Chapter 8

Breast and Axilla Treatment in Ductal Carcinoma In Situ

Ambrogio P. Londero, Serena Bertozzi, Roberta Di Vora, Fabrizio De Biasio, Luca Seriau, Pier Camillo Parodi, Lorenza Driul, Andrea Risaliti, Laura Mariuzzi and Carla Cedolini

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.74340

Abstract

Ductal carcinoma in situ (DCIS) represents a challenge for the breast unit team, beginning from its difficult radiological detection and continuing with its controversial multimodal treatment and management. With the introduction of the mammographic screening, DCIS has become a common diagnosis. In fact, today DCIS is mostly identified by mammography or magnetic resonance imaging (MRI). The increased prevalence of DCIS diagnosis, in the past, raised the problem of the therapeutic management. In this chapter, the breast and axillary surgery in case of DCIS and the most controversial aspects regarding DCIS management are reviewed based on international guidelines and on the current literature.

Keywords: ductal carcinoma in situ, ductal intraepithelial neoplasia, breast-conserving surgery, sentinel lymph node biopsy, breast cancer, breast surgery

1. Introduction

Ductal carcinoma in situ (DCIS) represents a current challenge for the breast specialists, beginning from its difficult radiological detection and continuing with its controversial surgical and nonsurgical management. In this chapter, breast surgery and axillary surgery in case of DCIS are reviewed, as well as some aspects of its preoperative evaluation, based on the more recent international guidelines, and the controversial issues are discussed.

2. Histopathological aspects

The breast gland contains a ductal system that, with successive branches, ends distally in the terminal ductal-lobular units. Ducts and lobules are coated with two types of cells: luminal epithelial cells and myoepithelial cells. The myoepithelial cells contain myofilaments, have contractile capacity, and form a network structure located on the basal membrane. Histologically, the retention of the myoepithelial cell layer helps to distinguish in situ forms from invasive ones.

DCIS is a neoplastic breast lesion, characterized by the presence in the ductal-lobular terminal unit of a malignant epithelial cell clone that does not exceed the basal membrane. DCIS includes a spectrum of different lesions from the histological point of view, with different architecture, nuclear morphology, degree, and the eventual presence of necrosis and calcifications.

DCIS has been historically divided into five histological subtypes, based on the tumor cell growth modality: comedogenic, solid, cribriform, papillary, and micropapillary; however, in most cases the appearance is composite.

Comedogenic DCIS is characterized by a solid proliferation of large pleomorphic cells, with abundant eosinophilic cytoplasm and high-grade hyperchromatic nuclei. A peculiar aspect of this DCIS is the presence of central necrosis which may give place to dystrophic calcifications, which are usually detected by mammography as clustered microcalcifications. Frequently, these lesions contain periductal fibrosis, due to the fibroblast response in the surrounding stroma, and a chronic inflammation component which may sometimes make these lesions clinically palpable.

Noncomedogenic DCIS consists of a population of smaller and monomorphic neoplastic cells, with variable nuclear grading. Necrosis is minimal or absent and the periductal fibrosis is unfrequent. In the cribriform subtype, neoformed glandular spaces are uniformly distributed and have a regular shape. In the solid DCIS, neoplastic cells completely fill in the interested tissue. The papillary subtype grows, giving rise to papillary formations with the fibrovascular axis missing in the micropapillary DCIS, also characterized by interstitial papillary protrusions.

The importance of this morphological classification has been downsized in recent years since this distinction does not take into account important prognostic factors such as nuclear grading, necrosis, and architecture [1, 2]. However, a distinction between comedogenic and noncomedogenic DCIS remains very significant, because of the poorer prognosis of the comedogenic type, which is at higher risk of evolution toward invasive carcinoma and of local recurrence [3].

Several classifications were subsequently proposed [1], taking into consideration nuclear grading, presence of necrosis, histological architecture and pattern, lesion size, number of involved ducts, cell polarization, and positivity for some receptors. The most used classification systems are those endowed with prognostic power.

2.1. Natural history

Several recent studies have shown that invasive breast cancer results from a progression of in situ cancer that proliferates and increases to overcome the basal membrane of the ductal epithelium, thus becoming infiltrating. However, the probability that all invasive carcinomas

originate from in situ forms is difficult to demonstrate, despite the many studies that have tried different approaches to achieve this. In particular, some studies focused on women with untreated DCIS, and some others used animals, as well as genomic studies of expression of cellular markers.

DCIS greatly differs from benign proliferative breast lesions for its biological and clinical features. Alterations in the normal number of chromosomes occur in the evolution of breast lesions from benign hyperplasia to preinvasive malignant forms [4]. Heterozygosis lost occurs in more than 70% of high-grade DCIS, in 35–40% of atypical ductal hyperplasia, and in 0% of normal mammary tissue samples [5–7]. The p53 oncosuppressor gene is mutated in 25% of DCIS and only rarely in benign breast lesions [8]. Genomic analyses identified some genetic alterations related to the nuclear grading of DCIS [9]: loss of genetic material in the chromosome 16q resulted associated with well or moderately differentiated DCIS, while DNA amplifications were related to a poorer differentiation. Thereafter, the genetic characteristics of DCIS were also compared with those of the adjacent invasive cell carcinomas, showing almost identical patterns.

Several other studies reported genetic similarities between invasive carcinoma and DCIS, especially high-grade DCIS, supporting the hypothesis that invasive carcinomas derive from the progression of preexisting DCIS [4, 10, 11]. The first step might be the abnormal response to growth factors, for example, mediated by estrogen receptors, which let the benign cells lose their ability to respond to normal apoptosis signals. Then, there would be the loss of function of some oncosuppressor genes as p53, the acquisition of some genetic instability with the loss of heterozygosity, and the onset of abnormal oncogenes such as HER2/neu. Finally, also changes in the surrounding stroma and neoangiogenesis occur, so that the preinvasive lesion becomes capable of invading the surrounding tissues for an imbalance between the gain of function by malignant cells and loss of function by the surrounding normal cells.

Many of the typical molecular characteristics of invasive lesions are already present in DCIS, such as genetic mutations, oncogenic expression, and loss of normal cell cycle regulation ability. The expression of molecular markers seems to have many points in common between in situ and invasive ductal carcinoma, supporting again the evolution of invasive carcinoma from DCIS. In the following section, these markers are discussed.

2.2. Biomolecular markers

The estrogen receptor is expressed in about 60% of DCIS [1] especially in those that exhibit less aggressive histological features such as low grading of differentiation and necrosis. The progesterone receptor expression seems to be consensual to that of the estrogen receptor.

HER2/neu is a member of the epidermal growth factor receptor (EGFR) family and is routinely studied in invasive carcinomas. It seems to be expressed by more than 40% of DCIS, especially by high-grade or comedogenic ones [12], so it would appear to be expressed in these lesions with a much higher frequency than that of invasive forms.

The expression of markers differs according to the nuclear grading of DCIS. In fact, considering only low-grade DCIS, some studies showed that in over 90% of cases it expresses the estrogen receptor, while in less than 20% of cases, it overexpresses HER2/neu or presents p53

mutations. In contrast, HER2/neu overexpression and p53 mutations are found in two thirds of high-grade DCIS, which expresses the estrogen receptor in only the 25% of cases.

2.3. Multifocal and multicentric disease

For its ability to spread within the ductal system, DCIS frequently presents with multiple outbreaks within the same quadrant (multifocality) or in different quadrants (multicentricity). Multifocality occurs in two thirds of patients with low- or intermediate-grade DCIS, characterized by a discontinuous growth. On the other hand, high-grade lesions tend to be continuous, with neoplastic cell outbreaks usually not farer than 5 mm [4, 13, 14]. Other reports, albeit with lower incidence, show a higher frequency of multifocality and multicentricity in DCIS, and many authors highlighted how mammography is less sensitive than magnetic resonance imaging in such cases and underestimates the extent of the disease [4, 15].

In a very old study, Lagios and colleagues found that the incidence of multicentricity increases with the lesion size [16]. In addition, DCIS can spread through the ducts within the ductal system to reach the nipple, without ever overcoming the basal membrane. This mode of growth characterizes Paget's disease of the nipple, a rare manifestation of breast cancer that occurs with crusty and pruriginous nipple erythema.

3. Diagnosis and imaging

In the past, DCIS was clinically identified by objective examination by the presence of nipple discharge, Paget's disease, or a palpable mass. Today, clinical finding is rare, and DCIS is mostly identified by mammography or magnetic resonance imaging.

3.1. Mammography

The sensitivity of mammography in detecting DCIS varies in the literature between 87 and 95% [17–19]. In a comparative study of mammographic and anatomopathological findings, the number of high-grade lesions not detected in mammography was significantly low [18]. Microcalcifications are the expression of cellular debris and calcified secretions within the intraductal lumen; can be extremely variable in size, shape, and appearance; and account for about 60–75% of all mammographic abnormalities in case of DCIS [20–25].

The diagnostic approach to breast microcalcifications is the analysis of morphology, distribution, and eventual modifications over time. According to the terminology of BI-RADS, the morphology can be classified as "pleomorphic," "linear," "branched linear," "amorphous," or "indistinct." The distribution of calcifications can be widespread or scattered throughout the breast, regional or distributed within a large volume of breast tissue (>2 cc), clustered if there are at least five calcifications in a small breast volume, segmental in the case where calcific deposits lie in ducts or branches of a lobe or breast segment.

Considering the changes in microcalcifications over time, in the presence of doubtful but probably benign mammographic findings, the absence of modifications after a certain period of time is reassuring. On the other hand, as underlined in a retrospective study, in the case

of suspicious microcalcifications, the morphological aspect stability is not enough to exclude malignancy [26]. In this study, 25% of patients with malignancy finding at biopsy had microcalcifications with a stable appearance for 8–63 months. It is thus evident that morphology and distribution of microcalcifications are much more relevant in the decision-making process of clinicians.

Several studies attempted to correlate the appearance of microcalcifications and other DCIS mammographic findings with the biology of these lesions [13, 20, 21, 26–34]. The layout of calcifications reflects the localization of DCIS in the ductal system. Calcifications in a subareolar major duct may appear as a bundle of calcifications oriented toward the nipple. Calcifications in smaller ducts may have a branched appearance that reflects the extralobular endpoints, where most of the carcinomas originate. A branched radial pattern of calcifications means that intralobular endpoints are involved [21].

