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ARTICLE

Imaging in evaluation of response to neoadjuvant breast cancer treatment

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Abstract

The role of imaging for patients treated with neoadjuvant therapy for breast cancer is not only to evaluate the therapeutic response in terms of tumour shrinkage, but also to predict the histological response to chemotherapy, which is correlated to survival. Surgery and histopathological analysis after neoadjuvant therapy allow for an objective assessment of the accuracy of imaging techniques in evaluating response. The aim of this study is to compare the value of the different conventional and functional imaging techniques for determining response to neoadjuvant chemotherapy in breast cancer treatment.

Keywords: *Breast carcinoma; neoadjuvant therapy; diagnostic imaging.*

Introduction

Neoadjuvant therapies for breast cancer allow conservative surgery in patients with large tumours and *in situ* evaluation of the efficacy of chemotherapy. The response to chemotherapy is an important prognostic factor that influences surgical management and the type of postoperative chemotherapy.

A complete tumour response to neoadjuvant chemotherapy increases the disease-free interval and patient survival. The parameter with the greatest predictive value is the absence of any gross residual tumour[1,2]. Limited microscopic residual tumour does not play any significant role, and is found nearly constantly (95% of complete responses). In the series of Feldman *et al.*[1], patients without gross residual tumour after induction chemotherapy had a survival rate at 6 years of 93% vs. only 34% for those with residual tumour. An excellent therapeutic response is defined as complete absence of any gross tumour mass or the presence of a fibrotic mass containing only degenerated tumour cells. In the literature, the response to neoadjuvant chemotherapy is partial in 75% of patients and complete in 10%; response to hormone therapy is complete in 27% and partial in 61%[3].

Physical examination is often unsatisfactory for assessment of the response of locally advanced breast cancer to primary medical treatment. Feldman *et al.*[1] reported that 45% of complete clinical responders had macroscopic tumour at histological examination; inversely, 60% of patients without any histological gross residual tumour had an incomplete clinical response. In the series of 49 patients studied by Cocconi *et al.*[4], physical examination overestimated tumour regression in 23% of cases and underestimated the response in 9%. The accuracy of physical examination is mediocre because palpation of a fibrotic and necrotic mass may mimic a residual tumour mass. In other cases, the apparent clinical regression is due to resolution of post-biopsy phenomena such as haemorrhage and oedema. Tumours in a progressive phase are difficult to assess by physical examination; regression of inflammatory phenomena is

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often the sole objective parameter as the tumour mass itself changes very little.

Several imaging modalities can be used to evaluate the tumour and the tumoral response. Physical examination combined with mammography and sonography is the method most utilized in routine practice. These methods essentially appreciate the evolution of the tumoral volume. Evolution of imaging techniques means that other modalities can be considered, not only based on measurements of the size and the number of lesions, but on a functional analysis (uptake of contrast media, richness of neo-vascularization), or on the detection of a physiopathological tumoral activity (scintigraphy, PET scan). Considering the individual importance for the patient and economical interests for society, it is mandatory to evaluate the reliability and the relevance of these techniques, their advantages and their limits.

Mammography and ultrasound

Conventional radiology using mammography and ultrasound is the method most used for the initial staging and the assessment of tumour response to neoadjuvant chemotherapies. The main objective is the comparative measurement of the tumoral volume. The accuracy of this measurement depends on the contrast between the tumour and the surrounding normal tissue. The accuracy of the measurement increases with the difference in densities or echogenicity, specially when the limits of the tumour are sharp. Radiological measurements are more difficult to appreciate when lesions are ill-defined or when the breast is dense. Only the dense centre must be measured in spiculated lesions. Architectural distortions do not allow precise or reproducible measurements. In the majority of cases (96% in the Helvie study)[5], chemotherapy induces a partial or complete response, which leads to a decreased in size or disparity of the lesions. This response is measurable only if the mass or the calcifications are clearly defined on the first mammogram. In some cases of advanced or inflammatory tumours, lesions are ill-defined, diffuse, without a delineated mass, and quantitative evaluation is not possible. Helvie *et al.*[5] have found a greater sensitivity to mammography (79% vs. 49%) but there were more false positives with mammography (3/37) than with physical examination (1/22) with a respective specificity of 77% and 92%. Vinicombe *et al.*[6] observed a mammographic response in 82% of cases: seven times the mass disappeared but the microcalcifications persisted, 46 times the mass decreased in size but not in density and 11 times in density but not in size. The architectural distortion was not modified in most cases. Even though mammography shows a response to chemotherapy in most patients, it does not allow prediction of the histopathological response. Microcalcifications especially are not a reliable witness of persistence of residual tumour. Microcalcifications of a ductal carcinoma may persist in a good response and calcifications secondary to necrosis may appear. Huber *et al.*[7] showed that the most significant criterion was the length of the well-defined part of the tumour. In 70% of patients with more than 50% of well-defined contour, there was a good correlation between the mammogaphic diameter and the size of the residual tumour on histological examination. When less than 50% of the contour of the tumour was well-defined, then the correlation with histology was weak. They concluded that in these cases the assessment of response has to be done with another modality such as ultrasound or magnetic resonance imaging (MRI).

