The management of ductal intraepithelial neoplasia (DIN): open controversies and guidelines of the Istituto Europeo di Oncologia (IEO), Milan, Italy

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Running Head:

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose. *The management of ductal intraepithelial neoplasia (DIN) has substantially changed over the past 30 years, as its incidence has increased (from 2-3% to more than 20%), mainly due to the widespread use of mammography screening. This article describes not only the more widespread theoretical concepts on DIN but also the differences in the practical applications of the theory between different countries, different oncology specialists and different cancer centers.*

Methods. *Papers related to the international multicentric randomized trials and retrospective studies were analyzed. We include articles and papers published between 1993 and 2010 related to patients with DIN, and abstracts and reports from MEDLINE and other sources were indentified.*

Results. *The standard of care for DIN consists of a) breast conservative surgery (mastectomy is still indicated in large lesions -masses or microcalcifications- in about 30% of cases); b) radiotherapy after conservative surgery and c) medical treatment in estrogen receptors (ER)+ patients. However, most studies have shown significant differences between theory and practical application. Moreover, there are differences regarding a) the indications of sentinel lymph node biopsy (SLNB), b) the definition and identification of low risk DIN subgroups that can avoid radiotherapy (RT) and tamoxifen and c) the research into new alternative drugs in adjuvant medical therapy.*

Conclusion. *A general agreement on the best management of DIN does not exist as yet. New large trials are needed in order to define the best management of DIN patients which is (in most respects) still complex and controversial.*

Keywords: ductal intraepithelial neoplasia – breast cancer – surgery – radiotherapy – medical treatment – new agents -

Introduction

DIN, is the new acronym (corresponding to ductal intraepithelial neoplasia) that replaces the traditional definition of ductal carcinoma in situ (DCIS) of the breast. This is because some authors [1] found it difficult to accept the intraductal proliferation of tumor cells being defined as a malignant tumor and others [2-3] think that in these cases, the N and M categories should not be applied and that there is therefore no reason to keep them within the TNM classification, as "intraductal carcinoma".

The incidence of breast DIN has been progressively increasing; it currently represents 15-25% of all breast carcinomas and approximately 35% of those diagnosed only by mammography. For example, in the USA, DIN increased from 1.87/100.000 in 1973-1975 to 32.5/100.000 in 2004 [4]. Being overall 10-year survival close to 100% of affected patients, the surgery and radiotherapy interventions employed are sometimes more aggressive for this condition than those used for invasive cancer [2].

Some aspects of DIN management are still controversial, as reported in studies across the United States and Europe [5-7] and in different areas within the United States [8]. These controversies are mainly due to the heterogeneity of its clinical presentation and of its biological and pathological characteristics.

BIOLOGICAL FEATURES OF DIN

DIN is characterised by multiple clinical-pathological and biological features which differentiate it from both normal breast tissue and other benign proliferative breast lesions. As hyperplastic lesions progress through ductal carcinoma in situ to invasive breast cancer, chromosomal alterations usually occur with gain or loss at multiple foci[9]. Estrogen receptors (ER) are usually expressed in more than 70% of DIN lesions. The HER2/neu proto-oncogene is over-expressed in roughly half of all DIN lesions but not in atypical hyperplasia[10]. The p53 tumor-suppressor gene is mutated in approximately 25% of all DIN lesions, but is rarely mutated in normal proliferative breast tissue [11]. The most dramatic changes in patterns of gene expression during breast tumorigenesis appear during the transition from normal tissue to DIN [12], which is biologically heterogeneous, with variable molecular features. The gene-expression profile of grade 3 (G3) DIN differs from that of grade 1 (G1) lesions and exhibits a greater overall genetic change from normal breast tissue[13-14]. A great majority of G1 DIN lesions are positive for estrogen receptors, and less than

20% exhibit overexpression of HER2/neu or p53 mutations. In contrast, overexpression of HER2/neu or p53 mutations[15] arise in more than 75% of G3 DIN lesions, whereas only one quarter of them express ER[16]. DIN can be considered a step in the development of breast cancer in which most of the molecular changes that characterize invasive breast cancer are already present[17].