In several studies, most DCIS presented with granular microcalcifications [20, 27–31], but a radio-pathological correlation study showed that the histological type of DCIS cannot be accurately determined on the basis of the morphological aspect of microcalcifications found in mammography [31]. However, in this study, almost 80% of linear microcalcifications were associated with the comedogenic subtype, while granular microcalcifications were associated with non-comedogenic DCIS subtypes in more than half cases [31]. Fine pleomorphic or linear-branching calcifications were significantly associated with high-grade DCIS and necrosis [25, 31], whereas round calcifications were significantly associated with low-grade DCIS [25]. Similarly, other mammographic studies showed that linear calcifications are most frequently expression of high-grade DCIS, while fine granular ones are more typical of well-differentiated DCIS [32–35].

Although microcalcifications are the most frequent mammographic finding in the diagnosis of DCIS, this may assume less commonly other radiological aspects. Various studies in the literature report more than 10% of DCIS presenting with solid mass aspect, usually with well-defined margins [20, 21, 25]. This percentage rises if narrowing the survey to low-grade DCIS [17]. A mass-like aspect of DCIS may be the direct manifestation of a soft tissue mass or may be the result of periductal fibrosis, causing in this latter case an irregular or a bulging aspect of the mass [36].

Further mammographic manifestations include architectural distortion and focal asymmetries. Architectural distortion may also be determined by the sclerosis of the interstitial tissue surrounding the DCIS [21] or the tumor invasion of Cooper's ligament [37]. Many low-grade DCIS appear to be mammographic masses or asymmetries [25] and, as a result, appear more frequently to be noncalcific lesions [34, 36]. Finally, Tabar et al. reported that the survival of women with masses or linear and linear-branching calcifications is considerably worse than women with other types of microcalcifications [38].

3.2. Magnetic resonance imaging

The use of magnetic resonance imaging (MRI) in the diagnosis of DCIS remains still an argument of great debate. The interest in using this tool for DCIS has grown following the brilliant results of its use in the invasive carcinoma. Initially, due to the different appearance of the two pathologies, this instrument was not considered adequate alone for the study of in situ

lesions. A fundamental factor which led MRI to become an important tool in the preoperative diagnosis and evaluation of DCIS was the transition from high time resolution to high spatial resolution [39]. Another important factor is that MRI was used to study patients who had already been diagnosed with cancer by mammography, and only when MRI began to be used as a tool for screening on high-risk patients allowed more data to be compared about the accuracy of the two different diagnostic tools.

Several studies have been conducted to find out the multiple manifestations of DCIS by MRI and to correlate these with the biological characteristics of the disease. The superiority of MRI in the diagnosis of DCIS has been demonstrated in numerous studies with sensitivity ranging from 86 to 92% [15, 40–43]. MRI sensitivity is higher for high-grade lesions, regardless of whether or not there is necrosis, which instead affects the sensitivity of mammography in identifying high-grade DCIS [41, 42, 44, 45]. The pattern of breast lesion enhancement correlates with the biological profile of DCIS [46], because the diagnosis is based on tissue enhancement after administration of a contrast medium and to the hyperdensity of neoplastic lesions due to vascular permeability [47].

Angiogenesis in DCIS may be partly due to the destruction of the cellular myoepithelial cell surrounding the ducts [48]. Myoepithelial cells tend to be more preserved in low-grade DCIS while being lost or significantly absent in high-grade DCIS or with comedic necrosis. Recent studies also show that focal damage to the myoepithelial layer could trigger tumor invasion. The tumor cells adjacent to the point of damage tend to be more frequently associated with genetic and phenotypic alterations, such as loss of estrogen receptors, reduced expression of oncosuppressors, and increased expression of genes related to the cell cycle, angiogenesis, and invasive capacity [49].

The terminology of BI-RADS includes three types of responses to breast MRI: “mass-like enhancement” defined as a three-dimensional injury occupying a generally rounded area of oval or irregular shape, “focal enhancement” defined as a small enhancement spot <5 mm that does not allow a further morphological description, and “non-mass-like enhancement” described as enhancement of an area without forming a mass. This last manifestation is most common in DCIS, present in 60–80% of cases [15, 24, 39, 41], while invasive or mixed ductal lesions appear in over 75% of cases as “mass-like enhancement” [41].

Non-mass-like enhancement lesions are distinguished on the basis of the distribution pattern as segmental, linear, ductal, focal, regional, multiregional, and diffuse. Segmental means a triangular enhancement area with the apex toward the nipple suggesting the distribution of a duct and its branches. Linear is defined as an enhancement area that may not correspond to a duct, while ductal indicates a linear enhancement zone with ramifications like a duct. The regional pattern has a large volume of enhancement that cannot be assimilated to a duct, and the focal enhancement is confined to a smaller area than 25% of a quadrant. The segmental distribution is the most common non-mass-like DCIS presentation [15, 24, 41].

On the basis of the internal enhancement pattern, non-mass-like enhancement lesions are distinguished also as clumped, heterogeneous, and homogeneous. The internal enhancement pattern can be clumped if it takes a cobbled appearance with occasional confluence areas. It may be homogeneous or otherwise heterogeneous when it is or not uniform. The most

common internal enhancement pattern is the clumped one (51.5%), followed by the heterogeneous (21%) and homogeneous ones (15%) [41].

Evaluation of kinetics in DCIS is less significant compared to invasive lesions, and in fact the extent of perfusion increases with the progression of lesions from benign to in situ and even more invasive lesions [47]. Based on the BI-RADS classification, the kinetic aspect of DCIS has been standardized, and two phases of the enhancement can be recognized: an initial phase, within the first 2 minutes after administration of the contrast medium, and a delayed phase after 2 minutes. The initial phase can be rapid, intermediate, or slow; the delayed phase can be classified as persistent (the signal continues to increase), plateau (the signal density does not change after the initial increase), or washout (the signal decreases after the initial climb). DCIS is usually characterized by the fast initial phase and a washout in the delayed phase [24, 50]. Moreover, there is no statistically significant difference in the kinetic characteristics between DCIS of different grading [24, 51].

Despite the superiority of MRI in terms of sensitivity, its role in the management of in situ disease remains still controversial. According to recent studies, the routine use of MRI in DCIS does not change the clinical management in 99% of patients and lead to more unnecessary reexamination and longer time interval before surgery [52]. In a recent meta-analysis, the proportion of patients who changed the treatment based on MRI findings results about 15% [53]. Available evidence suggests that the percentage of patients with noninvasive cancer who may benefit from a preoperative MRI assessment is not very high and should be weighed with the economic availability and the delay in definitive treatment resulting from the increase in preoperative investigations.

Patients undergoing MRI do not show a significant reduction in the re-intervention rate for positive margins after conservative surgery [53]. Several studies also show that the routine use of preoperative MRI is associated with a greater incidence of mastectomy for invasive carcinoma and the trend seems to be the same for DCIS [43, 53–56]. On the contrary, conservative surgery rates are higher among women who do not undergo preoperative MRI [53], and this probably reflects the MRI ability to detect multifocal and multicentric disease and results in a greater number of women who are not candidates for conservative surgery.

The identification of a subgroup of patients with DCIS that could benefit from preoperative MRI needs further studies on DCIS biology, in particular on its potential to progress and recur. In fact, as outlined in the literature, only 30–50% of cases of DCIS evolve to invasive disease if untreated [57, 58], and consequently many patients who undergo mastectomy for DCIS would receive an overtreatment; whether preoperative MRI results an advantage in terms of local control of disease and survival in patients with DCIS is still unclear.

However, many agree that there is definitely an improvement of surgical outcomes [52–54, 59], and a study on DCIS and early invasive breast cancer does not reveal, after 4.6 years of median follow-up, significant differences in terms of recurrence, metastasis occurrence, mortality, or contralateral lesions rate between patients undergoing or not preoperative MRI [60]. The use of MRI in addition to mammography could help in defining the exact extension of DCIS, although MRI often overestimates the size of the primitive tumor [59].

3.3. Screening

Mammography is considered to be the most effective screening test for the detection of early breast cancer. In Italy, biennial mammography is recommended in women aged between 50 and 69 [61, 62]. In women aged between 40 and 49, it should be performed only based on the familiar history, individual risk, and breast density, possibly accompanied by an ultrasound examination. In women aged over 70, there is no evidence of the effectiveness of mammographic screening, but the possibility of extending it to 75 years is considered. The relative reduction in mortality for breast cancer is 14% in women aged between 50 and 59 and 32% in the 60–69 range, reflecting the direct correlation of mammography sensitivity with age, related to the reduction in breast density [63].

MRI is not recommended as a screening survey in the general population [64] due to its low specificity and hence its higher number of false positives. The use of MRI as a screening method, in addition to mammography and clinical examination, is justified in high- and moderate-risk women, who include women with BRCA1 or BRCA2 mutations; previous chest wall radiotherapy between 10 and 30 years of age; Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndrome; personal history of DCIS; atypical ductal hyperplasia; and lobular intraepithelial neoplasia.

Tomosynthesis, which combines conventional, two-dimensional images with three-dimensional, multilayer images, appears to be particularly effective in case of dense breasts, where the volumetric overlap of traditional mammography images prevents some lesions from being identified. In a study of 9672 women, the combination of mammography and tomosynthesis increased not only the cancer detection rate but also the number of false positives [65].

The incidence of screen-detected DCIS varies between 15 and 30% [66–70]. It is greater in women aged between 40 and 49 (28.2%) than in older women (16–20.5%). The age-adjusted incidence rate increased from 2.4 to 27.7 per 100,000 women between 1981 and 2001 [36]. In line with these data, some studies reported an estimated annual DCIS incidence of 32.5 per 100,000 women [71]. The overall screen-detected DCIS rate results 0.78 per 1000 mammograms, indicating that one DCIS is approximately identified every 1300 screening mammograms [66].

The mammographic screening resulted in a mortality reduction of about 20–30% [72–74], but screening value remains uncertain in the case of DCIS. Some authors argue that it prevents the incidence of a large number of invasive tumors and contributes substantially to survival improvement. Others claim that this type of injury does not always progress to invasive cancer and in those cases it would not lead to death, and indeed, its response to screening would be a source of overdiagnosis, resulting in more harm than good [75]. The epidemiological definition of overdiagnosis is the difference between observed and expected incidences [70].

