The response of the surgeon to changing patterns in breast cancer diagnosis

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Introduction

In the past few years, treatment of breast cancer has undergone an incredible sequence of changes. Modern diagnostic techniques, greater awareness among women of breast cancer incidence and screening and the widespread development of screening programmes have made it easier to diagnose small sized tumours, both palpable and not palpable, invasive and non invasive (Table 1). Cady [1] on the basis of a recent analysis of the variation in the size of breast cancers, diagnosed in the Boston area from 1989 to 1993, has forecast that in about ten years the average size of breast tumours will be 1 cm at diagnosis.

Besides, a surgeon frequently finds himself faced with patients who have had preoperative diagnosis, and he can therefore plan the best possible surgical treatment. Today, there is a greater integration between surgical oncology and plastic surgery which allows technical procedures to combine radical surgery with preservation of good cosmetic results.

Better knowledge of the biology of the early tumour, the possibility to evaluate the status of the axillary nodes by means of non-invasive or mini-invasive techniques and the awareness that most patients receive adjuvant systemic therapy, allows different surgical choices and strategies.

Table 1
Frequency variation of breast cancer smaller than 2 cm by time period (Clinica Chirurgica 1, University of Florence)

	No. of cases	DCIS		T1		Mic	
		No.	%	No.	%	No.	%
1981–1985	392	13	3.3	136	34.7		
1986–1990	819	36	4.4	431	52.6		
1991–1995	1051	65	6.2	643	61.2		
1996–2000	1072	80	7.5	652	60.8	23	2.1
Total	3334	194	5.8	1862	55.8	23	0.7

BC = breast cancer; DCIS = ductal carcinoma *in situ*.

However, new problems have emerged in the last few years such as the progressive increase in the incidence of non-invasive tumours, micro invasive tumours, axillary and internal mammary lymph nodes micrometastases. Moreover, there is a need to have quality control strictly applied to every step from diagnosis to therapy [2–5]. All this leads to the fact that a surgeon, like any other specialist in the diagnosis and treatment of breast cancer, should have a deep knowledge of the multiple problems they may face and be able to set all the pieces of this difficult mosaic so that they work together.

Localisation of non-palpable lesions

The increasing frequency of non-palpable and small breast cancers requires a rigorous diagnostic process and rational methodology. Close cooperation between the radiologist, surgeon and pathologist is essential.

Once mammography or ultrasound reveals a lesion of doubtful nature, the radiologist will define the lesion as 'probably benign', 'suspect' or 'positive'. The next step is stereotactic or ultrasound-guided cytology or histology. It is always a good thing to follow less invasive methods i.e. cytology in those cases where results are the same.

However, core biopsy, in expert hands, shows greater sensitivity and specificity with respect to fine needle aspiration cytology and allows preoperative diagnosis, histological typing and grading evaluation and biological characterisation of the lesion on tissue sampling.

If ultrasound reveals the lesion, as often happens with solid lesions, ultrasound-guided sampling is reasonable. With microcalcifications or parenchymal distortions, stereotactic core biopsy is compulsory, with X-ray of the specimen to show the presence of microcalcifications.

Recent reports have shown significant advantages using a stereotactic or ultrasound-guided vacuum-assisted breast biopsy in achieving definitive preoperative diagnosis [6–8] and reducing the false-negative biopsy rate.

According to the 'European Society of Mastology (EUSOMA) guidelines on quality assurance in the diagnosis of breast disease' [4] the minimum standard for women with breast cancer, having a preoperative diagnosis of malignancy, should be over 70% and the expected optimal standard over 90%. Very occasionally there may be a significant discordance between suspicious radiological features and benign sampling where no reasonable pathological correlation can be made. Under these circumstances, open surgical excision is advisable.

At the end of the diagnostic phase, the radiologist should indicate on the mammographic report the site of the lesion in the two orthogonal mammographic views and the possible presence of multifocal or multicentric cancer foci. This occurs more frequently in the presence of microcalcifications. On the contrary, opacities are usually isolated, occasionally multifocal, but very rarely multicentric. Parenchymal distortion, which is usually monofocal, is very often a benign lesion, but should always be confirmed histologically.

Nevertheless, before surgical excision, magnification mammography of the tumour site is appropriate. It is therefore essential that the surgeon and the radiologist together should devote a few minutes to a joint thorough examination of the mammogram.

When breast cancer has been diagnosed and the patient agrees to conservative surgery, localisation procedures are mandatory. The target is the full excision of the tumour with uniform margins. In the past, the standard approach to tumour localisation has been hook wire or dye localisation. An ultrasound- or mammographic-guided hook wire is inserted in the breast and placed by the radiologist within 1 cm. from the lesion, if possible in at least 90% of cases [4]. This method is particularly useful for deep lesions, mainly in dense breasts, where it can be anchored more surely. It is very accurate, economical and rapid, as only about half an hour is required for the entire localisation procedure. The disadvantage is that this procedure must be carried out shortly before surgery and it requires accurate planning. The hooked wire may move away from its original position; this happens more frequently in fatty breasts. For dye localisation, it is important to use a sterile charcoal suspension that does not diffuse into the surrounding tissue and that stays in for a long time. The injection of the charcoal is guided by mammographic, stereotactic or ultrasound examination. The trace goes from the lesion to the skin where a small spot is evident. With stereotaxis the spot can be located far from the site of the lesion according to the view used. In this case, the spot reflects only one of the two coordinates of the skin projection of the lesion itself. If the craniocaudal view is used, the spot is in the upper quadrant on the vertical line of the lesion; if the medio-lateral or latero-medial view is used, the spot is in the internal or external quadrants on the horizontal line of the lesion. Obviously the surgeon will remove only the part of the breast which surrounds the lesion. With ultrasound, the spot is on the skin projection of the lesion. The indications for this method are the same as for the hooked wire, but the advantage is that it can be carried out at the moment of cytology.