MANAGEMENT OF DIN PATIENTS

Surgical Treatment

Mastectomy is considered today an overtreatment in most DINs due to the biological and pathological features and also its high survival rate and low absolute risk of local recurrences (LR). However, mastectomy is still indicated in DIN patients with multicentricity, diffuse microcalcification or large palpable masses, as well as when there is an inability to obtain negative margins.

The main goal of surgical treatment for women with DIN is **breast conserving surgery** (BCS) [18-20] particularly for those patients with small solid masses, mammographically-detected lesions, or limited microcalcification areas, and because it is a disease with an extremely high survival rate and low absolute risk of LR.

At present, mastectomy is performed in about 30%, BCS without radiotherapy in about 30% and BCS followed by radiotherapy in about 40% in DIN patients [21-23].

One important issue in breast cancer surgery is that of **surgical margins**, mainly in DIN patients, since these lesions are typically vague masses, which often cannot be adequately seen or felt and, thus, the pathological sampling of margins is fairly random [24-25]. There are two currently-held concepts that meet with general agreement on this topic: the first is the evidence that wide surgical excision and negative margins of resection decrease the risk of LR in patients with mammographically-detected DIN treated with BCS and radiation[26]. The second concept is a general consensus that patients with positive margins show a significantly higher rate of LR than do patients with negative margins, regardless of irradiation or tamoxifen administration[27-28].

In practice, there are two opposite approaches to surgical margins in a DIN patient: the *anatomical approach*, for which a clear margin width (of at least 10 mm) is more important than any other prognostic factor or subsequent adjuvant therapy[29-30]; and the *biological approach*, for which the pathological

characteristics of the lesion (G, comedo-necrosis, etc) are decisive in decision-making related to surgery and radiotherapy.

The current treatment of "positive" or focally involved margins in DIN patients is **re-excision**. Results of the UK Sloane Project showed that in 30% of patients undergoing BCS for DIN, preoperative imaging underestimates the extent of disease resulting in a requirement for further surgery[31]. On the other hand, some authors suggest that re-excision may be avoided and satisfactory local control achieved by increasing the radiation dose to the tumour bed to at least 66 Gy[32].

Regarding the width of surgical margins, about ten years ago, the "Consensus on DCIS of Philadelphia" [19], and Silverstein et al[30] proposed 10 mm as a limit of oncological safety. Since then other authors proposed progressively smaller measures, i.e., 3mm[33-35], 2-3 mm[136-37], 2 mm[38-40] and 1mm [41]. At the 2009 Saint Gallen International Experts Consensus, there was consensus in avoiding the need to insist on a large (e.g. 1 cm) free margins[42].

The issue of surgical margins is closely related to another important issue in DIN patients: LR. The risk of LR for DIN after BCS is the main concern, because approximately 50% of the recurrences are invasive[43]. LR is rare after total mastectomy, while it is observed at a higher rate in patients treated with breast conservation, even if the impact of these LR on overall survival is small. LR after 10 years of follow-up in DIN patiens is about 1% when mastectomy is performed, 30% in case of BCS alone and about 10-15% when BCS is followed by radiotherapy[44].

An interesting study (with a four-decade-long follow up) of women with G1 DIN treated by biopsy alone from 1950 to 1968 reveals the natural history of this poorly understood breast cancer[45]. This study shows that even G1 DIN left without further treatment have a risk of LR and will eventually develop invasive carcinoma in the same site in 30% of cases within 15 years.

Most LR in patients undergoing BCS and radiation for DIN occur in the proximity of the primary tumor. Virtually all patients who develop a non invasive LR, and approximately 75% of those with an invasive LR, are long-term survivors after mastectomy[46]. The risk of LR for clinically-evident DIN is approximately twice that of mammographically-detected DIN[47]. However, the recurrences after BCS are today diagnosed at a very early stage and almost always treated successfully; for that reason, breast cancer

mortality in these patients is very low, about 1%[48-49] and probably due to an underestimated histological evaluation.