A study estimated that, of the 141 screened deaths, 17 were determined by the progression of DCIS to invasive carcinoma and therefore concluded that the detection of DCIS at screening prevented 12% of the overall avoided deaths with screening [75]. Another interesting evidence is that the majority of screen-detected DCIS are of high-grade and have a more pronounced tendency to present necrosis, suggesting that screen-detected lesions have a higher risk of progression [76].

The main objection to the screen detection of DCIS comes from the observation that misdiagnosed DCIS is much less likely than invasive tumors to become clinically evident [66]. In fact, it is evident that there are breast cancers that will never become lethal and that many women receive systemic therapies without knowing who will benefit from it, but the risk of overdiagnosis is lower than the benefits [70]. From a clinical point of view, the best and most prudent way to deal with DCIS is to consider it as a potential future invasive carcinoma [71].

4. Surgical treatment

The uncertainty about the natural history of DCIS and the impossibility to determine predictive factors for which lesions will progress to invasive forms make the therapeutic choice extremely difficult. Initially, standard therapy was the simple mastectomy in 98–99% of patients [77]. Subsequently, with the introduction of always more conservative treatments for invasive carcinomas, the breast-conserving surgery (BCS) became progressively the most frequently used surgery for DCIS. There are, however, no randomized studies comparing outcomes after mastectomy and BCS [12, 64].

The currently recommended therapeutic options of the National Comprehensive Cancer Network (NCCN) include mastectomy and lumpectomy with or without radiotherapy and with the possible addition of tamoxifen in the case of hormone-positive DCIS. Randomized trials indicate that lumpectomy associated with radiotherapy results in the lowest recurrence rate but does not show any difference in overall and disease-free survival [78].

According to a recent article by Worni and colleagues, among 121,080 women with DCIS diagnosed from 1991 to 2010, most patients received radiotherapy (43%) after lumpectomy, followed by lumpectomy alone (26.5%), unilateral mastectomy (23.8%), bilateral mastectomy (4.5%), and ultimately no treatment (2.3%) [78]. In the 20 years of study, trends in the treatment choice have changed, with a considerable increase in lumpectomy with radiotherapy (100% increase). Also, the significant increase in the number of bilateral mastectomies, a trend that seems to be driven more by the choice of bilateral prophylactic mastectomy than by the need to treat bilateral disease, is interesting.

4.1. Conservative breast surgery

Breast-conserving surgery (BCS) in the treatment of invasive breast cancer has gone affirming over the years, thanks to studies that demonstrated no significant difference in survival rates compared to mastectomy. However, this evidence has not yet been reached in the case of DCIS, and to date there are no randomized comparisons of mastectomy and BCS in women with DCIS. However, retrospective studies did not show any difference in the overall and disease-free survival between the two strategies [79, 80].

Several studies have been conducted in the attempt to determine the magnitude of the recurrence risk in patients with DCIS, in order to use this information to improve the therapeutic approach, but there are no definitive results on the effectiveness of BCS without radiotherapy, which, according to Worni et al., is still used today in about a quarter of cases [78].

BCS consists in the excision of the lesion surrounded by about 1 centimeter of macroscopically health tissue. It may be a simple wide excision of breast parenchyma, also called lumpectomy, or a cylindrical excision of breast tissue including the overlying skin and the underlying muscle fascia, also known as quadrantectomy [81]. In case of nonpalpable breast lesions, many different techniques can be used in order to intraoperatively guide the surgical resection, such as the preoperative placement of a wire hook or a radioactive tracer [82].

The specimen is then oriented with some stitched in order to facilitate the margin evaluation by the pathologist [83]. In particular, a negative margin greater than 2 mm represents nowadays the adequate margin for DCIS [84]. Moreover, in some cases also a cavity shaving may be performed, although there is no evidence that this procedure will significantly reduce reinterventions for margin positivity.

4.2. Mastectomy

Mastectomy consists in the complete mammary gland excision together with the overlying skin and the nipple-areola complex, as well as the underlying muscle fascia. Nowadays, even more conservative techniques have been developed, so that it is possible to spare the skin with or without the nipple-areola complex by performing the so-called nipple-sparing mastectomy or skin-sparing mastectomy [85–91].

For what concerns these two last procedures, there are still controversies about the long-term oncological results, as, for example, the nipple includes the terminal portion of the breast ducts and may then represent a place at risk of recurrence. However, the esthetic results are undiscussed, and these kinds of techniques result in an essential improvement in the psychophysical wellness of women undergoing breast demolition.

Mastectomy is a healing process in 98–99% of patients with DCIS. The relapses after this intervention may be in situ but also invasive and can occur both as a local recurrence and a distant metastasis [77]. After mastectomy, the reported recurrence rate is less than 1.5% in most studies [92, 93]. The use of skin-sparing mastectomy does not correlate with a significant increase in local recurrences [93].

Recurrence after mastectomy for DCIS could be due to the lack of sampling or recognition of an invasive component or incomplete removal of the involved breast tissue. However, the fact that the majority of recurrences after mastectomy occur in the first 5 years suggests that most of these are due to the lack of recognition of an invasive carcinoma rather than the malignant transformation of the residual breast tissue [77].

Finally, mastectomy is an effective treatment for DCIS, but its use should be carefully evaluated in the light of a pathology that does not present the risk of remote metastasis, typical of infiltrating forms, which will not necessarily become invasive.

5. Adjuvant treatments

Although DCIS is a local disease, the use of both local and systemic adjuvant therapies is widespread. In particular, adjuvant radiotherapy after BCS and the use of tamoxifen or

aromatase inhibitors are considered, while no evidence supports the use of adjuvant chemotherapy in the treatment of DCIS [64].

5.1. Radiation therapy

With the introduction of adjuvant radiotherapy after BCS for invasive breast carcinoma, the interest in radiotherapy application for DCIS has also greatly increased. A lot of studies in the literature evaluated the efficacy of this treatment in DCIS patients, and according to the current guidelines, radiotherapy after BCS results is strongly recommended in patients with DCIS [64].

Breast irradiation usually includes all the residual breast (whole breast irradiation), is classically performed within 6 months after surgery, and usually consists in 25 sessions, even if also shorter hypofractionated protocols are described. Anyway, radiation therapy may be also limited to the area surrounding the tumor (partial breast irradiation) and be performed intraoperatively immediately after the tumor excision, as happens for the intraoperative radiotherapy (IORT) [94].

A recent meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) on individual data from four randomized studies showed that adjuvant radiotherapy reduces 15.2% of the absolute risk of 10-year ipsilateral invasive relapse after surgery for DCIS, anyway without any significant effect on survival [95]. These data confirm the findings of previous international randomized trials that generally showed a reduction by about 50–60% in ipsilateral breast recurrences in patients who received radiotherapy after BCS compared to BCS alone [96–99].

Recurrences after BCS for DCIS are usually half invasive and half in situ. With the addition of radiotherapy to BCS, the annual invasive recurrence rate results about 0.5–1%. The possible benefits of this therapeutic choice on survival would be the reduction of invasive recurrences and the consequent reduction of mortality [77, 98].

According to recent reports, most patients are subjected to lumpectomy followed by radiotherapy, and this therapeutic option raised from the 25% of treatments in 1991 to the 50% in 2010 [78]. Patients who refuse radiotherapy after BCS should be properly informed of the potential for greater local recurrence risk, although a survival benefit may not yet be evidenced by studies due to the insufficient number of patients examined and to the very low mortality rate for this disease [71].

5.2. Hormonal therapy

Given the important role of the estrogenic pathway in the pathogenesis of breast carcinomas, many strategies have been developed which can control estrogen-sensible tissues. The first experimented drug was tamoxifen, a selective estrogen receptor modulator (SERM), which has the ability to act as an estrogenic agonist in certain tissues such as bone and endometrium, while it acts as a powerful estrogenic antagonist in others including the breast. For these properties it is widely used in the treatment of invasive breast cancer, where it has been shown to reduce the risk of relapse and death after surgical treatment [100].

The role of adjuvant therapy with tamoxifen for DCIS was analyzed in two major randomized trials. The NSABP B-24 study randomized 1804 women with DCIS between BCS followed by

radiotherapy and tamoxifen for 5 years versus BCS followed by radiotherapy and placebo for 5 years [101]. This study demonstrated a significant reduction of events after 5 years in the tamoxifen group compared to the placebo one. In particular, a reduction was observed in the risk of invasive relapse in both the ipsilateral and the contralateral breasts. However, for what concerns noninvasive relapses, the addition of tamoxifen was not proven to be significant.

The benefit in women treated with tamoxifen was also significant after 163 months of follow-up [95], and over 15 years of follow-up, adjuvant tamoxifen reduced the risk of recurrence of ipsilateral breast cancer by 31% [99]. A retrospective analysis, conducted on 41% of the original study population, evaluated the relationship between estrogen receptor expression and tamoxifen benefit. It has been shown that treatment with tamoxifen significantly reduced the risk of subsequent breast cancer at 10 and 14.5 years, while in patients without expression of estrogen receptors, no benefit was observed. Finally, there were no differences in survival between the two arms of the NSABP B-24 trial.

The randomized phase II trial UK/ANZ DCIS93 evaluated the role of radiotherapy and tamoxifen in the treatment of patients undergoing BCS for DCIS, enrolling 1701 patients [102]. It analyzed the following therapeutic approaches: surgery alone, surgery followed by radiotherapy, surgery followed by tamoxifen for 5 years, and surgery followed by both radiotherapy and tamoxifen for 5 years. As for the use of tamoxifen, at 12 years of median follow-up, the study showed a reduction of ipsilateral in situ relapses, while there seemed to be no effect on the invasive ipsilateral recurrence.

Considering these two trials as a whole, it emerges that adjuvant tamoxifen, associated with radiotherapy, reduces the risk of in situ ipsilateral recurrences in the case of DCIS which expresses hormonal receptor, independently by the patient's age [48, 64]. Thereafter, the decision whether to propose tamoxifen as adjuvant treatment should be based on the evaluation of its side effects and potential benefits.