In the series of Balu-Maestro *et al.*[8], ultrasound has been found to be poorly reliable, evaluating the size of residual tumour after chemotherapy only in 43% of cases. In other series[9,10] ultrasound was found to be superior to physical examination and mammography especially when the tumour was hypoechoic. Modification of tumoral echogenicity induced by chemotherapy limits the reproducibility of the measurements after treatment. During the treatment the tumoral density decreases on successive mammograms. This density diminution cannot be measured and may even interfere with the measurements because of the decreased contrast ratio between tumoral and normal tissue. Ultrasound may then be more reliable. When the tumour is fractionated, plurifocal, or when it is larger than the field of the probe, the ultrasound measurements are not so reliable. In multifocal disease, the advantage of ultrasound is controversial. Infra-clinical or infra-mammographic lesions may be found that will change the therapeutic strategy[11] but will not be characterized with certainty by this method. Ultrasound is able to measure the skin thickness and oedema and to follow their evolution. Ultrasound is the best modality for examining lymph nodes (sensitivity 72%–84%, specificity up to 97% with high frequencies probes)[12,13]. Controversial results about ultrasound in the literature emphasize the importance of parameters that interfere with the accuracy of the method. The main one is operator dependence. However, the technique is changing and must not remain only morphological especially in monitoring treatment of cancers.

Magnetic resonance imaging

MRI allows morphological analysis of tumours and kinetic study of the contrast enhancement reflecting the richness of the vascularization. It is the most reliable method for appreciating multifocality. Its role is essential in pre-therapeutic staging and in the assessment of chemotherapy efficacy. Most authors find an excellent correlation between the macroscopic tumour size and the tumour established by MRI and think this method is better than mammography and mammography combined with ultrasound[14,15]. The series of Balu-Maestro *et al.*[8] reporting 60 tumours in 51 patients showed that clinical examination correctly evaluated residual tumour

in 52%, mammography in 38%, ultrasound in 43% and MRI in 63% of the cases. MRI is performs particularly well in premenopausal women with dense breasts. Overestimation of the size is higher in small tumours[16]. The method has a high sensitivity (95%–97%) but a poor specificity (30%–97% depending on the series)[17,18]. The diagnostic criteria is early tumoral enhancement after intravenous injection of a gadolinium chelate. Gilles *et al.*[19] showed a correlation (in 83% of the cases) between the intensity of enhancement on dynamic MR and the importance of residual tumour after treatment. In the series of Abraham *et al.*[20], in 97% of the cases, the results of MRI after treatment correlated with the pathological findings. In the series of Balu-Maestro *et al.*[8], the disappearance of the early enhancement was found in the five cases of complete histological responses. In 45 cases out of the 55 partial responses, the early enhancement persisted, and disappeared in the ten other cases. These ten false negative cases corresponded to two *in situ* carcinomas, and eight invasive carcinomas. In the other series, false negative cases are rare and correspond to *in situ* carcinoma with linear or patchy enhancement and small tumours less than 5 mm. False positive cases are represented by epithelial hyperplasia. The study of enhancement determines a characteristic curve with a wash-out pattern which is highly suggestive of malignancy but not constantly seen. The modification of this curve ('en plateau' or progressive) after the first course of chemotherapy can distinguish responders from non-responders[21]. The visibility of multifocal or multicentric tumours on MRI, not seen with other techniques, can modify the therapeutic choices. In the series of Balu-Maestro *et al.*[8], ultrasound and mammography showed six of the cases of multifocal tumours and MRI showed nine of them, as well as the three multicentric tumours. Nevertheless, because of the poor specificity of MRI, a suspect lesion has to be proven by guided biopsies, to avoid incorrect treatment. The impact on survival of the modification of pre-therapeutic staging by the use of MRI has not yet been evaluated.