A more recent method for localisation of non-palpable tumours is called ROLL (Radioguided Occult Lesion Localisation) [9]. The day before the operation, the patient is injected with 99mTc-labelled colloid particles of human serum albumin, ranging between 10 and 150 μm in diameter (Macrotec; Amersham Sorin, Saluggia Italy) into the centre of the suspicious lesion. Stereotactic or ultrasound-guided injection of a volume ranging from 0.2 to 0.3 ml is used when microcalcifications or opacities, respectively, are present. Front and lateral view planar scintigraphy images of the breast are obtained with a gamma camera immediately, and also 5 hours after the administration of the 99mTc-labelled colloid particles. The correct localisation of the tracer is verified before the operation by injecting a contrast medium under stereotactic guidance and superimposing these images on the mammogram.

The excision biopsy is performed the next day using a gamma-detecting probe. The site of the lesion shows the maximum radioactivity. Margins of resection are defined where radioactivity fell sharply. After excision, the probe is used to check the resection bed.

ROLL is particularly recommended in microcalcification-clusters, in parenchymal distortion and in single opacities. It allows exact localisation of the lesion independently of the injection site of 99mTc labelled colloid particles and the surgeon is able to localise the lesion most precisely during surgery. Moreover, it enables complete removal of the lesion in 99.5% of cases [9]. A preliminary study by Luini et al. [10] which compares wire localisation with radioguided excision shows reduced excision volume and better centring of the lesion within the specimen with the latter.

Whatever the method of localisation, it is extremely important to X-ray the specimen using clips

for orientation. Orthogonal X-ray views should be obtained when the excision does not include the whole thickness of the parenchyma from skin to fascia. Successful excision of non-palpable lesions is, therefore, a combination of surgical, as well as radiological, skill and the proportion of non-palpable lesions, successfully excised at the first operation, should be in excess of 95% [4].

Harlow et al. [11] describe a technique of intraoperative tumour localisation by ultrasound without the use of other methods to guide the excision of non-palpable breast cancers. The authors have achieved pathologically negative excision margins at first operation in 97% of cancers with a closest margin of 0.8 cm excision.

The conclusions are that ultrasound-guided excision of non-palpable breast cancers are feasible with results that are comparable to those reported with needle wire localisation procedures and eliminates the need for preoperative localisation. For patients with ultrasound detectable lesions of any size, this method has the potential to decrease cost and discomfort for the patient.

Treatment of early breast cancer

Whatever the localisation method, the problem clearly is full excision of the lesion i.e. a quantity of tissue must be removed around the tumour to achieve good local control and cosmesis. This same problem is present even when the tumour, although small, is palpable.

It is now clear that breast cancer may be more or less aggressive and that several prognostic and predictive factors may play a major role in the choice of the most appropriate therapy and in the final results. Modern imaging, morphological and biological characterisation of the lesion, (besides many other factors such as age, fitness and attitude of the patient towards the diagnosis of cancer), require a more flexible attitude from the surgeon. Moreover, the surgeon should never forget that correct treatment nowadays is the result of the correct blending of the surgical, radiotherapeutical and pharmacological techniques that are available. This obviously means that the surgeon is no longer alone when faced with the tumour. However, this demands great knowledge of the problems and the ability to face different situations and to evaluate each single situation in its entirety.

Surgical treatment may cure a high percentage of cases nowadays and this is due to early diagnosis. However, early diagnosis does not mean underestimating the risks and problems connected with breast cancer. The first problem is the choice between mastectomy and conservative surgery.

Mastectomy

As regards small tumours, that are often non-palpable, mastectomy plays a very limited role. On the contrary, it is in non-invasive tumours that mastectomy plays a very precise role (25% of the cases) [12], which will probably increase in the near future [13].

For these cases, skin-sparing mastectomy has a precise role and through it good cosmetic results can be obtained. When skin-sparing mastectomy does not guarantee good results cosmetically, it is better to perform a total mastectomy with immediate reconstruction. Both skin-sparing mastectomy and total mastectomy must be done following rigorous techniques. Oncological surgeons must excise all the breast tissue taking care not to prepare skin flaps too thin and at risk of necrosis. The essential element is to programme pre-operatively the procedure drawing the incision on the skin. A strategic point for a good reconstruction is the preservation of the inframammary fold. There are many technical variations that the surgeon must know. Classically after skin-sparing mastectomy, the reconstruction is realised with autologous tissue: recently the temporary expander reconstruction has being used more frequently (Fig. 1). After total mastectomy, the reconstruction can be carried out by means of implants or autologous tissue. Particular attention should be given to the contralateral breast in order to obtain better symmetry by correcting shape and volume. If reconstruction has been done with a temporary expander, this is usually performed during the operation for expander removal; if a permanent implant is used the contralateral breast is often corrected immediately.

