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TOPIC HIGHLIGHT

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# Main controversies in breast cancer

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## Abstract

In this article, we have reviewed available evidence for diagnosis, treatment, and follow-up in female breast cancer (BC). Into daily clinical practice some controversies are occurred. Especially, in the diagnosis field, despite the fact that the optimal age in which screening mammography should start is a subject of intense controversy, there is a shift toward the beginning at the age of 40 although it is suggested that the net benefit is small for women aged 40 to 49 years. In addition, a promising tool in BC screening seems to be breast tomosynthesis. Other tools such as 3D ultrasound and shear wave elastography (SWE) are full of optimism in BC screening although ultrasonography is not yet a first-line screening method and there is insufficient evidence to recommend the systemic use of the SWE for BC screening. As for breast magnetic resonance imaging (MRI), even if it is useful in BC detection in women who have a strong family history of BC, it is not generally recommended as a screening tool. Moreover, based on the lack of randomized clinical trials showing a benefit of presurgical breast MRI in overall survival, it's integration into breast surgical operations remains debatable. Interestingly, in contrast to fine needle aspiration, core biopsy has gained popularity in presurgical diagnosis. Furthermore, after conservative surgery in patients with positive sentinel lymph nodes, the recent tendency is the shift from axillary dissection to axillary conserving strategies. While the accuracy of sentinel lymph node after neoadjuvant chemotherapy and second BC surgery remains controversial, more time is needed for evaluation and for determining the optimal interval between the two surgeries. Additionally, in the decision between immediate or delayed breast reconstruction, there is a tendency in the immediate use. In the prevention of BC, the controversial issue between tamoxifen and raloxifene becomes clear with raloxifene be more profitable through the toxicities of tamoxifen. However, the prevention of bone metastasis with bisphosphonates is still conflicting. Last but not least, in the follow-up of BC survivors, mammography, history and physical examination are the means of an early detection of BC recurrence.



**Key words:** Breast cancer; Controversies; Diagnosis; Treatment; Follow-up

**Core tip:** Taking into consideration the progress in diagnosis and treatment in the female breast cancer, it is inevitable that some controversies will come up in daily clinical practice. The aim of this review is to illustrate some of these conflicting issues and make them less "ambiguous". Thus, this has been achieved in the issues of mammography, magnetic resonance imaging, fine needle aspiration and core biopsy, axillary dissection, internal mammary node sampling, accelerated partial breast irradiation, the sequence of chemoradiotherapy, negative margin width, while controversial are still remain the themes of tomosynthesis, 3D ultrasound, shear wave elastography, positron emission tomography-computed tomography (PET-CT), CT-scan and bone scintigraphy, hormonotherapy, bisphosphonates and sentinel lymph node biopsy.

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## INTRODUCTION

Globally, breast cancer (BC) is one of the most frequent diagnosed cancers[1]. More than 1.6 million new cases of BC are identified among women, according to the recent worldwide available data[2]. Especially, in North America, in western and in northern Europe the incidence rate is higher than in Asia and socioeconomical development seems to be the leading cause[1,3,4]. In addition, the cumulative incidence of BC raised by more than a quarter between 1980 and 2010 among 187 countries[2]. This raise has been succeeded thanks to BC awareness and early detection of breast malignancy.

Taking into consideration the progress in diagnosis and treatment, it is inevitable that some controversies will come up in daily clinical practice[5]. The aim of this review is to illustrate some of these conflicting issues and make them less "ambiguous". Especially, in the diagnosis field, the subjects which are discussed below are mammography, breast tomosynthesis, 3D ultrasound, shear wave elastography, magnetic resonance imaging, fine needle aspiration and core biopsy, computed tomography, positron emission tomography-computed tomography (PET-CT), axillary node dissection, sentinel lymph node biopsy, internal mammary node sampling and negative margin widths. As for the controversial issues based on treatment, these are partial breast radiotherapy, breast reconstruction, sequence of radiotherapy and chemotherapy, hormotherapy and biphosphonates. However, the follow-up of BC survivors has not been overlooked.

