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EDITORIAL

Nuclear medicine imaging of breast cancer

The best hope for improving survival among breast cancer patients is early detection. Standard mammography is the diagnostic tool of choice for the early detection of small breast lesions. Since the introduction of film-screen mammography and new magnification techniques, modern mammography has improved significantly over the last few years. However, approximately 10–15% of all palpable carcinomas cannot be detected on mammography and the treatment outcome may be adversely affected when a biopsy is delayed because of a negative mammography. The main reason for these negative findings is that dense breast tissue, which is most often seen in young women, may obscure tumours. On the other hand, only 15–20% of breast biopsy specimens of non-palpable lesions detected by mammographic screening prove malignant. Thus the specificity of mammography in deciding to perform an excisional biopsy for histological diagnosis is poor. Since axillary lymph node involvement is an important prognostic factor, axillary dissection still remains part of the primary treatment of breast cancer patients. This surgical procedure continues to have a high morbidity, and among patients with clinically negative axillary lymph nodes, only 30–40% may have histopathologically proven node metastases. Therefore, a number of new non-invasive imaging techniques are currently employed to improve the sensitivity of diagnosing a malignant or pre-malignant lesion without sacrificing specificity, and to detect axillary lymph node metastases in patients with clinically negative nodes. In this editorial, an overview will be given only of nuclear medicine techniques. Data on their usefulness for tumour detection, treatment evaluation and for choosing a specific treatment will be discussed.

Fluorine-18 fluorodeoxyglucose

Tumour imaging with fluorine-18 fluorodeoxyglucose (FDG) by means of positron emission tomography (PET) with PET cameras, planar imaging and/or tomography with the use of high-energy collimators on conventional single photon emission tomographic (SPET) cameras, is based upon the metabolic activity of malignant tumours, which tend to use more glucose than adjacent normal tissue. At the present time, no FDG data are available based on studies with dual-head cameras using coincidence systems. The majority of breast cancer patients studied with FDG have been studied with PET cameras only. Overall, good sensitivity (up to 100%) and specificity (85%) have been found [1]. FDG uptake by primary breast tumours has not been found to be correlated with age, menopausal status, histological differentiation, ploidy, pathological stage or oestrogen/progesteron receptor status. Only tumour nuclear grade and proliferation phase have been shown to be associated with FDG accumulation by the tumour compared with normal breast tissue. In most of these studies, only patients with advanced disease or large tumours were enrolled. Tumours smaller than 1 cm or pre-malignant lesions such as ductal-carcinoma *in situ* could not be visualized. The detection of metastases in clinically negative lymph nodes by FDG-PET should be further evaluated, although the first results are promising [2]. A negative study, however, should not cause the surgeon to abandon an axillary lymph node dissection, since patients with axillary micrometastases are thought to benefit the most from adjuvant chemotherapy or hormonal therapy.

From a clinical point of view, FDG-PET or FDG-SPET may be most useful as a non-invasive technique to predict and quantify tumour response to chemotherapy in patients with stage III and IV breast cancer (locally advanced or metastatic) [3]. Also, the effect of primary radiotherapy or radiotherapy for local recurrence could be evaluated with changes in FDG-activity, since uptake of FDG seems to correlate well with histopathological findings (e.g. tumour viability) [4].

$^{99}Tc^{m}$-sestamibi

Tumour imaging with $^{99}Tc^{m}$-sestamibi ($^{99}Tc^{m}$-MIBI) was first described in 1987. Although the exact mechanism of $^{99}Tc^{m}$-MIBI cellular uptake in cancer cells is not known, experimental studies have demonstrated a four- to eight-fold higher uptake by tumour cells than normal cells. Interestingly, this accumulation was shown to be higher at the periphery of solid tumours, which could be due to a better degree of local blood flow. $^{99}Tc^{m}$-MIBI is known to be transferred by a receptor mechanism across the cell membrane and taken up by the active mitochondria. Most studies have reported a specificity and sensitivity of between 80 and 90% for this relatively cheap tracer [5, 6]. The additional value of $^{99}Tc^{m}$-MIBI scintimammography in patients with small palpable lesions in dense breasts should be prospectively compared with ultrasonography followed by cytology. This combination of

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procedures is well-established in Europe and has been shown to give excellent results. Microcalcifications seen on screening mammograms, without a solid component, still need surgical excision after fine-needle localization, because it is not possible to differentiate on scintimammography between epithelial hyperplasia, severe atypia, and sclerosing adenosis or microscopic intraductal and/or infiltrating ductal carcinoma. The usefulness of scintimammography to diagnose axillary lymph node metastases in patients with known breast cancer is currently being determined in multicentre trials. Since technetium is used as the radionuclide, radio-guided surgery with a hand-held probe during surgery to detect lymph node metastases in sentinel nodes is also possible and could help the surgeon to avoid complete axillary lymph node dissection in patients with small primary tumours in whom the likelihood of a micrometastasis is very small.

The efflux of $^{99}Tc^{m}$-MIBI has been found to be related to the degree of the transporter glycoprotein Glp170, the same glycoprotein that is correlated to multi-drug resistance (MDR). So patients with a high efflux of $^{99}Tc^{m}$-MIBI, determined from the kinetic parameters of scintimammography, do have a high probability of developing MDR [7] and should therefore probably not be treated with neo-adjuvant chemotherapy. On the other hand, the indication to continue neo-adjuvant chemotherapy in patients with (initially) low efflux parameters could be defined in this manner. It is tempting to speculate that scintimammography with $^{99}Tc^{m}$-MIBI could be used to monitor *in vivo* the effect of drug interventions to suppress MDR (e.g. by cyclosporine-like agents). In this respect, a change in the $^{99}Tc^{m}$-MIBI scintigram result from negative to positive might indicate the moment to start chemotherapy and predict its usefulness.