In postmenopausal women with invasive breast cancer, the aromatase inhibitors have been shown to be more effective than tamoxifen in reducing recurrences and preventing new contralateral cancers after surgery [100]. The second International Breast Cancer Intervention Study (IBIS-II) had the aim of studying the role of aromatase inhibitors in both primary prevention and adjuvant therapy in women with DCIS [102]. The NSABP B-35 study had similar objectives and compared tamoxifen with anastrozole for 5 years in 3000 postmenopausal women who underwent surgery and radiotherapy for DCIS, and, at a median follow-up of 8.6 years of treatment, anastrozole significantly improved the disease-free survival [103].

5.3. Other medical therapies

HER-2/neu is overexpressed in a variable number of DCIS [100] and appears to be related to an increase in local recurrences [104]. A retrospective analysis of 10,853 women enrolled in the EORTC trial showed that, of the 31 local relapses occurring in patients with DCIS, 24 were associated with in situ lesions that overexpressed HER-2/neu. The real meaning of HER-2/neu overexpression in DCIS is currently the object of the study, given its importance as a prognostic and predictive factor in the invasive cancer. The use of trastuzumab, a monoclonal antibody targeting HER-2/neu, is interesting given the relative frequency of its presence in

the DCIS and the lack of effective medical therapies for DCIS which does not express estrogen receptors. These considerations have led to the development of two studies on the role of trastuzumab in DCIS. The first study, conducted by Gonzalez et al. with not yet conclusive results, evaluated the benefit of neoadjuvant trastuzumab in DCIS of less than 1 cm. The second one, conducted from the NSBP, has not yet been completed.

6. The microinvasive component

In agreement with the American Joint Committee on Cancer, microinvasive breast cancer is defined as a DCIS where the invasive component is microscopic and does not exceed the size of 1 mm [105]. In the current literature, microinvasive cancer prevalence accounts for about 10–20% of DCIS cases, and it does not represent more than 1% of all breast cancers [1, 106–110].

The natural history of these lesions is unclear; however, DCIS with microinvasion could be an intermediate stage in the invasive evolution. As a proof of this, the microinvasive carcinoma is often associated with DCIS, particularly large and with comedonecrosis [1, 64], and may be formed by small foci of tumor cells that, after crossing the basal membrane, infiltrate the surrounding stroma [64]. The age of presentation does not seem to be significantly different from that of invasive or in situ forms [106].

Almost all DCIS with microinvasion are identified by the presence of microcalcifications at mammography [111]. Occasionally, the microinvasive carcinoma appears as a palpable mass with serum or blood vessel secretions from the nipple or as Paget's disease [112–114]. Microinvasive lesions tend to be larger in size and therefore more often palpable than purely in situ lesions. The detection of a microinvasion within a DCIS can be extremely difficult for the pathologist because of the many patterns with which the lesion can invade the stroma [77]. Usually, the microinvasion foci tend to be accompanied by a stromal response characterized by inflammatory cells scattered in one neoformed connective matrix [115]. Moreover, the use of immunohistochemical markers specific for the basal membrane or myoepithelial cells can help identify microinvasion in doubtful cases [115].

Concerning the therapeutic implications, data is not uniform. Surgical treatment can be both conservative and radical. According to recent reports, the use of mastectomy is significantly less frequent for this type of lesion than for invasive carcinomas, and the same happens for adjuvant therapies, generally reserved only for patients with triple-negative carcinomas, HER2-positive breast cancer, or with lymph node involvement [106]. The use of adjuvant radiotherapy is even higher in the group of microinvasive carcinoma than in that of invasive one, possibly due to the higher prevalence of conservative surgery.

According to the AIOM guidelines, mastectomy is indicated in these tumors in the presence of large intraductal component, particularly unfavorable histological characteristics (high-grade and comedonecrosis), or when it is not possible to obtain an adequate resection margin with a conservative resection [64]. BCS is also contraindicated after previous chest wall irradiation, during pregnancy, or in the case of multicentric lesions or diffused microcalcifications [110].

Regarding the use of adjuvant systemic treatments, endocrine therapies may be administered in the case of hormone receptor expression, while chemotherapy is not indicated, except in patients with axillary lymph node metastases [64, 106]. There are currently no prospective randomized studies comparing BCS followed by radiotherapy with mastectomy in the subset of patients with microinvasive carcinoma [105].

Prior to the spread of the sentinel lymph node technique, due to its significant morbidity and poor clinical benefits, axillary dissection was not recommended in the management of noninvasive or microinvasive lesions [109]. With the introduction of the sentinel lymph node biopsy, burdened with much minor complications, axillary surgery has extended also to DCIS in the case of mastectomy, as the technique would not be reliable in the second time if needed [116, 117]. However, in the literature there is insufficient evidence of the efficacy of the sentinel lymph node biopsy for the microinvasive cancer, mainly because the studies are mostly retrospective and based on small sample sizes.

The detection of microinvasive foci at the definitive histological examination of specimen of women initially diagnosed with DCIS is quite frequent. In particular, the upstaging rate to invasive carcinoma varies in the literature about 10–20% of in situ or microinvasive lesions [118]. In the case of unexpected microinvasive carcinoma, the sentinel lymph node biopsy can be performed both in conjunction with the primary lesion excision and later on.

In the literature, the sentinel lymph node metastasis rates reported in the case of microinvasive carcinomas are about 6–10%, and about half of these are micrometastasis [77]. In a recent meta-analysis, Gojon et al. studied the role of the lymph node biopsy in 968 patients with microinvasive carcinoma [116]. It emerged that the macrometastasis rate in the sentinel lymph nodes was 3.2% (CI (95%): 2.1–4.6%) without significant differences between the data of the various considered studies. Patients with macrometastatic sentinel nodes would have a risk of almost 30% of having more non-sentinel lymph node metastases, but, due to the rarity of nodal macrometastases, the global incidence of non-sentinel metastases in microinvasive carcinoma resulted less than 1%. Thereafter, given the low rates of nodal positivity, this meta-analysis does not justify the routine use of sentinel lymph node biopsy in patients with microinvasive carcinoma.

Several studies have tried to identify predictive factors for lymph node involvement but with contrasting results [116]. In addition, many studies have reported excellent prognosis in patients with microinvasive carcinoma, irrespective of the eventual asynchronous lymph node involvement [116]. Some authors reported a similar local or distant recurrence risk in patients with in situ or microinvasive carcinomas and positivity for sentinel lymph biopsy [119]. Then, despite the absence of clear scientific evidence, in the case of microinvasive cancer, the use of the sentinel lymph node biopsy is still recommended, especially given the low morbidity of this practice [77].

The survival of patients with microinvasive carcinoma seems to be a halfway between that of pure DCIS and that of early invasive carcinoma [77]. Some dated studies reported no recurrence after average follow-up of 57 and 47 months, respectively [112, 113]. Kinne et al. reported a disease-free survival of about 94% at a median follow-up of 11.5 years [120]. Solin et al. compared the outcomes of invasive carcinoma with those of DCIS and microinvasive carcinoma treated in the same period [114] and found that patients with microinvasive cancer

had a higher local recurrence rate than those with pure DCIS, as well as an intermediate survival rate between in situ and frankly invasive carcinomas. In contrast, Silverstein and Lagios did not detect differences between patients with microinvasive carcinoma and DCIS in terms of overall and disease-free survival [121].

In a review of Adamovich and Simmons, the median time of appearance of a local relapse resulted in 42 months, most of the local recurrences of microinvasive carcinoma were invasive recurrences, and only the 7% were distant ones [110]. A study by Parikh et al. on 393 women with breast cancer treated with BCS and radiotherapy suggested that microinvasion is not predictive of a significant worsening of local recurrence and distant metastasis-free survival, overall survival, and disease-free survival [122]. This study concluded that, despite the greater aggressiveness in treating patients with microinvasion, clinical and pathological characteristics and outcome did not differ for DCIS with and without microinvasion. Even more recent data emerging from Fang et al.'s work confirmed that disease-free survival of over 2 years in patients with microinvasive carcinoma was significantly worse than that of pure DCIS and similar to that of invasive carcinoma smaller than 5 mm [106].

In conclusion, clinical and pathological features and outcomes do not significantly differ between DCIS with and without microinvasion [106]. Overall survival do not differ significantly in the two groups, which altogether have a good prognosis overall. The prevalence of lymph node metastases in the microinvasive carcinomas is low and does not associate with a prognosis worsening, as it does not lead to an increased risk of recurrence, either local or distant [119]. According with the ASCO guidelines published in 2016, a 6-month clinical follow-up together with annual instrumental examinations should be recommended [123].

7. The role of sentinel lymph node biopsy

Complete axillary dissection was the only possible approach in surgery until the early 1990s of the last century. Nowadays, the sentinel lymph node biopsy represents the standard in most centers that deal with mammary surgery [64, 82, 124–127] and significantly reduced the complications associated with axillary surgery [128] while providing high levels of accuracy in the staging [129–131]. The multicentric NSABP B-32 trial randomized 5611 women with clinically negative axillary nodes to the sentinel lymph node biopsy alone or followed by axillary dissection [131]. No significant differences in disease-free and overall survival and locoregional recurrences were observed between the two groups at a median follow-up of 96 months.

The concept of sentinel lymph node was born in the 1970s and completely developed 20 years later, based on the principle that tumors are drained from a lymphatic channel through the first sentinel node of that region. In 1991 Giuliano and colleagues first applied the method of sentinel lymph node biopsy at the John Wayne Cancer Institute in the context of breast surgery. They reached 100% accuracy in predicting axillary nodal status in a few years [125, 132, 133], opening the way to the spread of the method.

In a recent work, analyzing data from the Surveillance, Epidemiology, and End Results (SEER) registers, Worni and colleagues reported that in 2010 the sentinel lymph node biopsy

was performed in over 70% of mastectomies for DCIS and in at least 20% of lumpectomies. The indications of the sentinel lymph node biopsy for DCIS are not always supported by scientific evidence and are sometimes the result of a consensus of experts, leading to a significant variability among the various centers dealing with breast surgery.

8. Local recurrences

The local recurrence rate after surgery for DCIS, associated or not with subsequent radiotherapy, ranges from 0 to 10% at 5 years and from 8 to 23% at 10 years [77]. A study on a large number of patients undergoing conservative surgical excision and radiotherapy, conducted by an international group, described a recurrence rate at 5, 10, and 15 years of, respectively, 6, 11, and 16% [134]. The cumulative annual local recurrence rate found in this study was approximately 1% and was thus lower than that reported by the NSABP trial, which is 1.8%. This value is similar to that found for invasive carcinoma treated in the same way [77].