## IS MAMMOGRAPHY NECESSARY IN WOMEN BEFORE THE AGE OF 50?

According to prevailing belief, early detection is a vital first step in defense against BC. Undoubtedly, mammography is the gold standard in BC screening and is widely used in order to reduce BC deaths. The optimal age in which mammography screening should start is a subject of intense controversy. Specifically, while there is a consensus for routine screening in women among 50-69 years, it is still under debate whether women aged 40-49 years could benefit from screening with mammography[6]. As a result, there are different recommendations among organizations and by extension among countries concerning screening. The United States Preventive Services Task Force (USPSTF) recommended toward biennial screening at age of 50 and against screening in women aged 40-49 years[7], "overlooking" that a mammography screening reduces BC mortality by 15% for women aged 39 to 49 years[8] and sparking a controversy in the medical world. However, as it is shown by a recent study, the effect of those guidelines on mammography rates in women older than 40 years was negligible[9]. Conversely, some organizations such as American Cancer Society (ACS) and American College of Radiology (ACR) have different position than that of USPSTF, recommending annual mammography screening beginning at age 40[10,11]. It is noteworthy that a new study with 7301 patients argued in favor of screening before age 50 years, because it is proved that most deaths from BC occurred in women who were unscreened[12]. Additionally, a meta-analysis which conducted by Greek scientists indicated a significant reduction in BC mortality, as a result of screening mammography in women younger than 50[13]. Similar effectiveness is confirmed by a Sweden study[14]. Taking into account all the above and the fact that BC occurs in many cases in women under age 50, there is a tendency toward offering screening mammography before 50 years. As an example, in the United Kingdom in 2010, by the age of 50 around 10000 women were diagnosed with BC and 80% of all diagnoses were in the over 50s, concluding that about 1 in 5 women were diagnosed with BC by the age of 50[15]. It is worthwhile to note that guidelines vary between countries, depending on socioeconomic development of each one.

## CAN BREAST TOMOSYNTHESIS BE PROPOSED AS A SCREENING TOOL?

Great scientific interest has been focused on breast tomosynthesis (BT), which is a relatively new three dimensional imaging technology for the fight against BC nowadays. BT uses a digital detector and an X-ray source, which moves in an arc around breast and takes multiple images[16]. Then, BT's information is sent to a computer, where it is reconstructed in order to produce a 3D image of breast tissue thickness 1 mm. It seems that BT solves the problem of tissue overlap, which encountered in 2D mammography[16]. Despite, BT approved by the US Food and Drug Administration[17], it is a controversial issue whether it could be the standard care in BC screening. Although, it was found that BT has a marginally greater sensitivity and greater specificity, compared to digital mammography[18], there were conflicting findings regarding BT's sensitivity from other data. Some investigators found that traditional mammography was slightly superior to BT in sensitivity[19] and that BT potentially has worse performance in the detection of microcalcifications[20]. On the other hand, it was recently demonstrated that the usage of BT in combination with digital mammography ("adjunctive BT") has as a result an increase in BC detection rates[21]. Similarly, a recent study concluded that adjunctive BT could improve the diagnostic performance in mammography and, summarizing older data, mentioned that BT has probably a higher sensitivity when compared with 2D mammography and reduce recall rates[22], a similar conclusion of Haas *et al*[23] especially

in women under the age of 50 and in women with dense breast tissue. According to all aforementioned reasons, BT is a promising revolutionary tool in BC screening. At present, BT is used only as an adjunct to conventional mammography. Consequently, clinical trials are necessary in order to justify its routine use in screening population.

## SHOULD HIGH RESOLUTION 3D ULTRASOUND BE USED AS A SCREENING MODALITY IN YOUNG PATIENTS WITH DENSE BREASTS?

Although mammography is the gold standard in BC screening, it may not be effective in all patients, such as young women with dense breasts[24]. Also, it is noteworthy that women with dense breast tissue have a 3 to 5 fold increase in BC risk, in contrast to those women with a lack of dense breast tissue[25]. Owing to all aforementioned reasons, new tools for BC screening such as breast ultrasound, are needed. Remarkably, the United States Food and Drug Administration (FDA) approved in 2012 an automated breast ultrasound system (ABUS), as an adjunct to mammography, especially in women with dense breasts[26]. As a screening tool, the method could be proposed for the imaging evaluation of non-palpable masses in women under 30 years of age who are not at high risk for development of BC, and in lactating and pregnant women[27]. 3D breast ultrasound is a special advanced examination, which provides information of the coronal plane[28]. Recent available data are full of optimism about the utility of 3D breast ultrasound in young women with mammographically dense breasts. Specifically, a study indicated that the extra usage of 3D breast ultrasound was more efficient than mammography alone[27]. However, there is no evidence that 3D ultrasound decreases mortality rates[29]. Thus, 3D breast ultrasound is a promising tool and may be used in screening in women with dense breasts widely. Nevertheless, there are no guidelines for its use as screening, instead of mammography until now[30]. Summing up the discussion above, this issue remains a subject of intense controversy and randomized clinical trials are required.