Several **prognostic factors** (PF) influencing LR in DIN patients have been identified[21,28, 50-56]. The most important PFs are the following: *a) High nuclear grade and/or necrosis (particularly extensive comedo-necrosis); b) Tumor size; c) Margin status;* and *d) young age.* In this respect, a recent study observed that DIN in younger women is more often symptomatic, is more extensive and more often shows cancerization of lobules than DIN in older women, although it requires further studies to conclude if these features contribute to the higher local recurrence risk in young patients[54]. In fact, another analysis concludes that young age may be a smaller contributor to LR risk in DIN than previously suggested[55]. In order to organize the information about PF, Silverstein[56] developed the Van Nuys Prognostic Index (VNPI), (including tumor size, margin width, histological classification and age), to define three risk groups of patients. But this Index was criticized by most authors[24,36].

One important controversial topic in DIN patients is the **management of the axilla**. We have recently examined this point[57] observing that, before the sentinel lymph node biopsy (SLNB) era, axillary dissection (AD) was a part of the standard surgical treatment for these patients. Thanks to this procedure, the status of the axillary lymph nodes was reported as metastatic between 1-2%[34, 58-59]. A logical and consequent conclusion from these low percentages, would be that AD should never be indicated as first treatment in DIN patients. However, both in theory and in practice it happens the contrary[34,59-61]. In the light of these analyses, we can conclude that AD should no longer be performed as a first indication of treatment in patients with pure DIN and that AD should be considered in these cases an unnecessary overtreatment without any rational justification.

But not only is AD not necessary, neither should SLNB always be required. However, this is still controversial in DIN patients. In fact, for some authors SLNB should not, in general, be indicated[62]; for others, SLNB should always be carried out[63-64], and for others still, it should be performed only in certain specific and particular cases[65-68]. Major cancer centers agree that SLNB should be conducted a) always when mastectomy is performed [66,68-70]; b) with large lesions (masses or micro-calcifications) and G3 tumors[66-67]; c) after performing core or mammotome biopsies. In these cases, because an invasive ductal carcinoma can be found at the final pathological diagnosis after surgery: generally, this upstaging

represents about 16-20% of these cases, with variations from 11-13% (in cases of either T1 or G1 lesions) to 36-45%(in cases of extended or G3 lesions) [71-78].

The last question related to the management of the axilla in DIN patients is: should we perform AD in cases of positive SLNB in DIN patients, as we do in cases of infiltrating breast carcinoma? In the few cases published in the literature[63,68-70,78-81], in which AD was performed after an positive SLNB, in all cases but one (67/68, 98,5%) all the non-SLNs were negative and the SLN already biopsied was the only positive LN. That is why we conclude that in cases of DIN patients with a positive SLNB, AD should not be immediately performed except for only those cases that present mammary invasion on final pathologic evaluation.

Open questions remain regarding the significance of isolated tumor cells or micrometastases in the lymph nodes as well as the role SLNB plays in DIN with microinvasion[34,82].

Radiation Therapy

External RT

The role of radiotherapy in DIN patients with conservative treatment has been mainly defined by four randomized trials: the NSABP B-17[83], the EORTC 10853[84], the United Kingdom-Australia-New Zealand (UK-A-NZ) trials[85] and the Swedish study on women screened with mammography[86]. A recent review of these trials confirm the following results[87]: all four studies demonstrated that additional radio-therapy reduced the LR rate by about 50%, with no effect on survival. Comparable reductions were seen for the risk of invasive and non invasive LR. Non-significant long term toxicity from radiotherapy was found. These trials were organized to discover whether radiation therapy decreases LR and this was something they clearly demonstrated.

The controversy is, instead, related if all DIN patients have to undergo RT. According to the 2009 St Gallen Consensus[42], RT could be avoided in elderly patients and in those with G1 DIN and clearly negative margins. There are two aspects that are to be taken into consideration at the moment of performing RT in DIN: the margins of resection and the tumor grading. Regarding ***margins***, the recent ECOG report[35] showed that a margin of 3 mm or wider could be an adequate width for only excision without irradiation (in

G1-G2 DIN patients). Regarding ***tumor grading,*** clinicians agree that patients with *high-grade DIN* and with close margins benefit from adjuvant radiotherapy. However, there are controversies regarding the need for radiotherapy in patients with *low-grade DIN* which has been resected with wide (>10 mm) negative margins. Two prospective studies showed contradictory results: in the trial from the Dana-Farber Cancer Institute[88-89], the omission of radiation therapy after wide excision alone resulted in a high cumulative LR rate of 12% at 5 years of follow-up in patients with G1 DIN. On the contrary, the EORTC 10850 trial showed that within the group of DIN, patients treated with BCS alone (with 26% of 10-year LR-free rate) in the subgroup G1 DIN after surgery alone, presented a risk of LR <10% at 10 years' follow up[84].