In some breast cancer cases, for which mastectomy is indicated, a contralateral prophylactic mastectomy must be carefully evaluated with the patient with reference to some risk factors [14]. This may be advisable in the following situations:

- family history of breast cancer in patients under 40 years of age,
- expression of mutant genes (*BRCA1*, *BRCA2*) following genetic investigation [15] (contrary to what is generally believed, genetic investigation should mostly concern patients with breast and ovarian cancers),
- previous diagnosis of contralateral ductal or lobular atypical hyperplasia,

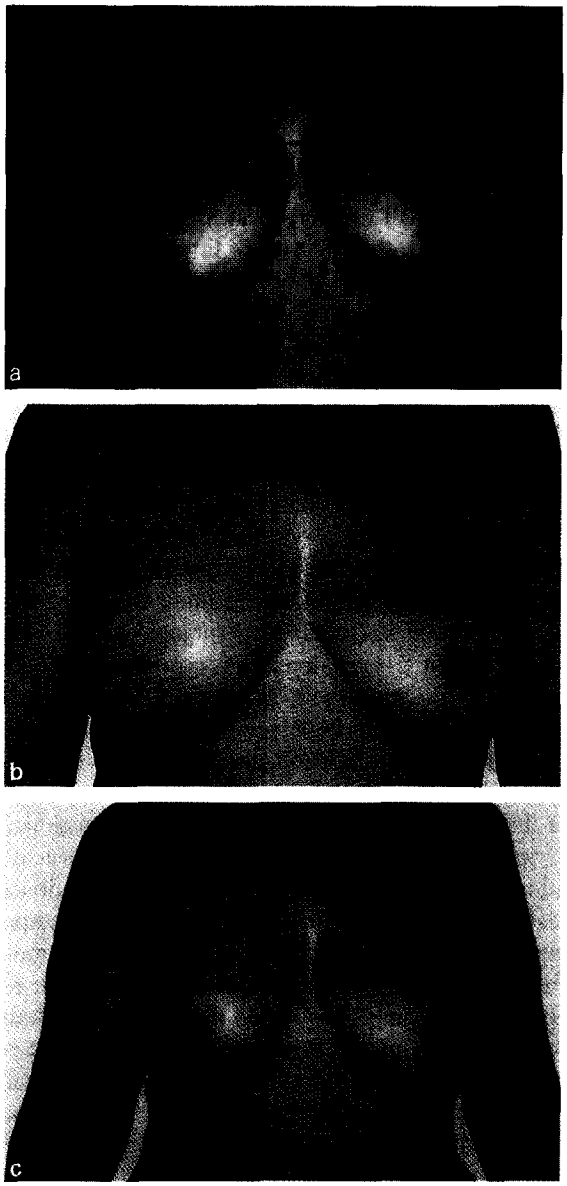

Fig. 1. (A) Preoperative view of 54 year old patient with multicentric infiltrating carcinoma in the right breast: 6 mm in the central quadrant, 7 mm in the inner superior. (B) Skin sparing mastectomy and immediate reconstruction in a single stage with permanent tissue expander (pT1b, pN1bi) — axillary dissection was performed through a small axillary incision. (C) The procedure completed with nipple and areola reconstruction. Any correction in the controlateral breast.

- difficulties in clinical examination and imaging of the breast because of its anatomical structure with risk of delayed diagnosis of cancer,
- patient preference.

A problem which accompanies mastectomy for DCIS (Ductal Carcinoma In Situ) is the possible successive diagnosis of micro-invasive or invasive breast cancer after final histology. Wahedna et al. [16] have not identified any factor capable of predicting a higher likelihood of invasive focus on 140 patients with core-biopsy diagnosis of DCIS without invasion. In this series, the proportion of patients with an invasive focus on surgical excision was 44%. Of the 100 patients with microcalcifications at mammography, occult invasion was found in 48% of cases without correlation between calcification cluster size and risk of an invasive focus. However, using a stereotactic core needle biopsy, with a 11-gauge vacuum-assisted device, the underestimation of DCIS is only 18% according to Lee et al. [7]. The possibility of axillary metastases, in the presence of an occult invasion has caused some surgeons to carry out routine prophylactic first level axillary dissection to avoid doing it later even if patients with pure DCIS have a very low risk of nodal involvement and should not undergo axillary surgery [17]. During mastectomy, however, some lymph nodes are removed together with the breast and can be examined by the pathologist [12].

Conservative surgery

Conservative surgery is now the usual therapy for small *in situ* or invasive tumours, but many problems must be solved by both the surgeon and the pathologist.

First of all, the surgeon must combine the width of the excision with the cosmetic result. From a practical point of view, he may have two different attitudes not always justified by the oncological situation. Firstly, carrying out as large an excision as possible with the smallest cosmetic damage. Secondly, doing the smallest possible excision with minor oncological risk. On the other hand, conservative surgery is always followed by radiotherapy particularly with invasive tumours and therefore the role the latter can play in the local control of the disease should not be forgotten. Tumour radiosensitivity evaluation is an important parameter to consider.

Practically, one can either be a maximalist, doing the upmost independently of the histology and biology of the tumour, or a minimalist, guided by global evaluation of the situation and therefore highly personalised. Certainly the former is easier, more traditional and more easily repeatable in terms of respecting guidelines. The second is more eclectic, requires a deep knowledge of the problem and therefore patient management becomes more complex and difficult.

Published guidelines of each of the diagnostic and therapeutic phase of breast cancer must be maximalist as they cannot ignore different environmental situations. However, if in the future, diagnosis and treatment of breast cancer are managed in Breast Units, there will certainly be quality improvement

and keener attention to individual situations. In particular, everything should be codified, registered and subject to quality control.