## IS SHEAR WAVE ELASTOGRAPHY A VALUABLE TOOL?

Elastography is a technique of breast imaging tissue stiffness which has been introduced into ultrasound in order to contribute to lesion differentiation[31,32]. Namely, shear wave elastography (SWE) uses the acoustic radiation force provided by the ultrasound beam itself. Although, the predictive significance of this method remains to be elucidated, most recent studies pointed out that SWE improves the specificity of B-mode ultrasound[33-36] and provides a good diagnostic performance during breast ultrasound[32,34,36,37]. Interestingly, SWE increased the specificity of breast mass assessment from 61.1% to 78.5% and the positive predictive value from 52.6% to 67.1% in a multicenter study with 939 breast masses, while the improvement in sensitivity was insignificant[36]. Moreover, it is noteworthy that several studies demonstrated that SWE may has an important role in reducing the number of unnecessary breast biopsies[34] and that could be useful to assess the cystic content of a breast lesion[35] and axillary lymph node status[38].

## WHO SHOULD HAVE BREAST MRI FOR SCREENING?

Potential use of breast magnetic resonance imaging (MRI), a specialized non-invasive test is extensively studied nowadays. This method uses radio waves and strong magnets in order to determine the morphology of the inner breast. Latest studies, indicated that breast MRI is a valuable screening modality in women with a family history suspicious for inherited predisposition to BC [39,40]. In fact, from these women, annual MRI in accordance with mammography is the current recommendation of several organizations such as American Cancer Society[41], National Institute for Health and Care Excellence[42] and European Society of Mastology-EUSOMA[43]. Specifically, according to the recent guidelines, the main indication for annual MRI screening is the existence of BRCA1 or BRCA2 gene mutation. Moreover, there is some suggestion that women who have a first-degree relative (parent, brother, sister or child) with a BRCA1 or BRCA2 gene mutation, but personally have not been genetic tested, ought to be screened by MRI once a year [41]. Similar recommendation applies for women who have a strong family history of BC[42]. The prevalent age for starting breast MRI screening ranges from 25 to 30 years[41,43]. However, several organizations recommend to women with family history of BC, MRI starting 10 years earlier than the age of diagnosis of the youngest affected relative[11]. According to all aforementioned reasons and the limitation of evidence about the best age in which to start screening[41], this decision should tailored to women's unique situation. As an example, in women with Li-Fraumeni syndrome [an autosomal dominant disorder associated with abnormalities in the tumor protein p53 gene (TP53)], breast surveillance with breast MRI should be considered beginning at 20 years of age[44]. Similarly, consensus recommendations for BC surveillance in women with Cowden syndrome [an autosomal dominant disorder associated with abnormalities in the phosphatase and tensin homolog (PTEN) gene] include annual mammogram and/(or) breast MRI starting at age 30 to 35 or 5 to 10 years before the earliest known BC in the family[45]. Nowadays, another main debate is about the possibility of moving from the old recommendation of "MRI as an adjunct" to the new one "MRI alone"[46]. Currently, MRI is not generally recommended as screening tool by itself, despite the fact that it has better sensitivity than mammography (especially in young women), it still has more false positive recalls[39,41].

Furthermore, MRI is a quite expensive procedure[47] and has no evidence on reducing BC mortality[48].

## DOES PRESURGICAL BREAST MRI INFLUENCE OVERALL SURVIVAL?

According to general belief, breast MRI is an extremely sensitive imaging assessment tool, which is able to detect BC[40]. However, the integration of MRI into breast surgical operations remains debatable. Specifically, whether presurgical breast MRI has some impact on overall survival is a controversial and complex subject[49]. Some investigators who support the use of breast MRI preoperatively argue that it may have an influence in overall survival rates[50]. This view is supported because of the potential benefits of MRI in decrease of recurrence rates[51,52]. Conversely, recent available data has shown that this approach does not improve patient's outcomes[53]. Interestingly, a meta-analysis which conducted in 2013 pointed out that MRI leads to overtreatment with probably unnecessary mastectomies[54], a different conclusion than that of Killelea *et al*[52]. Furthermore, a United Kingdom randomized trial (COMICE) indicated that preoperative MRI did not change the re-operation rates[55]. In conclusion, there is a lack of randomized clinical trials showing a benefit of presurgical breast MRI in overall survival. Thus, in order to exist a definitive answer to this issue, additional studies are required.