In fact this is one of the more important controversies regarding the management of DIN patients: are all these patients candidates to receive RT after BCS? At the IEO in Milan, the answer to this question has been no, for more than a decade. In fact, RT is not administered to DIN patients with G1 or G2 without comedonecrosis. On the other hand, only last year, at least four significant papers (from the Saint Gallen Consensus[42], the ECOG trial [35], the Newport Consensus Conference III [90], and from the National Consensus Cancer Network [91]) suggested that some DIN patient sub-groups (i.e., G1 or G2 tumors without comedonecrosis, and other low-risk sub-grups) could not be candidates to receive RT after BCS.

Another open question is related to the use of a boost after RT in DIN patients. In a multicentric, retrospective study, Omlin et al [92] demonstrated that an RT boost decreases LR in patients <45 years of age. The ten-year relapse-free survival was 46% for patients not receiving any RT, 72% for patients with RT without boost and 86% for patients receiving RT including a boost, thus suggesting that an RT boost should be considered in addition to surgery for BCS in patients with DIN. A French multicentric randomized trial, the first study evaluating in young DIN patients the impact of a 16 Gy boost after 50 Gy delivered to the whole breast in 25 fractions and 33 days, has started inclusions recently[93].

Intraoperative Radiotherapy (IORT).

The standard course of current external RT after BCS for DIN, delivers a total dose of 50 Gy in daily fractions of 1.8/2 Gy without boost. Intraoperative Radiotherapy (IORT), instead, is an attractive new treatment, an accelerated partial breast irradiation (APBI), and offers a new approach to irradiate the breast directly during the surgery itself when BCS is performed. The recent Consensus Statement from the

American Society for Radiation Oncology agreed that IORT can be used in some particular group of breast cancer patients[94], but there is no significant data of the use of APBI in DIN patients. The American Society of Breast Surgeons Registry Trial includes the largest published collection of DIN treated with APBI. In this series, four-year follow-up shows result similar to those with invasive cancer treated with APBI, as well as DIN treated with whole breast irradiation[95]. In some cases with DIN, IORT is also used on the nipple-areola- complex (NAC) when a NAC-sparing mastectomy in performed. This is a new surgical procedure whose risks and complications are acceptable when compared to the traditional surgical treatment of breast cancer[96]. In some institutions, such as the IEO in Milan, the NAC-sparing mastectomy is associated with IORT (so-called E[1]LIOT, one shot of 16 Gy) to the NAC[96]. In other centres, it is performed without IORT[97-98].

Medical treatment

Two known international trials studied tamoxifen effects after BCS and RT. One of them (NASBP B-24) [27], showed that tamoxifen reduces LR of DIN patients, whereas the other trial[85] did not demonstrate that advantage.

Currently, systemic therapy is related to ER status and is only considered for ER-positive patients. Barnes et al[99] found that most DIN lesions are ER-positive, especially in well and moderately differentiated G1 and G2 tumors, while a large fraction of G3 and comedonecrosis DIN lack or have less marked ER expression.

Patients with ER-positive tumors

The role of tamoxifen was addressed in the above- mentioned NSABP B-24 trial[27], reducing the number of overall breast cancer events by 37% (43% in invasive and 31% in noninvasive breast cancer events). This overall reduction was secondary to a 31% decrease in the incidence rate of ipsilateral breast tumors ($p = 0.02$) and a 47% reduction in contralateral breast cancers ($p = 0.01$). With regard to ER, there were 77% ER-positive patients and 23% ER-negative patients. The reduction of all breast cancer events was 58% for ER-positive patients (p. 0.0001) and 23% for ER-negative patients (p. 0.45) [83]. In women under 50 years of age, tamoxifen reduced the risk of ipsilateral breast tumors by 38% whereas in patients aged 50 and older the

reduction was 22%. On the other hand, tamoxifen was found to reduce the risk of recurrence in patients with both positive and negative margins. However, even with tamoxifen there were fewer local failures in the group with negative margins (22%) than in the group with positive margins (44%)[27]. The risk/benefit ratio should be considered in each patient: women undergoing BCS, premenopausal women, and postmenopausal histerectomized women are likely to achieve the greatest benefit from tamoxifen.

