these features were related to risk and timing to recurrence. They observed that in 683 patients with negative-node involvement, the outcome risk for hormone receptor-positive and HER2-negative cancer was partitioned by tumour grade: lower grade cases had very low early recurrence risk but a 20% fall in ten or more years after diagnosis, and higher grade cases had a risk over 20 years. On the contrary, triple-negative and HER2-positive cancer showed a primary recurrence within the first five years, independently from the grade. Thus the recurrence of disease can be stratified based on cancer characteristics.

The site of relapse can also be different in these subtypes; e.g. Musolino et al. (Musolino et al., 2011) conducted a large epidemiological study, concluding that patients with HER2-positive breast cancer have a significantly higher incidence of central nervous system metastasis, especially after treatment with trastuzumab (Herceptin®). Concerning the loco-regional relapse, breast cancer subtypes have a different risk. Gabos et al. (Gabos et al., 2010) identified the hormone receptor negative/HER-2 positive status and the triple negative status as risks for local relapse, and suggested the possibility of a different follow-up and loco-regional treatment for these subtypes. Montagna et al. (Montagna et al., 2011) concluded that loco-regional relapse correlates with a high risk of subsequent events, and death in particular, in patients with the triple-negative subtype. Based on these observations, we can assume that a biological features based approach should be considered for follow-up too.

The technological development in diagnostic techniques could also have a role in follow-up changing. Regarding conventional radiological imaging, MRI could have a role in surveillance especially for BRCA1 or BRCA2 positive breast cancer, but currently the best

way to integrate mammography and breast MRI and their frequencies are unresolved areas of controversy. The major innovations come from nuclear medicine, e.g. the last introduction of hybrid devices (e.g. PET/CT and PET/MRI) useful for the evaluation of disease represents a great technology development. Furthermore, new devices such as positron emission mammography (PEM) represent a technological challenge both in primary diagnosis and in loco-regional recurrence, especially in women treated with conservative surgery. Moreover, the innovations from the radiopharmaceutical field with the introduction, in clinical practice, of new tracers such as 18F-fluoroestradiol (known as FES), which is mainly employed for evaluating the hormone receptor expression, a specific target for hormonal therapy.

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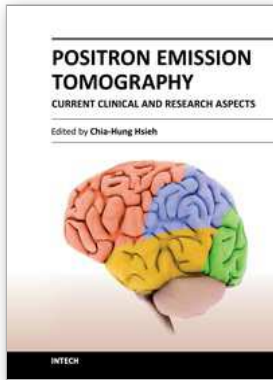
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This book's stated purpose is to provide a discussion of the technical basis and clinical applications of positron emission tomography (PET), as well as their recent progress in nuclear medicine. It also summarizes current literature about research and clinical science in PET. The book is divided into two broad sections: basic science and clinical science. The basic science section examines PET imaging processing, kinetic modeling, free software, and radiopharmaceuticals. The clinical science section demonstrates various clinical applications and diagnoses. The text is intended not only for scientists, but also for all clinicians seeking recent information regarding PET.

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