## PRESURGICAL DIAGNOSIS: FNA OR CORE BIOPSY?

Both fine-needle aspiration (FNA) and core biopsy (CNB) are the current procedures of choice for the detection of BC. FNA is executed with the use of a 10 or 20 mL plastic syringe and a 23 to 27 gauge needle. The syringe can adapted to a special device, which brought negative pressure. As keeping negative pressure, syringe makes reciprocating movements into the mass, while rotating physician's wrist[56]. Also, in order to succeed nipple aspiration, a specially constructed syringe can be applied by Zervoudi's technique[57]. On the other hand, CNB is a method that removes small solid samples of tissue using a needle with wide lumen. Both of these aforementioned procedures have advantages and disadvantages, as it is shown in Table 1[58-61]. In recent years, there is a shift toward the use of CNB. However, whether FNA or CNB is better remains contentious and there is a lack of consensus among different BC centers. Specifically, some investigators summarized that FNA has superiority over CNB and that may be useful and reliable as a first diagnostic step for the detection of palpable breast lesions[62,63]. Moreover, they found that FNA had a same predictive value with CNB[64]. Conversely, other researchers demonstrated that CNB offers a more definitive histologic diagnosis in contrast to FNA, which has limitations in diagnostic accuracy, sensitivity and specificity[56,58]. A main disadvantage of FNA cytology is the "inability" to distinguish between *in situ* and invasive cancer[65]. On the contrary, CNB may permit the distinction between *in situ* and invasive cancer. As a result, CNB has gained popularity widely, but the final decision on whether to use one or another is based on a number of factors, such as the clinical features of the lesion, the likelihood of achieving an indicative diagnosis and the experience of the operator[58].

## FOLLOW-UP TO DETECT METASTASIS: CT SCAN AND BONE SCINTIGRAPHY OR PET/CT?

Currently, if computed tomography (CT) scan and bone scintigraphy could be used as a standard practice in BC follow up or whether PET/CT is more efficient, is controversial. Most published scientific studies, indicated that whole body PET/CT has greater sensitivity and specificity in detecting metastasis, compared to other approaches[66]. In other words, recent available data revealed that PET/CT is superior to CT scan and bone scan and provides better accuracy in bone metastases detection, in patients with BC[67-69]. However, an individual multicenter study concluded that bone scintigraphy, which is inexpensive[68], is more effective in bone metastases determination than PET/CT[70]. Moreover, PET/CT is related with low sensitivity in identification of tumors, smaller than 1 cm[71]. Furthermore, in asymptomatic patients, it is noteworthy that none of the imaging tests, including CT scan, bone scintigraphy and PET/CT provides survival improvement[72]. According to the above, imaging studies (apart of mammography and breast MRI in special occasions) are not recommended as a routine practice in people with no symptoms of metastases[72-74]. However, in symptomatic patients, there is not enough evidence whether PET/CT could be replaced CT scan plus bone scintigraphy.

## AFTER CONSERVATIVE SURGERY, IN PATIENTS WITH POSITIVE SENTINEL LYMPH NODES, SHOULD AXILLARY DISSECTION BE PERFORMED OR NOT?

Axillary dissection was considered as the gold standard practice for many years in patients with a positive sentinel lymph node. Nowadays, in accordance with the counterintuitive results of many studies, there is a key controversy on whether this approach is always necessary after a positive sentinel lymph node[75]. In fact, both the ACOSOG ZOO11 randomized trial and the IBCSG 23-01 controlled trial indicated that the routine use of axillary dissection could be safely omitted in women with early BC who have only one or two positive sentinel nodes[76,77]. Interestingly, they showed that there is no statistical difference in overall survival and in disease free

**Table 1 Comparison between fine needle aspiration and core biopsy**

| | FNA | CNB |
|---|---|---|
| Ability to distinguish invasive from *in situ* lesions | No | Yes |
| Accurate for palpable lesions | Yes | Yes |
| Accurate for non palpable lesions | No | Yes |
| Useful for hypocellular and sclerotic lesions | No | Yes |
| Diagnosis of papillary lesions | Low | Moderate |
| Distinction of low grade lesions | Very difficult | Difficult |
| Suitable for difficult or superficial sites | Yes | No |
| Appropriate for patients with coagulation abnormalities | Yes | No |
| Complication rate | Very low | Low |
| Minimal invasiveness | Yes | No |
| Special experience required | Yes | No |
| Rapid (initial) diagnosis | Yes | No |
| Patient discomfort | No | Yes |
| Long tissue processing time | No | Yes |
| Cost | Inexpensive | More expensive than FNA |
| Requirement of anesthesia | No | Yes |

FNA: Fine needle aspiration; CNB: Core biopsy.

survival between patients who underwent axillary dissection and those that did not, but who received systemic therapy and radiation therapy (RT). These results were also confirmed by AMAROS study, which found that radiotherapy may be sufficient for most patients with a positive sentinel node[78]. Indeed, the 2013 St. Gallen Consensus Conference recommended that in patients with macrometastasis in 1-2 sentinel lymph nodes, completion of axillary dissection can be avoided in patients who receive RT[79]. On the other hand, individual studies pointed out that the omission of axillary dissection in women with sentinel node micrometastases is related to an increased 5-year reccurence rate[80]. Summarizing all the above data and taking into account a recent review, a complete axillary node dissection is suggested in patients with positive sentinel node undergoing a mastectomy without RT[81]. Furthermore, for patients with micrometastases (> 0.2 mm and no greater than 2.0 mm) or macrometastases in three or more nodes, after sentinel lymph node dissection, completion of axillary dissection is recommended for staging purposes and to ensure local control[82]. In conclusion, according to the above data, the recent tendency is the shift from axillary dissection to axillary conserving strategies in selected patients with positive sentinel lymph nodes.