Many prognostic factors of local recurrence have been hypothesized in patients with DCIS treated with BCS, associated or not with complementary radiation therapy. In almost all studies, the margin involvement was correlated with a higher local recurrence rate. On the other hand, the local recurrence rate is lower after radical excision with negative margins. However, the adequate distance of the excision margin from the lesion is not precisely defined [77].

In some studies, negative margins of 0 mm (also defined "no ink on tumor") were compared with negative margins up to 10 mm from the lesion, concluding that wider margins give more protection against recurrences [135]. In a meta-analysis conducted by Dunne et al., considering the effect of the state of margins after BCS and radiotherapy, the highest recurrence rate was observed among women with excision margins of less than 2 mm, whereas for margins greater than 2 mm, no further benefits were observed in comparison to margins of 5 mm or more [136]. Therefore, these data imply that for women receiving BCS and radiotherapy, 2 mm margins can be considered adequate to reduce as much as possible the risk of recurrences.

However, without the addition of radiotherapy, conservative surgery with margins lower than 10 mm results in a greater recurrence risk (of more than fivefold), while with the addition of radiation therapy, there seems to be no additional benefit for larger margins [137]. Anyway, no successful study has been performed to compare women with greater or lesser margins, which may conclude for a benefit of a certain margin distance [71].

Young patients show a consistently higher risk of local recurrence than older patients. The reasons for this difference are not clear, but a study found that younger patients tend to have smaller excision volumes, higher prevalence of high-grade tumors, and higher frequency of necrosis [138, 139]. On the other hand, another study did not confirm these differences in terms of pathological characteristics between the two groups of patients and identified in younger women a higher rate of HER2/neu overexpression [140].

Histological features have been evaluated in several studies with different results. From the EORTC87 trial, the local recurrence rate at 5.4 years of follow-up proportionally increased

together with the increase of high-grade tumor (8, 14, and 18%, respectively, for low-, intermediate-, and high-grade lesions). This data is confirmed by the NSABP B-17.89 trial, which also revealed a difference between low-grade tumors with or without necrosis in terms of local recurrences. Between groups of patients with tumors of different grading, but both involving necrosis, recurrence rates did not seem to substantially differ. Moreover, necrosis has been identified as a risk factor for recurrence in many other studies, and comedonecrosis is strongly associated with worse outcome and increased risk of invasive recurrences [98, 140, 141].

The size of DCIS was evaluated in several studies but without definitive responses, also due to the difficulty and lack of uniformity in measuring this kind of lesions [77]. In general, larger tumors have been associated with higher rates of recurrence, both in situ and invasive [93, 142].

A further step forward in the prediction of relapse could be the evaluation of the biomolecular profile, through the study of molecular marker expression. In fact, the positivity for the estrogen receptor has been reported to be associated with a reduction in the risk of recurrence, while the HER2/neu overexpression seems to be associated with an increased incidence of local recurrences [143]. The frequency of expression of HER2/neu in DCIS in some reports exceeds the 40%.

In an attempt to summarize all these predictive factors of recurrence, Silverstein and colleagues developed the Van Nuys Prognostic Index that considers four important variables, each of which is assigned a score from 1 to 3, generating a total score ranging from a score of 4 (predicting the best prognosis) to 12 (predicting the worst prognosis) [144, 145]. The analyzed variables are the size of the lesion, the margin amplitude, the pathological classification including the nuclear grading and the eventual presence of comedonecrosis, and the patient age. The prognostic utility of this score was confirmed by NSABP B-17 trial, and, since half of the local recurrences after BCS were invasive carcinomas, it is very important to evaluate the outcome of the rescue treatment in these patients [146].

Solin et al. studied 41 cases of local relapse in 422 women with DCIS treated with BCS followed by radiotherapy [134]. The median time to local relapse was 4.8 years. In 22 of these 41 patients, the relapse was invasive. Among these lasts, after 4 years from the local recurrence, in 19% of cases, a distant metastasis occurred, and 13% died as a consequence. On the other hand, none of the patients with a noninvasive local relapse experienced metastasis or died due to cancer.

Another study presented similar data, with a 15% of distance metastasis rate after 12 years from invasive local relapse and a 12% mortality rate in this group of women [92]. These studies show how important it is, in the field of BCS, to minimize the risk of invasive local recurrence and consequently the risk of distant metastasis, which are associated with a significantly higher risk of death for cancer-related causes.

Acknowledgements

The authors would like to thank the whole collaborating staff of the Universitât dal Friûl and the support from the Ennergi Research, nonprofit association.

Author details

Ambrogio P. Londero[1,†*], Serena Bertozzi[2,†], Roberta Di Vora[2], Fabrizio De Biasio[3], Luca Seriau[2], Pier Camillo Parodi[3], Lorenza Driul[4], Andrea Risaliti[2], Laura Mariuzzi[5] and Carla Cedolini[2]

*Address all correspondence to: ambrogio.londero@gmail.com

1 Unit of Obstetrics and Gynecology, S. Polo Hospital, Monfalcone, GO, Italy

2 Clinic of Surgery, University of Udine, Italy

3 Clinic of Plastic Surgery, University of Udine, Italy

4 Clinic of Obstetrics and Gynecology, University of Udine, Italy

5 Institute of Pathologic Anatomy, University of Udine, Italy

† These two authors contributed equally to this work.

References

[1] Leonard GD, Swain SM. Ductal carcinoma in situ, complexities and challenges. Journal of the National Cancer Institute. 2004;**96**:906-920

[2] The Consensus Conference Committee. Consensus conference on the classification of ductal carcinoma in situ. The Consensus Conference Committee. Cancer. 1997;**80**:1798-1802

[3] Claus EB, Chu P, Howe CL, Davison TL, Stern DF, Carter D, et al. Pathobiologic findings in DCIS of the breast: Morphologic features, angiogenesis, HER-2/neu and hormone receptors. Experimental and Molecular Pathology. 2001;**70**:303-316. DOI: 10.1006/exmp.2001.2366

[4] Burstein HJ, Polyak K, Wong JS, Lester SC, Kaelin CM. Ductal carcinoma in situ of the breast. The New England Journal of Medicine. 2004;**350**:1430-1441. DOI: 10.1056/NEJMra031301

[5] O'Connell P, Pekkel V, Fuqua SA, Osborne CK, Clark GM, Allred DC. Analysis of loss of heterozygosity in 399 premalignant breast lesions at 15 genetic loci. Journal of the National Cancer Institute. 1998;**90**:697-703

[6] Aubele MM, Cummings MC, Mattis AE, Zitzelsberger HF, Walch AK, Kremer M, et al. Accumulation of chromosomal imbalances from intraductal proliferative lesions to adjacent in situ and invasive ductal breast cancer. Diagnostic Molecular Pathology: The American Journal of Surgical Pathology, Part B. 2000;**9**:14-19

[7] Farabegoli F, Champeme MH, Bieche I, Santini D, Ceccarelli C, Derenzini M, et al. Genetic pathways in the evolution of breast ductal carcinoma in situ. The Journal of Pathology. 2002;**196**:280-286. DOI: 10.1002/path.1048

[8] Rudas M, Neumayer R, Gnant MF, Mittelböck M, Jakesz R, Reiner A. p53 protein expression, cell proliferation and steroid hormone receptors in ductal and lobular in situ carcinomas of the breast. European Journal of Cancer (Oxford, England: 1990). 1997;**33**:39-44

[9] Buerger H, Otterbach F, Simon R, Poremba C, Diallo R, Decker T, et al. Comparative genomic hybridization of ductal carcinoma in situ of the breast-evidence of multiple genetic pathways. The Journal of Pathology. 1999;**187**:396-402. DOI: 10.1002/(SICI)1096-9896(199903)187:4<396::AID-PATH286>3.0.CO;2-L

[10] Buerger H, Otterbach F, Simon R, Schäfer KL, Poremba C, Diallo R, et al. Different genetic pathways in the evolution of invasive breast cancer are associated with distinct morphological subtypes. The Journal of Pathology. 1999;**189**:521-526. DOI: 10.1002/(SICI)1096-9896(199912)189:4<521::AID-PATH472>3.0.CO;2-B

[11] James LA, Mitchell EL, Menasce L, Varley JM. Comparative genomic hybridisation of ductal carcinoma in situ of the breast: Identification of regions of DNA amplification and deletion in common with invasive breast carcinoma. Oncogene. 1997;**14**:1059-1065. DOI: 10.1038/sj.onc.1200923

[12] Millis R, Bobrow L, Barnes D. Immunohistochemical evaluation of biological markers in mammary carcinoma in situ: Correlation with morphological features and recently proposed schemes for histological classification. The Breast. 1996;**5**:113-122. DOI: 10.1016/s0960-9776(96)90054-5

[13] Holland R, Hendriks JH, Vebeek AL, Mravunac M, Schuurmans Stekhoven JH. Extent, distribution, and mammographic/histological correlations of breast ductal carcinoma in situ. Lancet (London, England). 1990;**335**:519-522

[14] Faverly DR, Burgers L, Bult P, Holland R. Three dimensional imaging of mammary ductal carcinoma in situ: Clinical implications. Seminars in Diagnostic Pathology. 1994;**11**:193-198

[15] Menell JH, Morris EA, Dershaw DD, Abramson AF, Brogi E, Liberman L. Determination of the presence and extent of pure ductal carcinoma in situ by mammography and magnetic resonance imaging. The Breast Journal. 2005;**11**:382-390. DOI: 10.1111/j.1075-122X.2005.00121.x

[16] Lagios MD, Westdahl PR, Rose MR. The concept and implications of multicentricity in breast carcinoma. Pathology Annual. 1981;**16**:83-102

[17] Evans A, Pinder S, Wilson R, Sibbering M, Poller D, Elston C, et al. Ductal carcinoma in situ of the breast: Correlation between mammographic and pathologic findings. American Journal of Roentgenology. 1994;**162**:1307-1311. DOI: 10.2214/ajr.162.6.8191988

[18] Yang WT, Tse GMK. Sonographic, mammographic, and histopathologic correlation of symptomatic ductal carcinoma in situ. American Journal of Roentgenology. 2004;**182**:101-110. DOI: 10.2214/ajr.182.1.1820101