In a recent paper, Faverly et al. [18] tried to identify a group of tumours called 'breast carcinoma of limited extent' (BCLE). A BCLE was defined as having no tumour foci (of invasive carcinoma, DCIS and lymphatic emboli) beyond 1 cm from the edge of the dominant mass. These tumours should be the ideal candidates for classical conservative therapy and a subgroup of these might be treated with breast conservation without radiotherapy.

According to the authors, these tumours should be selected by using the most modern diagnostic techniques in order to exclude the possible presence of multifocality. Margins should not be under 2 cm and checked by an X-ray of the specimen. The margins should be microscopically examined, careful and rigorous procedures should be followed. Finally, postoperative mammography together with preoperative mammography, specimen X-ray and histological examination should confirm the full excision of the lesion.

In the paper of Faverly et al. [18], 11% of cases showed residual foci outside the 1 cm microscopically tumour-free margin, although all the above-mentioned criteria had been followed. The authors emphasise that, according to their morphological study, identification of BCLE is difficult and therefore requires a superb team approach of the radiologist, surgeon and pathologist.

The primary role of surgery is local control whether the tumour is invasive or *in situ*. In many cases, local control also means general control of the disease.

There are many risk factors for a local recurrence after conservative surgery. Some of these can be evaluated before surgery and must be taken into account by the surgeon's operative plan. Particularly, the surgeon should know the patient's age, tumour size, the presence or not of multifocality and the radiological pattern. If available, he should have cytological or histological results too [8,19,20].

This information often leads to a larger or smaller excision because his aim is to obtain a free margin. The wider the margin, the lower the frequency of local recurrences. Margin status is considered one of the most important factors in as much as it is a variable the surgeon can control, while the biological characteristics are not affected by treatment. The difficulty is to define which is an adequate margin and this, according to some authors, varies according to the tumour aggressiveness [13].

Voogd et al. [21] have published a case-control study in order to verify which histological factors are associated with an increased risk of local recurrence after conservative treatment for early breast cancer. The risk of recurrence was significantly increased with high grade extensive intraductal component (EIC) adjacent to the primary tumour and microscopic margin involvement in the presence of vascular invasion. Unfortunately, these factors are not known before surgery.

Peterson et al. [22] evaluated the significance of the final microscopic resection margin status on treatment outcome in 1021 patients with early breast cancer treated with breast conserving surgery and radiotherapy. They concluded that in selected patients with focally positive or close resection margins, the 8 year local control rates are similar to those seen in patients with negative or unknown final resection margins.

From a technical point of view, the surgeon has to choose the best procedure to obtain free margins not forgetting, however, the cosmetic result. The parenchyma excision may be lozenge-like, spherical or cylindrical. In any case, the tumour should be at the centre of the excised sector and this can be obtained with palpation if the tumour is palpable or with one of previously described localisation methods.

The integration of remodelling procedures is typically indicated for tumours located in the lower quadrants in order to obtain a safe oncological excision avoiding an insufficient cosmetic outcome (Fig. 2). The plastic surgeon has a wide choice of mammoplasty patterns which can be used for the different locations of the tumour (Fig. 3). In these cases, clips must always be left in the surgical bed to guide radiotherapy.

The pathologist must have all the necessary information about clinical and mammographic findings and the exact site of the lesion in the breast. The intact specimen with suture markers should be submitted to the pathologist. If the surgeon has to widen the excision, he must indicate the location of the new excision with respect of the previously removed specimen. A good method is to design how the surgeon performed the operation and in what part of the excision he re-excised the margin. If the lesion is non-palpable, the specimen must be accompanied by an X-ray.

Every phase of the surgical procedure must be accurately recorded to favour quality control. Quality objectives are:

- to ensure completeness of excision,
- to minimise the number of operations for therapeutic purposes (90% of operations should not require a further operation for incomplete excision),