## WHICH IS THE IMPACT OF MICROMETASTASIS IN SENTINEL NODE ON DFS AND OS?

The presence of micrometastasis in sentinel lymph nodes has raised the issue on whether has some impact on disease free survival (DFS) and overall survival (OS). Several studies indicated that women with micrometastasis in sentinel lymph node did not have significant difference in DFS and OS *vs* node negative patients[83]. Remarkably, in a study published by Hansen *et al*[84], patients with micrometastasis, pN0(i+) [regional lymph node(s) with (⩽ 200) malignant cells in an area ⩽ 0.2 mm] and pN1mi [regional lymph node(s) with malignant cells in an area > 0.2 mm but ⩽ 2.0 mm (and/or with > 200 cells in an area ⩽ 2.0 mm)] did not appear to have a worse 8-year DFS or OS in comparison with patients who were sentinel node negative[85]. The latter was also confirmed by another population based study in which has been proved that there is hardly any impact on OS during the first years after diagnosis in patients with sentinel node micrometastasis. In contrast to all aforementioned studies, other studies concluded that the appearance of sentinel node micrometastasis has been associated with shorter positive DFS and OS rates[86,87]. Summarizing, the influence of micrometastasis on BC outcomes remains uncertain, enhancing plenty of controversy among investigators.

## IS SENTINEL NODE AFTER NEOADJUVANT CHEMOTHERAPY ACCURATE?

Patients who are candidates for neoadjuvant chemotherapy (NACT) and have a clinically negative axillary examination at presentation (cN0) may have a sentinel lymph node biopsy (SLNB) either prior to or after neoadjuvant chemotherapy. The timing is often determined by preferences of the treating physician, and in the absence of data suggesting a preferred strategy, either is reasonable. It is suggested that if the SLNB is negative (pN0), before or after NACT, no further axillary evaluation is required[88]. Candidates for nodal evaluation who are about to undergo NACT are initially either clinically node-negative or clinically node-positive patients. However, the application of SLN surgery for staging the axilla, following NACT, for women who initially had clinically node-positive (cN1) BC [and, after NACT, clinically node-negative (cN0) BC] is unclear because of high false-negative rates (FNR) of SLNB reported in previous studies. Actually, considering that FNR is > 10%, changes in approach and patient selection that result in greater sensitivity would be necessary to support the use of SLN surgery, after NACT, as an alternative to axillary lymph node dissection (ALND)[89]. In addition, it seems "rationale" that SNDB is a more reliable diagnostic method before NACT and that after NACT, SLNB has a lower detection rate and a higher FNR compared with SLNB done before NACT. However, based on the results of the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial and the SENTINA (SENTinel NeoAdjuvant) study, a prospective, multicenter cohort study, a clear relationship was found between the number of SLNs and false negative rates[90]. Clearly, as much SLNs are removed, as low the false-negative rate is[89-91]. For patients initially presenting with clinically node positive disease who then

received NACT, it was convincingly demonstrated that only when ⩾ 3 nodes were harvested during SLNB, the FNR was comparable to that of patients initially presenting with clinically node negative disease[91]. Furthermore, it seems that the false-negative rate of SLNB after NACT is roughly comparable to the one of SLN biopsy in general (10.5%)[92,93], albeit it was suggested that there is insufficient evidence to recommend SLNB after NACT as a standard procedure[92]. As for the "accuracy", there are studies which confirm that SLN remains an accurate tool after NACT in selected patients with operable BC[94,95] while in contrary others conclude that the diagnostic reliability is better before the systematic treatment[90]. In conclusion, the accuracy of SLN after NACT remains a conflict through the published studies and further evaluation is needed.