A possible alternative for low-risk patients could be the use of low-dose tamoxifen, as shown by three IEO papers: firstly, Decensi et al. [100], demonstrated that the effects on Ki-67 expression of lower doses of tamoxifen (1mg, 5mg/day) were proven to be comparable to those achieved with the standard dose (20mg/day), although the effects on blood biomarkers were variable. Secondly, the cases of low-dose tamoxifen were confirmed in a randomized dose-ranging trial in hormone replacement therapy (HRT) users. A dose of 5 mg/day was the most effective and was selected for a phase III trial in HRT users; this dose modulates favourably biomakers of breast carcinogenesis and cardiovascular risk, with no increase of endometrial proliferation and menopausal symptoms[101]. Thirdly, low doses of tamoxifen were associated to a lower incidence of recurrence in patients with ER-positive and HER-2-negative disease[21].

At present two selective estrogen receptor modulators, tamoxifen and raloxifene, are approved in the US for reduction of breast cancer risk in high-risk women. Tamoxifen, but not raloxifene, is also approved for adjuvant therapy in patients treated with breast-conserving excision and radiation for DIN. In the NSABP-P2 prevention trial, raloxifene was as effective as tamoxifen in reducing the risk of Infiltrating Breast Cancer (IBC), but was 30% less effective than tamoxifen in reducing the risk of DIN[102].

Interestingly, the UK-A-NZ trial on adjuvant tamoxifen and radiation therapy in DIN patients found that tamoxifen did not significantly reduce the overall event rate or the rate of IBC events, but did reduce the overall rate of DIN (hazard ratio, 0.58; 95% CI, 0.49 to 0.96; P =.03) [85]. The different results may be a consequence of a different patient population: the NSABP B-24 study had a higher proportion of patients younger than 50 (34% vs 10%), and tamoxifen was associated with a greater risk reduction in this age group[27].

On the other hand, the impact of the NSABP B-24 results on tamoxifen use in patients with DIN was evaluated and it was reported that the overall acceptance was 41%[103]. That's why, considering *a)* this low acceptance, *b)* the controversy regarding tamoxifen benefit in ER-negative DIN and *c)* the side effects

related to therapy with tamoxifen (that might not be acceptable to an otherwise healthy women), other agents should be evaluated for adjuvant therapy in patients with DIN.

The aromatase inhibitors (AI) group[104] reduces the risk of contralateral breast cancer by 50% when compared with tamoxifen in adjuvant breast cancer trials. Two trials are currently evaluating the role of the aromatase inhibitor anastrozole as adjuvant therapy in patients with DIN: the NSABP B-35 and the International Breast Cancer Intervention Study-II. Furthermore, non-endocrine agents should also be considered, especially for high-grade DIN, including COX-2 inhibitors, retinoids and tyrosine kinase inhibitors such as trastuzumab[23].

Patients with ER-negative tumors

Patients with ER-negative DIN are not candidates for tamoxifen. However, a preventive strategy is needed to reduce the incidence of ER-negative tumors, which contribute to breast cancer–related mortality. Some studies suggest that the administration of COX-2 inhibitors to patients with ER-negative DIN may represent such a strategy[105-106]. The association of COX-2 with HER-2 expression, is a surrogate marker of an aggressive DIN phenotype and links non-estrogen growth factor–signaling pathways with COX-2 overexpression. There is no evidence that herceptin, the antibody approved for the treatment of HER-2-positive invasive breast cancer, is beneficial for patients with DIN (even if the lesion is HER-2 positive). At present, Lapatinib, an approved oral agent for HER-2-positive breast cancer, is under investigation for DIN[107]. There is an ongoing non-randomized clinical trial in the USA to find out whether a single dose of the drug Herceptin (trastuzumab) administered before surgery kills cancer cells or slows the growth of cancer cells in women who have DIN, and to evaluate the effect of a single dose of Herceptin on the apoptotic index of Her-2/neu-overexpressing DIN[108]. So, COX-2 inhibitors and trastuzumab could play a role in preventing invasive breast cancer in patients with ER-negative DIN[109] .