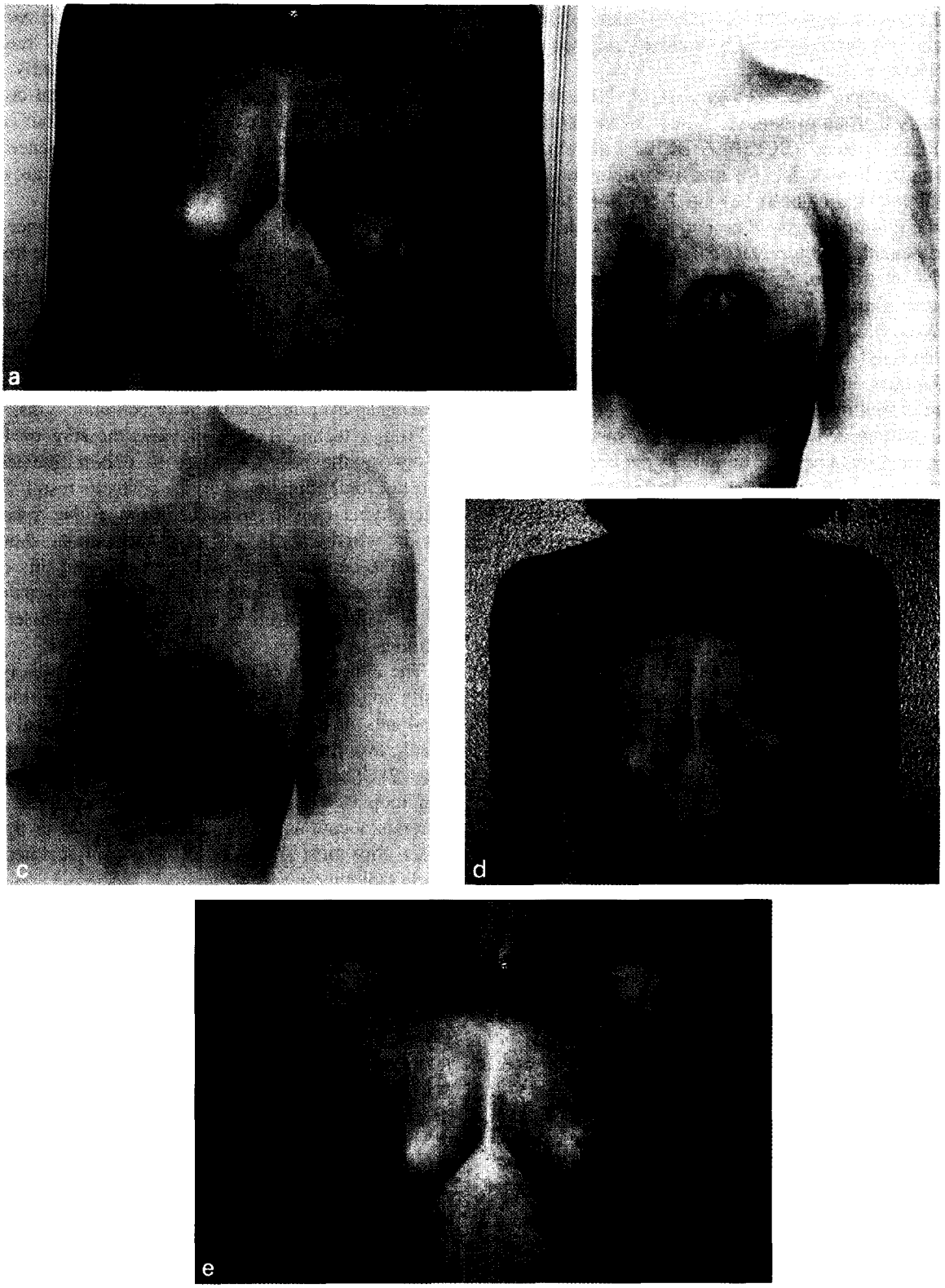

Fig. 2. (A) Preoperative view of 40 year old patient with breast asymmetry and a 12 mm ductal infiltrating carcinoma of the central lower quadrant in the left breast. Skin marker of the sentinel node. (B) The wide excision performed with the integration of a reduction mammoplasty with an inverted T pattern. The excision site is filled in by suturing together the glandular flaps. (C) The inverted T mammoplasty residual scar. (D) Postoperative result after wide excision, axillary dissection and monolateral mammoplasty. Any correction in the controlateral breast was performed (pT1c, pN1bi, pMx). (E) 2 years follow-up after radiotherapy.