## IS SENTINEL NODE IN SECOND BC SURGERY (PRIOR CONSERVATIVE SURGERY) ACCURATE?

Approximately 10 to 15 percent of the patients with early BC, who had undergone breast-conserving surgery (BCS), will develop loco-regional recurrence disease within 10 years[96,97]. Axillary staging in these patients is important for obtaining locoregional control and predicting prognosis[98]. Nowadays, the concept of repeating sentinel node biopsy (SNB) is a potential clinical scenario. Inquiring into published data, the dominant aspect is that SNB is technically feasible and accurate and can be successfully performed[99-101]. In similar assumptions ended a recent systematic review and meta-analysis of the literature published by Maaskant-Braat *et al*[99] after taking into account all studies on repeat SNB in locally recurrent BC. The main conclusions of the above review were that repeat SNB has a low false-negative rate, spares patients an unnecessary axillary lymph node dissection and its information can lead to a change in adjuvant treatment strategy. Nonetheless, more studies are required to determine the optimal interval before repeat SNB[82].

## INTERNAL MAMMARY NODE SAMPLING IN CENTRAL AND INTERNAL QUADRANT BC: USEFUL OR NOT?

Even if axillary sentinel lymph node (SLN) biopsy is a standard procedure for staging clinically node negative patients with BC, the value of sentinel lymph node biopsy for the internal mammary chain (IMC) remains marginally controversial[102]. As for the tumor location and the internal mammary node (IMN) involvement, Paredes *et al*[103] reported that the predictive factor for the IMC involvement was location of the tumors in the inner quadrants ($P < 0.001$), while Cserni and Szekeres pointed out that data from extended radical mastectomy series cannot be extrapolated to patients suitable for SLN[103,104]. Indeed, SLN biopsy does not reliably identify IMN involvement because of interference from radioactivity at the primary tumor site and there is a high rate of technical failure[82]. In addition, the axillary lymph node (ALN) involvement has been noticed as a predictive factor for IMN involvement[105]. It is rarely found IMN metastasis without ALN metastasis according to Ramsay *et al*[106]. Prognosis for patients with axillary and IM involvement is worst while axillary node negative patients will be found to have regional metastasis to the IMN in 8 to 10 percent of cases[82,104]. In case of positive diagnosis of IMN involvement, the treatment decisions may be affected regarding adjuvant systemic therapy and regional irradiation[82,105]. However, randomized trials show no evidence that IMN resection through extended mastectomy compared with radical or modified radical mastectomy improves survival[107,108]. Thus, the IMN dissection was abandoned. All these boils down to the fact that IM SLN biopsy is not routinely recommended (considered investigational) and further studies need to be undertaken[82,102,109,110].

## CAN PARTIAL BREAST RADIOTHERAPY BE SELECTED IN BIFOCAL CANCERS?

Accelerated partial breast irradiation (APBI) is used as an alternative technique to conventional whole breast irradiation (WBI) in selected patients with early BC after breast conserving surgery (BCS)[111]. Recommendations for the selection of patients have been published from the American Society of Breast Surgeons (ASBS), the American Brachytherapy Society (ABS), the American Society for Radiation Oncology (ASTRO) and the European Society for therapeutic Radiology and Oncology (ESTRO)[112-115]. The criteria for the selection conducted according to the published clinical evidence so as the APBI be effective. Polgár *et al*[115] argued that the relatively poorer results of early APBI studies with high local recurrence rates exceeding 1% per year could be attributed to inadequate patient selection criteria and/or suboptimal treatment technique and lack of appropriate QA procedures[116]. Particularly, APBI should be limited to patients between 45 (ABS ⩾ 50) and 70 years of age, with small (⩽ 3 cm), unifocal, unicentric and lymph node negative tumors resected with negative margins and without adverse histologic features (including lobular carcinoma, *in situ* ductal carcinoma and extensive intraductal carcinoma). Consequently, a patient with a bifocal tumor cannot be selected for partial breast irradiation.

## WHICH IS THE IMPACT ON RECURRENCE IN IMMEDIATE OR DELAYED RECONSTRUCTION AFTER MASTECTOMY?

Immediate (IBR) or delayed breast reconstruction (DBR) stipulates the time of reconstructive surgery after mastectomy. Even if the impact of loco-regional recurrence comparing IBR and DBR has not been evaluated, nu-

merous studies compare the recurrence ratio of IMR and DBR with mastectomy alone. Particularly, a published meta-analysis in 2012 demonstrates no evidence for increased frequency of local breast recurrence with IBR compared to mastectomy alone (OR: 0.98; 95%CI: 0.62-1.54) while another study reports that IBR had an acceptable 5-year local recurrence rate of 2.9% (95%CI: 0.1-5.7)[117,118]. In case of DBR, Lindford *et al*[119] (2013) concluded that delayed autologous reconstruction after mastectomy doesn't appear to adversely influence disease progression when compared to patients treated with mastectomy only. The appropriate time should be settled on minimizing the potential complications and optimizing the postoperative outcome. Nonetheless, in case of women who require postmastectomy radiotherapy (RT) the best option of reconstruction is controversial although need for postoperative RT is considered a relative contraindication to IBR[120]. On one hand, based in a retrospective study, DBR should be proposed to these women as the loco-regional recurrence rate is lower when RT is given before reconstruction and patient demise may be increased when radiation therapy is performed following breast reconstruction[121]. On the other hand, this was not proven by other data showing that mastectomy with immediate expander-implant reconstruction was associated with acceptable 5-year locoregional control, distant metastasis-free survival and overall survival[122]. All these boils down to the fact that there is no evidence cancelling IBR or DBR based on recurrence. There is a tendency more and more using IBR over DBR considering, among others, that several studies revealed that women undergoing IBR experienced significant psychosocial benefits[120].