[19] Wright B, Shumak R. Part II. Medical imaging of ductal carcinoma in situ. Current Problems in Cancer. 2000;**24**:112-124

[20] Stomper PC, Connolly JL, Meyer JE, Harris JR. Clinically occult ductal carcinoma in situ detected with mammography: Analysis of 100 cases with radiologic-pathologic correlation. Radiology. 1989;**172**:235-241. DOI: 10.1148/radiology.172.1.2544922

[21] Ikeda DM, Andersson I. Ductal carcinoma in situ: Atypical mammographic appearances. Radiology. 1989;**172**:661-666. DOI: 10.1148/radiology.172.3.2549563

[22] Dershaw DD, Abramson A, Kinne DW. Ductal carcinoma in situ: Mammographic findings and clinical implications. Radiology. 1989;**170**:411-415. DOI: 10.1148/radiology.170.2.2536185

[23] Stomper PC, Margolin FR. Ductal carcinoma in situ: The mammographer's perspective. American Journal of Roentgenology. 1994;**162**:585-591. DOI: 10.2214/ajr.162.3.8109501

[24] Jansen SA, Newstead GM, Abe H, Shimauchi A, Schmidt RA, Karczmar GS. Pure ductal carcinoma in situ: Kinetic and morphologic MR characteristics compared with mammographic appearance and nuclear grade. Radiology. 2007;**245**:684-691. DOI: 10.1148/radiol.2453062061

[25] Barreau B, de Mascarel I, Feuga C, MacGrogan G, Dilhuydy MH, Picot V, et al. Mammography of ductal carcinoma in situ of the breast: Review of 909 cases with radiographic-pathologic correlations. European Journal of Radiology. 2005;**54**:55-61. DOI: 10.1016/j.ejrad.2004.11.019

[26] Lev-Toaff AS, Feig SA, Saitas VL, Finkel GC, Schwartz GF. Stability of malignant breast microcalcifications. Radiology. 1994;**192**:153-156. DOI: 10.1148/radiology.192.1.8208928

[27] Ahmed A. Calcification in human breast carcinomas: Ultrastructural observations. The Journal of Pathology. 1975;**117**:247-251. DOI: 10.1002/path.1711170407

[28] Levitan LH, Witten DM, Harrison EG. Calcification in breast disease mammographic-pathologic correlation. The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine. 1964;**92**:29-39

[29] Egan RL, McSweeney MB, Sewell CW. Intramammary calcifications without an associated mass in benign and malignant diseases. Radiology. 1980;**137**:1-7. DOI: 10.1148/radiology.137.1.7422830

[30] Fechner RE. Ductal carcinoma involving the lobule of the breast. A source of confusion with lobular carcinoma in situ. Cancer. 1971;**28**:274-281

[31] Stomper PC, Connolly JL. Ductal carcinoma in situ of the breast: Correlation between mammographic calcification and tumor subtype. American Journal of Roentgenology. 1992;**159**:483-485. DOI: 10.2214/ajr.159.3.1323923

[32] Knutzen AM, Gisvold JJ. Likelihood of malignant disease for various categories of mammographically detected, nonpalpable breast lesions. Mayo Clinic Proceedings. 1993;**68**:454-460

[33] Holland R, Hendriks JH. Microcalcifications associated with ductal carcinoma in situ: Mammographic-pathologic correlation. Seminars in Diagnostic Pathology. 1994; **11**:181-192

[34] Slanetz PJ, Giardino AA, Oyama T, Koerner FC, Halpern EF, Moore RH, et al. Mammographic appearance of ductal carcinoma in situ does not reliably predict histologic subtype. The Breast Journal. 2001;**7**:417-421

[35] Tabar L, Gad A, Parsons W, Neeland D. Mammographic appearances of in situ carcinomas. In: Ductal Carcinoma In Situ of the Breast. Baltimore: Williams and Wilkins; 1997. pp. 95-117

[36] Yamada T, Mori N, Watanabe M, Kimijima I, Okumoto T, Seiji K, et al. Radiologic-pathologic correlation of ductal carcinoma in situ. Radiographics: A Review Publication of the Radiological Society of North America, Inc. 2010;**30**:1183-1198. DOI: 10.1148/rg.305095073

[37] Sekine K, Tsunoda-Shimizu H, Kikuchi M, Saida Y, Kawasaki T, Suzuki K. DCIS showing architectural distortion on the screening mammogram – comparison of mammographic and pathological findings. Breast Cancer (Tokyo, Japan). 2007;**14**:281-284

[38] Tabar L, Tony Chen HH, Amy Yen MF, Tot T, Tung TH, Chen LS, et al. Mammographic tumor features can predict long-term outcomes reliably in women with 1-14-mm invasive breast carcinoma. Cancer. 2004;**101**:1745-1759. DOI: 10.1002/cncr.20582

[39] Lehman CD. Magnetic resonance imaging in the evaluation of ductal carcinoma in situ. Journal of the National Cancer Institute Monographs. 2010;**2010**:150-151. DOI: 10.1093/jncimonographs/lgq030

[40] Berg WA, Gutierrez L, NessAiver MS, Carter WB, Bhargavan M, Lewis RS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. Radiology. 2004;**233**:830-849. DOI: 10.1148/radiol.2333031484

[41] Rosen EL, Smith-Foley SA, DeMartini WB, Eby PR, Peacock S, Lehman CD. BI-RADS MRI enhancement characteristics of ductal carcinoma in situ. The Breast Journal. 2007;**13**:545-550. DOI: 10.1111/j.1524-4741.2007.00513.x

[42] Kuhl CK, Schrading S, Bieling HB, Wardelmann E, Leutner CC, Koenig R, et al. MRI for diagnosis of pure ductal carcinoma in situ: A prospective observational study. Lancet (London, England). 2007;**370**:485-492. DOI: 10.1016/S0140-6736(07)61232-X

[43] Del Frate C, Borghese L, Cedolini C, Bestagno A, Puglisi F, Isola M, et al. Role of presurgical breast MRI in the management of invasive breast carcinoma. Breast (Edinburgh, Scotland). 2007;**16**:469-481. DOI: 10.1016/j.breast.2007.02.004

[44] Ottinetti A, Sapino A. Morphometric evaluation of microvessels surrounding hyperplastic and neoplastic mammary lesions. Breast Cancer Research and Treatment. 1988; **11**:241-248

[45] Brown LF, Guidi AJ, Schnitt SJ, Van De Water L, Iruela-Arispe ML, Yeo TK, et al. Vascular stroma formation in carcinoma in situ, invasive carcinoma, and metastatic carcinoma of the breast. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research. 1999;**5**:1041-1056

[46] Esserman LJ, Kumar AS, Herrera AF, Leung J, Au A, Chen YY, et al. Magnetic resonance imaging captures the biology of ductal carcinoma in situ. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2006;**24**:4603-4610. DOI: 10.1200/JCO.2005.04.5518

[47] Furman-Haran E, Schechtman E, Kelcz F, Kirshenbaum K, Degani H. Magnetic resonance imaging reveals functional diversity of the vasculature in benign and malignant breast lesions. Cancer. 2005;**104**:708-718. DOI: 10.1002/cncr.21225

[48] Rosen. Rosen Breast Pathology 3E. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2009

[49] Man Y. Focal degeneration of aged or injured myoepithelial cells and the resultant autoimmunoreactions are trigger factors for breast tumor invasion. Medical Hypotheses. 2007;**69**:1340-1357. DOI: 10.1016/j.mehy.2007.02.031

[50] Raza S, Vallejo M, Chikarmane SA, Birdwell RL. Pure ductal carcinoma in situ: A range of MRI features. American Journal of Roentgenology. 2008;**191**:689-699. DOI: 10.2214/AJR.07.3779

[51] Viehweg P, Lampe D, Buchmann J, Heywang-Köbrunner SH. In situ and minimally invasive breast cancer: Morphologic and kinetic features on contrast-enhanced MR imaging. Magma (New York, NY). 2000;**11**:129-137

[52] Lallemand M, Barron M, Bingham J, Mosier A, Hardin M, Sohn V. The true impact of breast magnetic resonance imaging on the management of in situ disease: More is not better. American Journal of Surgery. 2017;**213**:127-131. DOI: 10.1016/j.amjsurg.2016.05.002

[53] Fancellu A, Turner RM, Dixon JM, Pinna A, Cottu P, Houssami N. Meta-analysis of the effect of preoperative breast MRI on the surgical management of ductal carcinoma in situ. The British Journal of Surgery. 2015;**102**:883-893. DOI: 10.1002/bjs.9797

[54] Davis KL, Barth RJ, Gui J, Dann E, Eisenberg B, Rosenkranz K. Use of MRI in preoperative planning for women with newly diagnosed DCIS: Risk or benefit? Annals of Surgical Oncology. 2012;**19**:3270-3274. DOI: 10.1245/s10434-012-2548-3

[55] Morrow M, Waters J, Morris E. MRI for breast cancer screening, diagnosis, and treatment. Lancet (London, England). 2011;**378**:1804-1811. DOI: 10.1016/S0140-6736(11)61350-0

[56] Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: Meta-analysis of surgical outcomes. Annals of Surgery. 2013;**257**:249-255. DOI: 10.1097/SLA.0b013e31827a8d17

[57] Erbas B, Provenzano E, Armes J, Gertig D. The natural history of ductal carcinoma in situ of the breast: A review. Breast Cancer Research and Treatment. 2006;**97**:135-144. DOI: 10.1007/s10549-005-9101-z

[58] Jansen SA. Ductal carcinoma in situ: Detection, diagnosis, and characterization with magnetic resonance imaging. Seminars in Ultrasound, CT, and MR. 2011;**32**:306-318. DOI: 10.1053/j.sult.2011.02.007

[59] Allen LR, Lago-Toro CE, Hughes JH, Careaga E, Brown AT, Chernick M, et al. Is there a role for MRI in the preoperative assessment of patients with DCIS? Annals of Surgical Oncology. 2010;**17**:2395-2400. DOI: 10.1245/s10434-010-1000-9

[60] Solin LJ, Orel SG, Hwang WT, Harris EE, Schnall MD. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2008;**26**:386-391. DOI: 10.1200/JCO.2006.09.5448