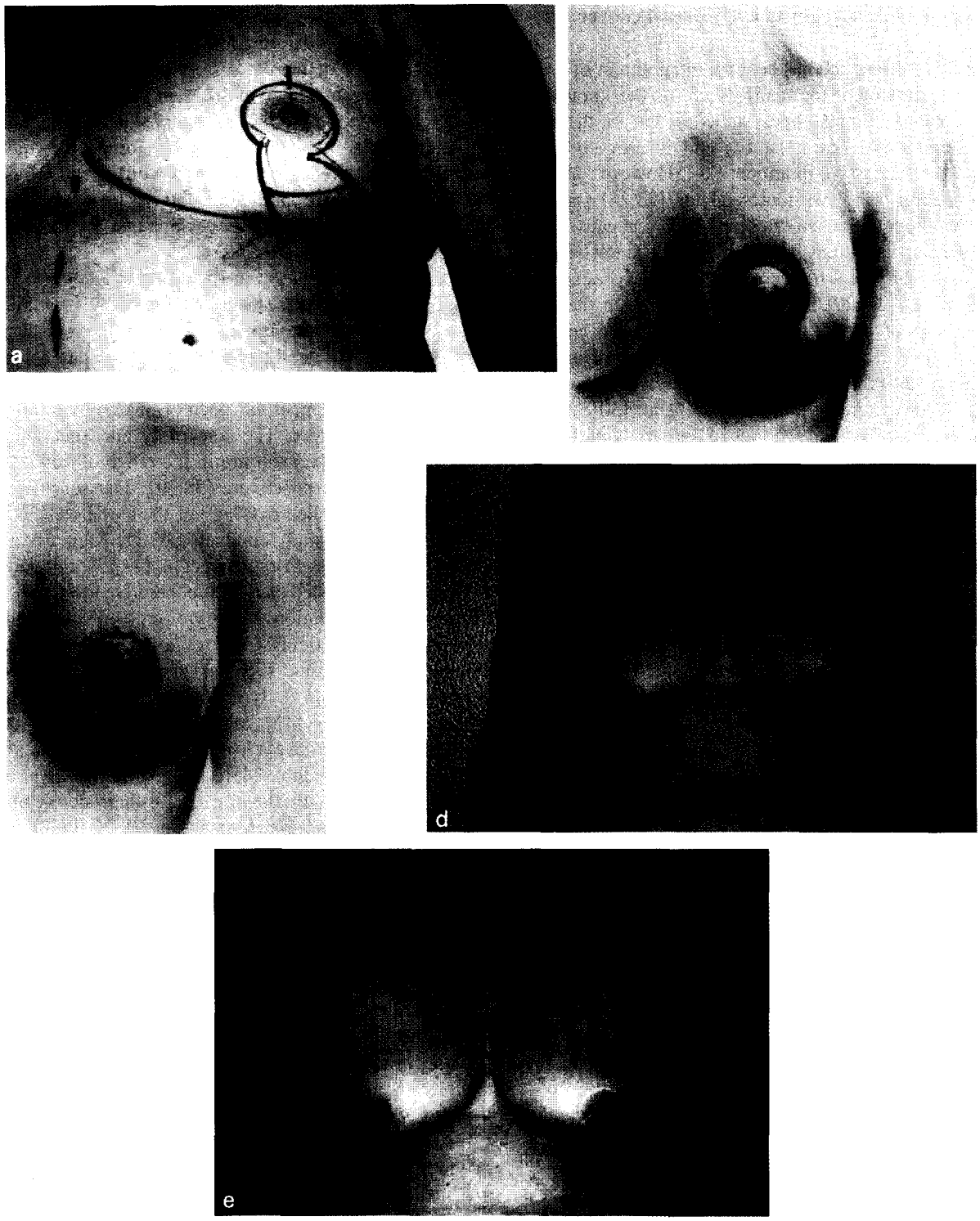

Fig. 3. (A) Preoperative view of a 68 year old patient with a 12 mm tumour of the lower external quadrant in the left breast. Plan of the associated mammoplasty. (B) Wide excision integrated in the B-modified pattern. (C) B-modified mammoplasty residual scar. (D) Postoperative view after wide excision, axillary dissection and monolateral mammoplasty (pT1mic, pTis, pNo). (E) 2 years follow-up.

- to avoid overtreatment of women with favourable lesions,
- to ensure that all necessary data are obtained for making decisions on adjuvant radiotherapy or adjuvant systemic therapy [5,23].

Lymph node surgery in early breast cancer

Axillary dissection has been an integral part of breast cancer treatment for many years, as the knowledge of axillary lymph nodes status is one of the most important prognostic factors and is used to establish the successive treatment [24]. However, axillary dissection is not without sequelae [25,26] and it is non therapeutic when lymph nodes are negative. This has been happening recurrently with small size tumours which less frequently have axillary metastases (Table 2) [27–29]. Actually, a decrease in the average size of breast cancer observed in the last few years [1] is accompanied by a decrease in axillary lymph nodes metastases if the latter are examined traditionally. According to Cady et al. [30], the examination of several sections of axillary lymph nodes has almost doubled the incidence of positive lymph nodes in T1a and T1b tumours (from 10% to 24%). This greater incidence is almost always due to the presence of micrometastases, the prognostic impact of which is uncertain at present.

Axillary dissection is arguably not only a staging procedure, but also a therapeutic treatment in patients without positive lymph nodes. The National Surgical Adjuvant Breast and Bowel Project (NSABP)-B04 study [31] showed, in fact, that prophylactic axillary dissection does not seem to offer significant advantages in terms of first relapse incidence, of metastases and survival compared with therapeutical axillary dissection. However, a recent meta-analysis of 4 studies [32] has demonstrated a survival advantage of 4.7% (95% confidence interval (CI) 1.9–7.5% $P < 0.01$) in patients who have had prophylactic axillary dissection. For such reasons, a great deal of research work has been carried out to try to identify cases with negative lymph-nodes without having to perform an axillary dissection. At the same time, a lot of research work has been done to study the primary tumour so as to be able to decide the adjuvant therapy on the basis of its pathobiological characteristics [33,34]. Ménard et al. [33] published an interesting study on the various biological and pathological characteristics of breast cancers and concluded that this tumour can show two different phenotypes: phenotype A with low relapse rate constant in time and found in elderly patients, and phenotype B which occurs more frequently in young women and which is more aggressive, particularly in the first years following surgery, with relapses which can appear even after a long disease-free interval.

Table 2
Frequency of positive axillary lymph nodes and number of nodes involved according to size of primary tumours (Clinica Chirurgica 1, University of Florence, 1981–2000)

	N+		1–3 nodes		>3 nodes	
	No. of cases	%	No. of cases	%	No. of cases	%
pT1a	138	10.1	8	57.1	6	42.9
pT1b	438	17.5	64	83.1	13	16.2
pT1c	1286	33.0	301	70.8	124	29.2
Total	1862					

Clinical examination of the axilla is known to be inaccurate with a false-negative rate of 39% to 45% [35,36]. Mammography may support the presence of enlarged axillary lymph nodes, but it has a low specificity [37]. The role of ultrasonography of the axilla in breast cancer has been evaluated by a number of investigators. The sensitivity and specificity for axillary involvement are in the range of 56–73% and 70–100%, respectively [38,39]. The sensitivity of ultrasound-guided cytology of the axilla was 36% in a multicentre study conducted by De Kanter et al. [38]. In the study of Bonnema et al. [40], lymph node metastases were detected by preoperative ultrasonography in combination with cytology in 63% of all node-positive patients (26% of all patients). Other imaging modalities such as magnetic resonance imaging (MRI) [41], lymphoscintigraphy, radioimmunoscintigraphy [42], and single-photon-emission tomography [43] have a lower accuracy than a surgical axillary procedure. More interesting results have been obtained with the use of 18-fluorodeoxyglucose-positron emission tomography (FDG-PET): in a series of 167 consecutive patients studied, this method showed a sensitivity of 94.4%, accuracy of 89.8%, and negative predictive value of 95.3% for the evaluation of axillary metastases (M. Greco, Istituto Tumori, Milan).