## WHICH IS THE OPTIMAL TIME TO START CHEMOTHERAPY AFTER BC SURGERY AND WHICH SEQUENCE OF RADIOTHERAPY AND CHEMOTHERAPY SHOULD BE ADMINISTERED?

Radiotherapy (RT) and chemotherapy (CT) are used to improve local control and reduce the risk of dying from BC. Nevertheless, for women with early stage BC who have been treated surgically, it remains marginally uncertain whether both treatments should be given at the same time (concurrently) or one after the other (sequentially) and in which order[123]. Four schemes of sequencing RT and CT have been tried or adopted: administering CT before RT (more frequently used), administering CT and RT concurrently with an overlap of at least 21 d[124], using a "sandwich" treatment schedule by administering three cycles of CT followed by RT and then administering three more cycles of CT[125] and administering RT before CT. Adjuvant chemotherapy can be administered within 4-6 wk after the surgery while a delay of more than 12 wk could be detrimental[126]. Abbas *et al*[127], in a total of 267 patients divided into 3 groups, found that disease free survival (DFS) at 2.5 years was 83.5%, 82.3% and 80% for patients receiving radiation before chemotherapy, sandwich and after finishing chemotherapy respectively concluding that DFS is not altered by treatment sequence. Pooling data of three randomized trials in women with early stage BC, Hichey concluded that local control and overall survival was similar comparing concurrent CT and RT, RT followed by CT and CT followed by RT when RT was commenced within seven months after surgery (as this was the maximum delay in the included studies). However, RT followed by CT was associated with an increased risk of neutropenic sepsis compared with CT followed by RT and concurrent chemoradiation increased anaemia, telangiectasia and pigmentation[123]. Similarly, a randomized trial including 2396 women with early stage BC who received CMF with or without an anthracycline and who were treated with concomitant or sequential radiation therapy, concluded that in concomitant therapy there was a significant increase in acute skin toxicity (25 *vs* 16 percent)[128]. It seems that concurrent chemoradiation is more toxic than sequential therapies. Taking everything into account, the concomitant use of RT and CT hasn't gain universal acceptance while the clinical practice uses CT before RT[129].

## HORMONOTHERAPY IN POSTMENOPAUSAL WOMEN: WHICH ONE AND FOR HOW LONG?

Undoubtedly, hormonotherapy constitutes a principal component in treatment of hormonal positive BC. Selective estrogen receptor modulators (*e.g.*, tamoxifen and toremifene), estrogen receptor downregulators (*e.g.*, fulvestrant) and aromatase inhibitors (*e.g.*, anastrazole, exemestane and letrozole) are all different types of hormonal therapy medicines[41]. It is noteworthy that despite tamoxifen was the previous established therapy, it was replaced by the usage of aromatase inhibitors (Als) in postmenopausal women. This shift is based on the positive findings in studies which compared Als to tamoxifen[130]. Notably, a meta-analysis indicated that Als significantly decrease the risk of recurrence and improve outcomes[131]. However, tamoxifen remains an option of therapy, particularly in women with contraindication to Als, but not as a first choice[132]. For many years, the ideal duration of tamoxifen treatment was 5 years. Nevertheless, recent randomized trials, such as ATLAS study demonstrated that the use of tamoxifen over 10 years has superiority in recurrence and mortality, compared to a 5-year therapy[133]. On the other hand, there are many unanswered questions that generate plenty of controversy regarding the use of Als, which is the initial treatment in postmenopausal women. Firstly, it is unclear which of aromatase inhibitor is better. However, all Als appear to have similar efficacy, as it is shown by MA.27 study[134]. Secondly, it is still uncertain which is the ideal duration of Als therapy. The standard treatment lasts 5 years, but

more studies are required in order to prove whether therapy with an AI could be efficient for more than 5 years. Thus, until now, for postmenopausal women, it is recommended by several organizations to begin treatment with an AI for 5 years, or with tamoxifen for 5 years followed by an AI for 5 years, or treatment with tamoxifen for 2 to 3 years followed by an AI in order to complete a 5-year therapy[41,72,132]. In conclusion, the choice of suitable hormonotherapy should be depend on patient's unique situation.