New agents and new strategies for medical treatment?

The biological alterations controlling DIN proliferation are not clear. The fact that antiestrogens are not effective in ER-negative breast cancers, suggests that other factors are promoting proliferation in ER-negative DIN. Mutated or over expressed tyrosine kinases are frequently associated with tumor development.

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase (TKI) that is involved with mitogenesis and is expressed in ER-negative DIN. It has been hypothesized that EGFR is central in driving proliferation in ER-negative/EGFR-positive DIN[110]. Preclinical studies have demonstrated that EGFR-TKI therapy reduces proliferation and increases apoptosis in the epithelium, and, either alone or combined with antiestrogen therapy, EGFR-TKI may represent a novel form of chemoprevention. Clinical trials should investigate evidence that breast cancers that have become tamoxifen-resistant use the EGFR signalling pathway which would suggest that the combination of tamoxifen and Iressa would be potent at chemopreventing cancer[111].

Preclinical studies have involved the development of genetically engineered mice (GEMs) to investigate cancer prevention. GEMs harbour activated oncogenes and/or inactivated tumour-suppressor genes that predispose them to develop cancer[112]. These studies provide evidence of the great potential of vaccines to induce prevention of cancer and demonstrate that a vaccine-alerted immune system effectively blocks the carcinogenesis process driven by the overexpression of specific oncogenes[112-114]. In GEMs that are transgenic for the rat HER2 oncogene, mammary and salivary carcinogenesis is driven by HER2-receptor expression, whereas down-modulation or loss of the receptor blocks tumor progression[115-117]. As preventive vaccines operate during the early phases of carcinogenesis, effective inhibition of the HER2 receptor arrests the whole process and renders the selection of HER2-receptor-loss variants unlikely. Preclinical data available in GEMs models cannot be directly translated to humans for preventive treatments; these require more attention since the plan would be to vaccine a healthy individual.

Vaccination against selected oncoantigens of healthy people who have a specific genetic risk of cancer, who have been exposed to an exogenous carcinogen, or who bear multifocal pre-neoplastic lesions would provide the most appropriate scenario. New clinical trial targeting HER-2/neu using a dendritic cell vaccine in a neoadjuvant trial for treatment of DIN patients are ongoing[118]. Starting from the hypothesis that trastuzumab will have substantial activity against DIN, some trials are studying the use of trastuzumab a) *after* breast-conserving surgery with negative margins, for patients with HER-2/neu–overexpressing DIN (NSABP phase III randomized trial) [23]; *b) before* surgery as neoadjuvant treatment in DIN patients (at the MDAnderson) [23] and *c)* some studies used trastuzumab *during* breast irradiation[119].

MANAGEMENT OF DIN PATIENTS AT THE Istituto Europeo di Oncologia (IEO)

Between June 1994 and December 2009, a total of 24,668 breast cancer patients were treated at the IEO, in Milan, Italy; 4,350 of these (17,6%) were DIN patients. About 80% of these patients received BCS and 20% mastectomy, in accordance with the following IEO guidelines for the management of DIN patients.

Guidelines for surgery

The surgical decisions depend on the amount of breast tissue with DIN, the size of the breast, other health and physical factors and the patient's preferences.

a. Indications for breast conservative surgery (BCS):

BCS is performed in cases of detected mammographically DIN lesions or palpable masses, without evidence of multicentricity or diffuse malignant calcifications. The extent of DIN for BCS should be near 3-4 cm but this depends mainly on an appropriate cosmetic final result (the rate tumor/breast side should be considered). In cases of non-palpable lesions the procedure is as follows: *a)* for small or non-palpable masses or for clusters of microcalcifications, the surgical excision is guided by the ROLL (Radioguided Occult Lesions Localization), a technique developed at the IEO[120]; *b)* for extended or diffuse microcalcifications, the skin over the area of microcalcifications is mapped by the radiologist, and the surgeon takes into consideration the extension of the mapped area to decide if performing either BCS or mastectomy.