The introduction of the sentinel node (SN) biopsy in the treatment of breast cancer has the aim of limiting the number of axillary dissections only to patients with positive lymph-nodes. Moreover, sentinel node biopsy is associated with negligible morbidity compared with complete axillary lymph node dissection [44]. The sentinel node is by definition "the first lymph node that receives afferent lymphatic drainage from a primary tumour" [45] and this reflects the concept of step-wise spread of cancer through the lymphatic system [46]. Skip metastases are less than 2% [47]. One of the first studies of the SN in breast cancer was published by Giuliano et al. [48] using blue dye. Later, in 1998, Krag et al. [49] published a study on the use of a radiopharmaceutical which was injected around the tumour and traced to the sentinel node using lymphoscintiscans preoperatively and a

gamma detector probe perioperatively. In the last few years, there has been a progressive increase of interest among surgeons for SN biopsy [50] in breast cancer and there are many papers on this subject. In many studies, only blue dye was used. In others, only radioisotope and both methods were employed. The literature shows that the combination of blue-dye and radiolabelled colloid gives better results [51,52], but in some institutions even the use of only one of these methods has given good results.

The non-eligibility criteria of the SN procedure include the presence of clinically positive axillary nodes and multicentricity [53] of the tumour because in such cases other nodes may be metastatic, while the SN is uninvolved. The accuracy of SN biopsy in women with larger primary breast cancers (>2 cm) is controversial [54–56].

Before using the SN technique in routine daily practice every group has to follow proper training through one of the available courses and an accurate learning phase in a number of patients undergoing an axillary dissection after sentinel node biopsy [57,58].

The SN technique has now reached noticeable standardisation and published experiences suggest "that SNB should become a standard method of staging in patients with small-sized breast cancers and clinically uninvolved axilla and that routine axillary dissection should be abandoned" [58–60]. Actually many studies, so-called of the first generation, were carried out by performing both the SN biopsy and full axillary dissection to check both the detection rate and sensitivity, specificity and positive and negative predictive values of the technique.

In a review of the literature on 4791 procedures, Sandrucci et al. [61] reported that identification and harvesting of the SN ranged from 65% to 98.7%. The combined use of radiotracers and dye has been reported to increase the SN detection from 19% to 34%; the overall mean sensitivity was 92.1% (range 84–100%), the specificity and positive predictive value 100%, the mean negative predictive value and diagnostic accuracy were 94.7% (range 83–100%) and 97.3% (range 92.3–100%), respectively.

In the use of this method there are many important variables, from the method used, up to the site of injection of the dye or of the radioactive colloid, to the dose of radioactivity used, to the use of lymphoscintiscans, to the timing and to the use of a hand-held probe to locate the node.

Another problem concerns the methods for the pathological evaluation of the SN and the role of the frozen section. The routine use of intraoperative haematoxylin and eosin staining of multiple sections of SN requires an experienced pathologist, and is time consuming. It should be completed by delayed haematoxylin and eosin staining and immunohistochemistry evaluation. According to Sandrucci et al. [61], frozen section evaluation has a sensitivity of 73%, 100% specificity, 88% negative predictive value and 91% accuracy. Veronesi et al. [62] reported a 32.1% false-negative rate of traditional frozen section evaluation of the SN. They introduced a new method of extensive intraoperative examination of the frozen SN. With this, the general concordance between sentinel and axillary lymph-node status was 96.7%, the negative predictive value of intraoperative examination was 94.1% [63]. Contrary to their expectations, rapid immunocytochemical staining for cytokeratins did not increase the detection rate of SN metastases which were identified on purely morphological grounds. With so many different variables, it would be logical to standardise the procedure of localisation and assessment of the SN in breast cancer.

Apart from the technical problems, the use of SN biopsy has given rise to a series of problems which make the scenario of breast cancer treatment even more complex.

With this method in fact, it is possible to identify the extra axillary lymphatic drainage particularly towards internal mammary nodes and to find a micrometastasis in a lymph node which might not have been seen with the conventional method.

As regards the drainage towards the internal mammary nodes, it is more evident when the traces have been injected peri or intra tumourally. The frequency is 14.4% (8.4–35%) in association with axillary drainage and of 2% (0.9–5.9%) as exclusive drainage [61]. In the experience of Jansen et al. [64], 21 (19%) out of 113 patients had sentinel nodes outside the axilla. It is difficult to say what is the meaning of a metastasis or a micro metastasis in the internal mammary node alone or together with the axillary lymph nodes.

Although it has been demonstrated that routine dissection of internal mammary nodes does not improve outcome, information on the status of the internal mammary chain is important for the prognosis of patients with breast cancer, especially those without axillary metastases [65]. Actually 20% of T1 patients with negative axillary lymph nodes have shown metastases in internal mammary lymph nodes [66] and prognosis is similar to patients with positive axillary lymph nodes. Metastases in both sites leads to worse prognosis. However according to Crowe and Temple [67] with SN biopsy less than 3% of patients with T1 can have further prognostic information from the examination of internal mammary nodes, which can modify the adjuvant treatment.