Computed tomography

Hagay[22] and Balleyguier *et al.*[23] have shown a significant correlation between the surfaces measured on CT and on histopathology, as well as a decrease in dynamic contrast enhancement of the lesions after treatment correlated with the decrease in tumoral volumes. Watteau *et al.*[24] comparing the evaluation of residual tumour on MR and CT have not found a significant difference between the two techniques. Moyses *et al.*[25] have correlated pre-surgical CT findings with histopathology in 43 patients and have found a very good correlation for round residual tumours but an overestimation in diffuse or multinodular tumoral patterns. CT has the advantages of simplicity, speed, and availability. Its reliability in assessment of response to neoadjuvant chemotherapy has the same limits as the other imaging modalities. Akashi-Tanaka *et al.*[26] compared the results in 42 cases of clinical examination, mammography, ultrasound and pre-surgical CT after four courses of chemotherapy and the results of histopathology. Considering all cancers, the best correlation with histopathology is obtained with clinical examination. There were two false positive and seven false negative cases with CT. Apart from invasive lobular carcinomas ($n = 5$) and inflammatory carcinomas ($n = 2$), the best correlation with histopathology concerning the residual tumoral extension is obtained by CT.

Doppler ultrasound

Doppler ultrasonography allows both a morphological study of tumours and an accurate analysis of tumour vascularity. The use of contrast media strongly increases the detectability of intratumour vessels. In addition, the ultrasound beam causes the injected microbubbles remaining in vascularized tissue to explode. In theory, any viable residual tumour can be detected because of this 'parenchymography' (parenchymal vascularization). Quantification of intratumour vascularity allows a more objective analysis and a better reproducibility than the only qualitative evaluation of the Doppler signal from tumour vessels. Kedar *et al.*[27] showed a greater sensitivity of colour Doppler (77%) than standard ultrasonography (58%) and clinical examination (50%) in tumour evaluation.

An early decrease or disappearance of tumour vascularity evaluated by Doppler ultrasonography may reflect the efficiency of chemotherapy before any decrease in tumour volume. On the contrary, an increase in tumour vascularity reflects tumour progression.

The series of Balu-Maestro *et al.*[28], about 25 patients, showed a good correlation between Doppler ultrasonography and histological analysis when there was no residual tumour, but there were 10 false negatives of Doppler ultrasonography in cases of residual tumour. Walsh *et al.*[29] found a Doppler ultrasonography specificity of 98% for the diagnosis of metastatic lymph nodes. Yang *et al.*[30] showed a high predictive value of malignancy (79%) in cases of peripheral vascularity depicted with Doppler in palpable axillary lymph nodes.

Mammoscintigraphy

Mammoscintigraphy uses the technetium-99m methoxy-iso-butyl-isonitrile (MIBI). The uptake of this tracer by the tumour after intravenous infusion is superior to that of the normal breast tissue. This uptake would be due to the hypervascularization and the alteration of the cellular membrane and metabolism. This marker has a relationship with tumoral physiopathology, thus it is useful to evaluate the response to chemotherapy. Images

are analysed both qualitatively and quantitatively with determination of the uptake ratio between the lesion and the normal tissue (L/N ratio). In the series of Mankoff *et al.*[31] the L/N ratio decreased by 35% in responders and only by 17% in non-responders. On pre-surgical examination, the ratio decreased by 58% in cases of complete histological response and by 18% in cases of partial response.

Positron emission tomography

[^{18}F]Fluorodeoxyglucose (FDG) is the tracer of glucose metabolism of the cancer cell, used by this technique. Its results are independent of breast density. In the series of Schelling *et al.*[32], significant differences in tracer uptake between responders and non-responders were found as soon as the first course of chemotherapy, before radiological response. This early assessment might lead to a change in an inefficient therapeutic protocol. Moreover, PET allows a pre-surgical staging by detecting eventual metastasis and adenopathies. Spatial resolution is improved by coupling a CT scan, associating morphological and metabolic imaging. Other limits are the high cost and the lack of availability of the technique. Studies on other markers, particularly one which could more specifically predict the response to hormone therapy are reported by Rigo and Mourou[33].

Conclusion

Physical examination and conventional imaging techniques still have an important place in the evaluation of breast cancer treated by neoadjuvant chemotherapy. At this time, this morphologic evaluation is the only one recognized by the international criteria. The new functional and metabolic imaging modalities, particularly MRI and PET scan, can approach the nature of residual tumour, allow early detection of bad responders and depict multifocal tumours and metastases. The use of these techniques can change the planning of therapy.

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