[61] Driul L, Bernardi S, Bertozzi S, Schiavon M, Londero AP, Petri R. New surgical trends in breast cancer treatment: Conservative interventions and oncoplastic breast surgery. Minerva Ginecologica. 2013;**65**:289-296

[62] Cedolini C, Bertozzi S, Londero AP, Bernardi S, Seriau L, Concina S, et al. Type of breast cancer diagnosis, screening, and survival. Clinical Breast Cancer. 2014;**14**:235-240. DOI: 10.1016/j.clbc.2014.02.004

[63] Nelson HD, Tyne K, Naik A, Bougatsos C, Chan B, Nygren P, et al. Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventive Services Task Force. Report No: 10-05142-EF-1. 2009

[64] AIOM. Linee guida neoplasie della mammella. Techreport, AIOM. 2016

[65] Bernardi D, Macaskill P, Pellegrini M, Valentini M, Fantò C, Ostillio L, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): A population-based prospective study. The Lancet Oncology. 2016;**17**:1105-1113. DOI: 10.1016/S1470-2045(16)30101-2

[66] Ernster VL, Ballard-Barbash R, Barlow WE, Zheng Y, Weaver DL, Cutter G, et al. Detection of ductal carcinoma in situ in women undergoing screening mammography. Journal of the National Cancer Institute. 2002;**94**:1546-1554

[67] Minister of Public Works and Government Services Canada. Organized Breast Cancer Screening Programs in Canada. Minister of Public Works and Government Services Canada. 1999. Cat. No. H1-9/13-1999. ISBN: 0-662-64516-2

[68] UK Trial of Early Detection of Breast Cancer Group. 16-year mortality from breast cancer in the UK trial of early detection of breast cancer. Lancet (London, England). 1999;**353**:1909-1914

[69] Fracheboud J, Groenewoud J, Boer R, Broeders M, Baan C, Verbeek A, et al. Landelijke evaluatie van bevolkingsonderzoek in Nederland (VIII), instituut Maatschappelijke Gezondheidszorg. Rotterdam: Erasmus Universiteit Rotterdam. 2000

[70] Kopans DB, Smith RA, Duffy SW. Mammographic screening and "overdiagnosis". Radiology. 2011;**260**:616-620

[71] Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: A systematic review of incidence, treatment, and outcomes. Journal of the National Cancer Institute. 2010;**102**:170-178

[72] Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, et al. Efficacy of breast cancer screening by age. New results swedish two-county trial. Cancer. 1995;**75**:2507-2517

[73] Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: Updated overview of the Swedish randomised trials. The Lancet. 2002;**359**:909-919

[74] Hendrick RE, Smith RA, Rutledge III JH, Smart CR. Benefit of screening mammography in women aged 40-49: A new meta-analysis of randomized controlled trials. JNCI Monographs. 1997;**1997**:87-92

[75] Duffy S, Tabar L, Vitak B, Day N, Smith R, Chen H, et al. The relative contributions of screen-detected in situ and invasive breast carcinomas in reducing mortality from the disease. European Journal of Cancer. 2003;**39**:1755-1760

[76] Evans A, Pinder S, Ellis I, Wilson A. Screen detected ductal carcinoma in situ (DCIS): Overdiagnosis or an obligate precursor of invasive disease? Journal of Medical Screening. 2001;**8**:149-151

[77] Harris JR. Diseases of the Breast. Philadelphia, PA, USA: Lippincott Williams & Wilki; 2014

[78] Worni M, Akushevich I, Greenup R, Sarma D, Ryser MD, Myers ER, et al. Trends in treatment patterns and outcomes for ductal carcinoma in situ. Journal of the National Cancer Institute. 2015;**107**:djv263. DOI: 10.1093/jnci/djv263

[79] Silverstein MJ, Cohlan BF, Gierson ED, Furmanski M, Gamagami P, Colburn WJ, et al. Duct carcinoma in situ: 227 cases without microinvasion. European Journal of Cancer (Oxford England: 1990). 1992;**28**:630-634

[80] Vargas C, Kestin L, Go N, Krauss D, Chen P, Goldstein N, et al. Factors associated with local recurrence and cause-specific survival in patients with ductal carcinoma in situ of the breast treated with breast-conserving therapy or mastectomy. International Journal of Radiation Oncology, Biology, Physics. 2005;**63**:1514-1521. DOI: 10.1016/j.ijrobp.2005.04.045

[81] De Biasio F, Zingaretti N, Marchesi A, Vaienti L, Almesberger D, Parodi PC. A simple and effective technique of breast remodelling after conserving surgery for lower quadrants breast cancer. Aesthetic Plastic Surgery. 2016;**40**:887-895. DOI: 10.1007/s00266-016-0709-7

[82] Bernardi S, Bertozzi S, Londero AP, Gentile G, Giacomuzzi F, Carbone A. Incidence and risk factors of the intraoperative localization failure of nonpalpable breast lesions by radio-guided occult lesion localization: A retrospective analysis of 579 cases. World Journal of Surgery. 2012;**36**:1915-1921. DOI: 10.1007/s00268-012-1577-1

[83] Bernardi S, Bertozzi S, Londero AP, Gentile G, Angione V, Petri R. Influence of surgical margins on the outcome of breast cancer patients: A retrospective analysis. World Journal of Surgery. 2014;**38**:2279-2287. DOI: 10.1007/s00268-014-2596-x

[84] Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsky P, Loibl S, et al. De-escalating and escalating treatments for early-stage breast cancer: The St. Gallen international expert consensus conference on the primary therapy of early breast cancer 2017. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2017;**28**: 1700-1712. DOI: 10.1093/annonc/mdx308

[85] De Biasio F, Zingaretti N, De Lorenzi F, Riccio M, Vaienti L, Parodi PC. Reduction Mammaplasty for breast symmetrisation in implant-based reconstructions. Aesthetic Plastic Surgery. 2017;**41**:773-781. DOI: 10.1007/s00266-017-0867-2

[86] De Biasio F, Zingaretti N, Mura S, Fin A, Riccio M, Parodi PC. A new method of salvaging nipple projection after secondary nipple reconstruction using locoregional flap. Indian Journal of Plastic Surgery: Official Publication of the Association of Plastic Surgeons of India. 2017;**50**:107-108. DOI: 10.4103/ijps.IJPS_47_17

[87] Zingaretti N, De Lorenzi F, Dell'Antonia F, De Biasio F, Riccio M, Parodi PC. The use of "Precapsular space" in secondary breast reconstruction. Aesthetic Plastic Surgery. 2016;**40**:716-723. DOI: 10.1007/s00266-016-0683-0

[88] Semprini G, Cattin F, De Biasio F, Cedolini C, Parodi PC. The bovine pericardial patch in breast reconstruction: A case report. Il Giornale di chirurgia. 2012;**33**:392-394

[89] Germanò D, De Biasio F, Piedimonte A, Parodi PC. Nipple reconstruction using the fleur-de-lis flap technique. Aesthetic Plastic Surgery. 2006;**30**:399-402. DOI: 10.1007/s00266-005-0199-5

[90] De Biasio F, Nadalig B, Salemi S, Parodi PC. Re: Nipple reconstruction: The top hat technique. Annals of Plastic Surgery. 2006;**56**:224. DOI: 10.1097/01.sap.0000194946.92450.52

[91] Parodi PC, De Biasio F, Guarneri GF, Rampino Cordaro E, Panizzo N, Riberti C. Microsurgical latissimus dorsi flap in a case of breast aplasia caused by radiation therapy. Microsurgery. 2005;**25**:473-476. DOI: 10.1002/micr.20151

[92] Lee LA, Silverstein MJ, Chung CT, Macdonald H, Sanghavi P, Epstein M, et al. Breast cancer-specific mortality after invasive local recurrence in patients with ductal carcinoma-in-situ of the breast. American Journal of Surgery. 2006;**192**:416-419. DOI: 10.1016/j.amjsurg.2006.06.005

[93] Boyages J, Delaney G, Taylor R. Predictors of local recurrence after treatment of ductal carcinoma in situ: A meta-analysis. Cancer. 1999;**85**:616-628

[94] Cedolini C, Bertozzi S, Seriau L, Londero AP, Concina S, Moretti E, et al. Feasibility of conservative breast surgery and intraoperative radiation therapy for early breast cancer: A single-center, open, non-randomized, prospective pilot study. Oncology Reports 2014;31:1539-1546. doi:10.3892/or.2014.3018.

[95] Correa C, McGale P, Taylor C, Wang Y, Clarke M, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. Journal of the National Cancer Institute Monographs. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 2010;**2010**:162-177. DOI: 10.1093/jncimonographs/lgq039

[96] Bijker N, Meijnen P, Peterse JL, Bogaerts J, Van Hoorebeeck I, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: Ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853 – A study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. 2006;**24**:3381-3387. DOI: 10.1200/JCO.2006.06.1366

[97] Emdin SO, Granstrand B, Ringberg A, Sandelin K, Arnesson LG, Nordgren H, et al. SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncologica (Stockholm, Sweden). 2006;**45**:536-543. DOI: 10.1080/02841860600681569

[98] Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. Prevention of invasive breast cancer in women with ductal carcinoma in situ: An update of the National Surgical Adjuvant Breast and bowel project experience. Seminars in Oncology. 2001;**28**:400-418

[99] Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: Randomised controlled trial. Lancet (London, England). 2003;**362**:95-102

[100] Schmale I, Liu S, Rayhanabad J, Russell CA, Sener SF. Ductal carcinoma in situ (DCIS) of the breast: Perspectives on biology and controversies in current management. Journal of Surgical Oncology. 2012;**105**:212-220. DOI: 10.1002/jso.22020

[101] Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and bowel project B-24 randomised controlled trial. Lancet (London, England). 1999; **353**:1993-2000. DOI: 10.1016/S0140-6736(99)05036-9

[102] Cuzick J, Sestak I, Pinder SE, Ellis IO, Forsyth S, Bundred NJ, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: Long-term results from the UK/ANZ DCIS trial. The Lancet Oncology. 2011;**12**:21-29. DOI: 10.1016/S1470-2045(10)70266-7

[103] Vogel VG, Costantino JP, Wickerham DL, Cronin WM. National surgical adjuvant breast and bowel project update: Prevention trials and endocrine therapy of ductal carcinoma in situ. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research. 2003;**9**:495S-501S