A new problem to be explored is the presence of micrometastasis. The frequency of micrometastasis in SN is nearly 50% of positive SN (43.6% [60], 45% [68]). The biological significance of micrometastasis has been already discussed in another chapter of this book. If the SN contains tumour cells, the incidence of non-SN metastases increases, but may still be very low in certain patients. The incidence of non-SN metastasis increases according to the size of the primary tumour and the size of the SN metastases [69]. In February 2001, Viale (IEO-Milan) presented at St. Gallen a study on 634 patients with SN biopsy and axillary dissection. 109 patients had micrometastases in the SN. In 21.8% of these patients, other positive nodes were present. This percentage was significantly correlated to the size of the metastases: 44.7% for macrometastases, 36.4% for >1 mm micrometastases and 15.6% for <1 mm micrometastases.

Reynolds et al. [68] published a paper in order to identify a subset of patients in whom axillary metastases where present only in the SN. Out of 60 patients with positive SN, 28 also had other metastatic lymph nodes. A multivariate analysis showed that the size of the primary tumour over 2 cm and macrometastasis in SN (>2 mm) were the only two significant factors associated with a greater probability of the involvement of the other axillary nodes. In fact, none of the 18 patients with tumours < 2cm. and micrometastases in the SN had other positive nodes.

Lindhal et al. [70] published a study to verify whether by increasing the biological characterisation of the primary tumour it is possible to avoid axillary dissection. They came to the conclusion that none of the present markers are capable of giving an accurate prediction on the state of axillary nodes. Silverstein et al. [71] suggested not performing axillary dissection in T1a breast cancers because in their experience the frequency of positive nodes is 3%. According to Shetty and Reiman [72], axillary dissection can be avoided in breast cancers under 4 mm and in non-tubular duct cancers with nuclear and histological grade 1.

Greco et al. [73] treated 401 breast cancer patients without axillary dissection, and showed that the nodal relapses after 5 years of median follow-up were 6.7%, thus suggesting that only a minimal part of axillary nodal micrometastases become clinically evident or may be some micro or macro metastases detected with axillary dissection or SN biopsy are treated by radiotherapy to the low axilla in conservative treatment. Certainly the rate of nodal relapses for T1a and T1b patients (2% and 1.7%, respectively) is so low that even the SN biopsy has to be questioned. Greco et al. [73] suggested to consider post surgical therapy in T1 breast cancers on the basis of biological characteristics of the primary.

The possibility to perform SN biopsy by following such micro-invasive methods has also led to the use, at the moment only in clinical trials, of this method also in DCIS where axillary dissection is not indicated. The first results of these studies showed an unexpected percentage of axillary micrometastatic involvement which open the way to further studies on the biology of breast cancer.

In the series of Klauber-Demore et al. [74], 9 (12%) out of 76 patients with high-risk DCIS had metastases in the SN, 7 of them micrometastases. The same authors observed 3 metastases (2 micrometastases) in the SN in 31 patients with micro-invasive DCIS. In the publication of Pendas et al. [75], 5 patients (6%) out of 87 with DCIS showed metastases in the SN. However, the authors concluded that lymphatic mapping and SN biopsy should not be considered routine for all patients with DCIS.

Actually, in accordance with Ellis et al. [76], it seems possible to state that micro-invasive breast cancer carries a very low risk of axillary metastases equivalent to high grade DCIS.

For this reason, SN biopsy might be appropriate in large DCIS with or without micro invasion. However, this is a sector which should be the subject of clinical trials in as much as there is no agreement either on the definition of micro-invasive cancer [77] or on the validity of SN biopsy in multicentric tumours. According to Silver and Tavassoli [78], patients with microinvasive breast cancer have a risk of axillary metastases of under 5%. According to Crowe and Temple [67], there are three groups of patients with a less than 5% risk of axillary metastases and for whom axillary dissection is not strictly necessary. These are patients with DCIS, microinvasive or pure tubular breast cancer under 1 cm. The same authors are convinced that patients with a low-grade T1a breast cancer without lymph vascular invasion have a 1% to 3% risk of axillary metastasis.

Conclusions

To conclude, the surgeon together with other specialists involved in the treatment of breast cancer should accept this new scenario: smaller and smaller tumours, less invasive tumours and fewer and fewer positive axillary lymph nodes.

Surgery will receive some help from the new technique of localisation (ROLL), but great care should be taken in excising the tumour with adequate

margins (1.5–2 cm). Plastic surgery can guarantee good cosmetic results also for those lesions located in the central or lower quadrants or when mastectomy has to be performed.

There seems not to be any safe methods yet which allow identification of the subset of small tumours without axillary metastases. FDG-PET is the most interesting non-invasive method for the evaluation of the axillary lymph nodes together with ultrasound-guided cytology which should always accompany the initial clinical examination.

SN biopsy can be performed by an experienced and dedicated team with little, if any, morbidity and will certainly substitute axillary dissection in the staging of axilla in patients with microinvasive or small-sized breast cancers (<2 cm).

The increase in detection of axillary and extra-axillary micrometastasis following SN biopsy must be carefully evaluated from a practical point of view. Above all, the prognostic meaning of micrometastasis, which cannot be considered at the same level as macrometastasis is important, with reference to postoperative adjuvant therapy.

The study of the primary tumour and of its pathological features together with a molecular portrait based on the gene expression patterns and modern technology in examining sentinel node (reverse transcriptase-polymerase chain reaction (RT-PCR)) will undoubtedly lead to a better understanding of breast cancers and probably to a general avoidance of axillary dissection.

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