^{201}Tl-chloride

Thallium-201 (^{201}Tl) chloride has properties similar to $^{99}Tc^{m}$-MIBI. Uptake of ^{201}Tl into tumour cells depends on the ATPase sodium/potassium transport system and breast cancer tissue has been found to exhibit higher concentrations of ^{201}Tl than normal breast tissue or benign lesions. Accumulation of ^{201}Tl in breast cancer cells is much lower than that of $^{99}Tc^{m}$-MIBI, but perhaps because of its lower accumulation it is more specific, since false-positive ^{201}Tl scintigrams for breast malignancy are rare [8, 9]. Tumour vascularization and membrane stability are necessary for an optimal scintigraphic result, which makes this technique unsuitable for larger tumours with poor viability. For nuclear scanning, ^{201}Tl is not an optimal radionuclide, due to its emission of only small numbers of gamma rays at acceptable energies.

The detection rate of small breast tumours as well as lymph node metastases is disappointing, so ^{201}Tl scintigraphy as an adjunct to mammography, ultrasonography and cytology might only help to select patients for excisional biopsy in whom previous investigations were inconclusive or not performed.

^{111}In-octreotide

Somatostatin receptors (SS-Rs) are present in part of human breast cancers. Somatostatin receptor scintigraphy using ^{111}In-DTPA-D-Phe^{1}-octreotide (OctreoScan), which recognizes two of the five subtypes of SS-R, is a technique which has been shown to localize the primary as well as metastatic spread of SS-R-positive tumours with a high sensitivity. With ^{111}In-DTPA-D-Phe^{1}-octreotide, we were able to visualize the primary tumour in about 70% of patients with breast cancer [10]. Using autoradiography, validation of this technique was obtained by the *in vitro* demonstration of high-affinity binding sites for somatostatin on those tumours which had been visualized *in vivo*. Axillary lymph node metastases in clinically unsuspected lymph nodes were found in only 4 of 13 patients. At the primary diagnosis, the ^{111}In-DTPA-D-Phe^{1}-octreotide scan seems of minor value in the detection of breast tumours or axillary metastatic spread. However, it would seem that in operated patients with SS-R-positive breast cancer, ^{111}In-DTPA-D-Phe^{1}-octreotide scintigraphy may be useful for the early detection of recurrence, since distant metastases of these tumours continue to express SS-Rs. In our follow-up study, this scintigraphic technique revealed the unexpected presence of (multiple) metastases in nearly 25% of symptom-free, initially SS-R-positive breast cancer patients. Tumour marker (CA 15–3 and CEA) serum values and radiological investigations were normal. At the present time, one can only speculate what the clinical relevance is of detecting recurrent disease at an early stage.

The expression of SS-Rs of breast tumours in our group of patients was strongly correlated with a higher mortality and shorter symptom-free survival. In another, *in vitro* study, the results were in the opposite direction [11]. It is anticipated that ^{111}In-DTPA-D-Phe^{1}-octreotide scintigraphy may be used in the future for the selection of patients who can be treated with somatostatin analogues, possibly in combination with tamoxifen [12]. Also, radionuclide therapy with a β-emitting radionuclide coupled to a somatostatin analogue might be considered, especially when disseminated disease is recognized. The heterogeneous distribution of SS-Rs, especially in breast cancer, precludes radionuclide therapy with Auger electrons using high doses of ^{111}In-DTPA-D-

Phe[1]-octreotide, as is currently being performed successfully in patients with neuroendocrine tumours [13].

Other radiopharmaceuticals

In recent years, a number of other radiolabelled substances (e.g. antibodies and hormones) have been used in imaging [14–17]. $^{99}Tc^{m}$-methylene diphosphonate ($^{99}Tc^{m}$-MDP) has been used and compared to $^{99}Tc^{m}$-MIBI [14]. $^{99}Tc^{m}$-MDP was found to have the higher specificity when the images were obtained 10–20 min post-injection. Small tumours (≤ 0.7 cm) were difficult to detect; positive lymph nodes were found in only 21% of cases. Several analogues of oestrogens, progestins and androgens have been radiolabelled (with ^{18}F and ^{123}I) and evaluated both *in vivo* and *in vitro* for receptor binding affinity and selectivity [15, 16]. Scintigraphic images with these labelled hormones may be useful for selecting inoperable or very old patients for anti-hormonal treatment (e.g. tamoxifen) or for monitoring the efficiency of this form of therapy.

By radiolabelling antibodies against gene products of breast cancer specific protooncogenes such as c-erbB-2, a highly sensitive staging method could be developed as a potential means of selective immunotherapy [17].

Conclusion

It is our view that mammography in combination with ultrasonography and cytology will remain, for the present time, at least in Europe, the procedure of choice in screening asymptomatic patients and evaluating patients with stage I and II breast cancer. Nuclear medicine imaging with various pharmaceuticals, however, now plays an important role in the differentiation of malignant and benign lesions greater than 1 cm in size. Furthermore, scintigraphy using these radiopharmaceuticals needs to be studied in prospective randomized trials, to determine the clinical impact with regard to staging, prognostic factors, new treatment modalities and evaluation of therapy.

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