[104] Bijker N, Peterse JL, Duchateau L, Robanus-Maandag EC, Bosch CA, Duval C, et al. Histological type and marker expression of the primary tumour compared with its local recurrence after breast-conserving therapy for ductal carcinoma in situ. British Journal of Cancer. 2001;**84**:539-544. DOI: 10.1054/bjoc.2000.1618

[105] Edge S, Byrd D, Compton C, Fritz G, Greene F, Trotti A. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2009

[106] Fang Y, Wu J, Wang W, Fei X, Zong Y, Chen X, et al. Biologic behavior and long-term outcomes of breast ductal carcinoma in situ with microinvasion. Oncotarget. 2016;**7**:64182-64190. DOI: 10.18632/oncotarget.11639

[107] Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, et al. Revision of the American joint committee on cancer staging system for breast cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2002;**20**:3628-3636. DOI: 10.1200/JCO.2002.02.026

[108] Bianchi S, Vezzosi V. Microinvasive carcinoma of the breast. Pathology Oncology Research. 2008;**14**:105-111. DOI: 10.1007/s12253-008-9054-8

[109] Baxter NN, Virnig BA, Durham SB, Tuttle TM. Trends in the treatment of ductal carcinoma in situ of the breast. Journal of the National Cancer Institute. 2004;**96**:443-448

[110] Adamovich TL, Simmons RM. Ductal carcinoma in situ with microinvasion. American Journal of Surgery. 2003;**186**:112-116

[111] Prasad ML, Osborne MP, Giri DD, Hoda SA. Microinvasive carcinoma (T1mic) of the breast: Clinicopathologic profile of 21 cases. The American Journal of Surgical Pathology. 2000;**24**:422-428

[112] Rosner D, Lane WW, Penetrante R. Ductal carcinoma in situ with microinvasion. A curable entity using surgery alone without need for adjuvant therapy. Cancer. 1991; **67**:1498-1503

[113] Wong JH, Kopald KH, Morton DL. The impact of microinvasion on axillary node metastases and survival in patients with intraductal breast cancer. Archives of Surgery (Chicago, IL: 1960). 1990;**125**:1298-1301; discussion 1301-2

[114] Solin LJ, Fowble BL, Yeh IT, Kowalyshyn MJ, Schultz DJ, Weiss MC, et al. Microinvasive ductal carcinoma of the breast treated with breast-conserving surgery and definitive irradiation. International Journal of Radiation Oncology, Biology, Physics. 1992;**23**:961-968

[115] Padmore RF, Fowble B, Hoffman J, Rosser C, Hanlon A, Patchefsky AS. Microinvasive breast carcinoma: Clinicopathologic analysis of a single institution experience. Cancer. 2000;**88**:1403-1409

[116] Gojon H, Fawunmi D, Valachis A. Sentinel lymph node biopsy in patients with microinvasive breast cancer: A systematic review and meta-analysis. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2014;**40**:5-11. DOI: 10.1016/j.ejso.2013.10.020

[117] Lyman GH, Giuliano AE, Somerfield MR, Benson AB, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2005;**23**:7703-7720. DOI: 10.1200/JCO.2005.08.001

[118] Dominguez FJ, Golshan M, Black DM, Hughes KS, Gadd MA, Christian R, et al. Sentinel node biopsy is important in mastectomy for ductal carcinoma in situ. Annals of Surgical Oncology. 2008;**15**:268-273. DOI: 10.1245/s10434-007-9610-6

[119] Murphy CD, Jones JL, Javid SH, Michaelson JS, Nolan ME, Lipsitz SR, et al. Do sentinel node micrometastases predict recurrence risk in ductal carcinoma in situ and ductal carcinoma in situ with microinvasion? American Journal of Surgery. 2008;**196**:566-568. DOI: 10.1016/j.amjsurg.2008.06.011

[120] Kinne DW, Petrek JA, Osborne MP, Fracchia AA, DePalo AA, Rosen PP. Breast carcinoma in situ. Archives of surgery (Chicago, IL: 1960). 1989;**124**:33-36

[121] Silverstein MJ, Recht A, Lagios MD, editors. Ductal Carcinoma In Situ of the Breast. Philadelphia, PA, USA: Lippincott Williams & Wilkins; 2002

[122] Parikh RR, Haffty BG, Lannin D, Moran MS. Ductal carcinoma in situ with microinvasion: Prognostic implications, long-term outcomes, and role of axillary evaluation. International Journal of Radiation Oncology, Biology, Physics. 2012;**82**:7-13. DOI: 10.1016/j.ijrobp.2010.08.027

[123] Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2016;**34**:611-635. DOI: 10.1200/JCO.2015.64.3809

[124] Bertozzi S, Londero AP, Giacomuzzi F, Angione V, Carbone A, Petri R, et al. Applicability of two different validated models to predict axillary non-sentinel lymph node status by sentinel node biopsy in a single Italian center. Breast cancer (Tokyo, Japan). 2015;**22**:350-355. DOI: 10.1007/s12282-013-0485-z

[125] Bernardi S, Bertozzi S, Londero AP, Angione V, Petri R, Giacomuzzi F. Prevalence and risk factors of intraoperative identification failure of sentinel lymph nodes in patients affected by breast cancer. Nuclear Medicine Communications. 2013;**34**:664-673. DOI: 10.1097/MNM.0b013e328361cd84

[126] Bernardi S, Bertozzi S, Londero AP, Giacomuzzi F, Angione V, Dri C, et al. Nine years of experience with the sentinel lymph node biopsy in a single Italian center: A retrospective analysis of 1050 cases. World Journal of Surgery. 2012;**36**:714-722. DOI: 10.1007/s00268-011-1420-0

[127] Cedolini C, Bertozzi S, Seriau L, Londero AP, Concina S, Cattin F, et al. Eight-year experience with the intraoperative frozen section examination of sentinel lymph node biopsy for breast cancer in a North-Italian University Center. International Journal of Clinical and Experimental Pathology. 2014;**7**:364-371

[128] Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: The ALMANAC trial. Journal of the National Cancer Institute. 2006;**98**:599-609. DOI: 10.1093/jnci/djj158

[129] Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. The New England Journal of Medicine. 2003;**349**:546-553. DOI: 10.1056/NEJMoa012782

[130] Veronesi U, Viale G, Paganelli G, Zurrida S, Luini A, Galimberti V, et al. Sentinel lymph node biopsy in breast cancer: Ten-year results of a randomized controlled study. Annals of Surgery. 2010;**251**:595-600. DOI: 10.1097/SLA.0b013e3181c0e92a

[131] Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: Overall survival findings from the NSABP B-32 randomised phase 3 trial. The Lancet Oncology. 2010;**11**:927-933. DOI: 10.1016/S1470-2045(10)70207-2

[132] Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Annals of Surgery. 1994;**220**:391-8; discussion 398-401

[133] Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 1997;**15**:2345-2350. DOI: 10.1200/JCO.1997.15.6.2345

[134] Solin LJ, Fourquet A, Vicini FA, Haffty B, Taylor M, McCormick B, et al. Mammographically detected ductal carcinoma in situ of the breast treated with breast-conserving surgery and definitive breast irradiation: Long-term outcome and prognostic significance of patient age and margin status. International Journal of Radiation Oncology, Biology, Physics. 2001;**50**:991-1002

[135] Kerlikowske K, Molinaro A, Cha I, Ljung BM, Ernster VL, Stewart K, et al. Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy. Journal of the National Cancer Institute. 2003;**95**:1692-1702

[136] Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2009;**27**:1615-1620. DOI: 10.1200/JCO.2008.17.5182

[137] MacDonald HR, Silverstein MJ, Mabry H, Moorthy B, Ye W, Epstein MS, et al. Local control in ductal carcinoma in situ treated by excision alone: Incremental benefit of larger margins. American Journal of Surgery. 2005;**190**:521-525. DOI: 10.1016/j.amjsurg.2005.06.005

[138] Jhingran A, Kim JS, Buchholz TA, Katz A, Strom EA, Hunt KK, et al. Age as a predictor of outcome for women with DCIS treated with breast-conserving surgery and radiation: The University of Texas M. D. Anderson Cancer Center experience. International Journal of Radiation Oncology, Biology, Physics. 2002;**54**:804-809

[139] Vicini FA, Recht A. Age at diagnosis and outcome for women with ductal carcinoma-in-situ of the breast: A critical review of the literature. Journal of Clinical Oncology:

Official Journal of the American Society of Clinical Oncology. 2002;**20**:2736-2744. DOI: 10.1200/JCO.2002.07.137

[140] Rodrigues NA, Dillon D, Carter D, Parisot N, Haffty BG. Differences in the pathologic and molecular features of intraductal breast carcinoma between younger and older women. Cancer. 2003;**97**:1393-1403. DOI: 10.1002/cncr.11204

[141] Goldstein NS, Vicini FA, Kestin LL, Thomas M. Differences in the pathologic features of ductal carcinoma in situ of the breast based on patient age. Cancer. 2000;**88**:2553-2560

[142] Carlson GW, Page A, Johnson E, Nicholson K, Styblo TM, Wood WC. Local recurrence of ductal carcinoma in situ after skin-sparing mastectomy. Journal of the American College of Surgeons. 2007;**204**:1074-1078; discussion 1078-80. DOI: 10.1016/j.jamcollsurg.2007.01.063

[143] Provenzano E, Hopper JL, Giles GG, Marr G, Venter DJ, Armes JE. Biological markers that predict clinical recurrence in ductal carcinoma in situ of the breast. European Journal of Cancer (Oxford, England: 1990). 2003;**39**:622-630

[144] Silverstein MJ, Lagios MD, Craig PH, Waisman JR, Lewinsky BS, Colburn WJ, et al. A prognostic index for ductal carcinoma in situ of the breast. Cancer. 1996;**77**:2267-2274. DOI: 10.1002/(SICI)1097-0142(19960601)77:11<2267::AID-CNCR13>3.0.CO;2-V

[145] Silverstein MJ. The University of Southern California/van Nuys prognostic index for ductal carcinoma in situ of the breast. American Journal of Surgery. 2003;**186**:337-343

[146] Fisher ER, Dignam J, Tan-Chiu E, Costantino J, Fisher B, Paik S, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of protocol B-17: Intraductal carcinoma. Cancer. 1999;**86**:429-438