b. Indications for mastectomy

Mastectomy is performed in cases of *a)* large and extended DIN areas, in which BCS would create a bad final cosmetic result; *b)* multiple areas of DIN in the same breast, i.e., multicentricity or extended multifocality. The NAC-sparing mastectomy, with IORT (ELIOT) applied to the nipple areola complex is more often proposed.

c. Breast reconstruction after mastectomy: When mastectomy is performed, immediate breast reconstruction is always proposed to the patient, via different techniques (expander, definitive prostheses or flap) depending on the size of the breast, the local situation, the possible contraindications and the wishes of the patient.

d. Surgical treatment of recurrences:

The decision to perform a new BCS or a mastectomy after a LR, depends on the cosmetic final results and the patient's opinion: both are important elements to be considered when making the decision. Regarding the width of surgical margins, the IEO considers 1 mm as a limit of oncological safety.

e. Axillary management:

AD is never indicated as a first surgical treatment in DIN patients. SLNB is only considered: *a)* in all cases of mastectomy; *b)* when there exists a strong doubt of invasion or microinvasion (i.e., in cases of large solid lesions or diffuse microcalcifications) and *c)* after a DIN diagnosis by core or mammotome biopsy. If the SLNB is positive, AD should be performed only in cases with mammary invasion on final pathologic evaluation.

Guidelines for radiotherapy

DIN patients are divided into two groups based on the pathological features as follows: on the one hand, radiotherapy (50 Gy to the whole breast, without boost) is given to all patients with Grade 3 and with Grade 2 and comedonecrosis, considering that radiotherapy is more effective over cells in phase G2 of the cellular cycle. On the other hand, no radiotherapy after BCS is indicated in Grade 1 and Grade 2 in patients without comedonecrosis; in these cases, RT is considered an overtreatment.

Guidelines for systemic treatment

DIN patients are divided according to their ER status:

a. ER-positive patients: premenopausal and postmenopausal patients receive low-dose tamoxifen (20mg/week) or participate in the IBIS-2 trial, which has 2 arms: after quadrantectomy, Tamoxifen 20mg/day**)** vs Anastrazole (100mg/day); after mastectomy, Anastrazole (100mg/day) vs placebo.

b. ER-negative patients: The standard for ER-negative both pre and postmenopausal patients is no treatment. As an alternative a randomized pilot study of pharmacoprevention is proposed to high risk patients. This study includes 150 patients divided into three groups, receiving during one year: a) Nimesulide (100mg/day), b) Sinvastatina (20mg/day) and c) placebo

FINAL CONSIDERATIONS

Data for irradiation in DIN patients are strong and consistent, after the results of the known randomized trials[83-86], while the recommendations for adjuvant tamoxifen must be reviewed in light of the differences in reported outcomes from two mentioned randomized trials[27,85]. Treatment with radiation and tamoxifen can reduce the risk of recurrence, including invasive recurrence, but for the overall population of patients with DIN, such risk reduction comes with the knowledge that most patients would be over-treated.

Moreover, some questions remain open and call for new international consensus and agreements, i.e.: *a) Regarding surgery:* Which margin width can be considered oncologically safe (1 mm? 3 mm? 10 mm?). Are micrometastasis in a SLNB of any clinical significance in DIN patients? Are macrometastasis in DIN patients responsible for long term axillary recurrences? Could macrometastasis be the only situation that justifies a complete axillary dissection? Is it necessary to perform a complete axillary dissection in cases of SLNB positivity in DIN patients? If not, why perform SLNB in this group of patients? *b) Regarding radiotherapy:* Which group of DIN patients does not need RT after BCS? Do young DIN patients benefit from the application of a boost after 50-Gy radiotherapy? Is RT really needed when there are safe margins of 10 mm or more, regardless of tumor size, nuclear grade and the presence or absence of comedo-necrosis? *c) Regarding systemic therapy*: Are collateral effects of tamoxifen justified in low-risk ER-positive DIN patients? How should ER-negative DIN patients be treated? What is the potential role of vaccines and Trastuzumab in cancer prevention (including DIN)?.

The variations on DIN management in practice, demonstrated, for example, by the ASTRO/ESTRO investigation[8], the UK Sloane Project [60]and the French experience[61] show that breast cancer

professionals are not convinced about the optimal method to treat DIN patients. New large trials are needed in order to evaluate the best management of DIN which is in most respects still complex and controversial.

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