## TAMOXIFEN-RALOXIFEN: WHICH IS BETTER FOR BC PREVENTION?

Focusing on tamoxifen and raloxifene, many trials have been conducted in order to point out which one is the most effective for BC prevention. The STAR trial (Study of Tamoxifen and Raloxifene) compared tamoxifen with raloxifene in 19490 high-risk postmenopausal women for a 5-year period. The initial results were almost equal with both drugs reducing the risk of BC approximately 50%. In the long-term follow-up, tamoxifen had a greater chemoprevention effect than raloxifene [1.24, 95%confidence interval (CI), 1.05-1.47]. Actually, long-term raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive BC[135]. However, there are other trials which compared tamoxifen and raloxifene with placebo. In MORE (Multiple Outcomes of Raloxifene Evaluation) trial, 13 cases of BC were confirmed among the 5129 women assigned to raloxifene *vs* 27 among the 2576 women assigned to placebo [relative risk (RR), 0.24; 95%CI: 0.13-0.44][136]. In CORE (Continuing Outcomes Relevant to Evista) trial, the 4-year incidences of invasive BC and estrogen receptor (ER)-positive invasive BC were reduced by 59% [hazard ratio (HR) = 0.41; 95%CI = 0.24 to 0.71] and 66% (HR = 0.34; 95%CI = 0.18 to 0.66), respectively, in the raloxifene group compared with the placebo group[137]. Finally, in Raloxifene Use for the Heart (RUTH) trial, in 10101 postmenopausal women with coronary heart disease or multiple risk factors for this disease, raloxifene reduced the incidence of invasive BC by 44% (HR = 0.56; 95%CI = 0.38-0.83)[138]. Similarly, after 7 years of follow-up, the cumulative rate of invasive BC was reduced from 42.5 per 1000 women in the placebo group to 24.8 per 1000 women in the tamoxifen group (RR = 0.57, 95%CI = 0.46 to 0.70) in the National Surgical Adjuvant Breast and Bowel Project P-1 (NSABP-1) study. Furthermore, in the International Breast Cancer Intervention Study (IBIS-I), after a median follow-up of 96 mo after randomization, 142 BCs were diagnosed in the 3579 women in the tamoxifen group and 195 in the 3575 women in the placebo group (4.97 *vs* 6.82 per 1000 woman-years, respectively; RR = 0.73, 95%CI = 0.58 to 0.91). Although this study showed a somewhat "smaller" reduction of the risk of BC, the risk-reducing effect of tamoxifen appeared to persist for at least 10 years and, equally important, most side effects of tamoxifen did not continue after the 5-year treatment period[139]. The rates of BC were much lower in the tamoxifen group among women at high risk for BC (placebo, 6.26 per 1000 women-years, tamoxifen, 1.50 per 1000 women-years; RR = 0.24, 95%CI = 0.10 to 0.59) in the Italian Randomized Tamoxifen Prevention Trial[140]. On the contrary, an interim analysis of the Royal Marsden Hospital tamoxifen randomised chemoprevention trial, with 2494 healthy women, the overall frequency of BC was the same for women on tamoxifen or placebo [tamoxifen 34, placebo 36, RR=1.06 (95%CI = 0.7-1.7)][141]. Summarizing the facts (not all included above) for the comparison of tamoxifene *vs* raloxifene, it can be concluded that postmenopausal women can choose the most effective tamoxifen (accepting its toxicities), or they can choose the (slightly) less effective (but more tolerable) raloxifene[142]. Furthermore, according to recent data, anastrozole effectively reduces incidence of BC in high risk postmenopausal women[143]. Finally, it must be emphasized that United States Preventive Services Task Force (USPSTF) recommends against the routine use of medications for risk reduction of primary BC in women who are not at increased risk for BC[144].

## DO BISPHOSPHONATES DECREASE THE RISK OF BONE METASTASIS?

Bone metastasis is the most common metastasis in women with BC[145]. The effects of bisphosphonates in women with early-stage BC (EBC) have been evaluated after several meta-analyses as an adjuvant therapy with aromatase inhibitors (AI). In 2010, a meta-analysis, which included data from 13 eligible trials involving 6886 patients randomized to treatment with bisphosponates or either placebo or no treatment, concluded that there is no significant reduction in bone metastasis (BM) and overall disease recurrence. Only in a subgroup analysis, use of zoledronic acid (ZOL) was associated with a statistically significant lower risk for disease recurrence (OR, 0.675; 95%CI: 0.479-0.952, $P = 0.025$)[146]. Furthermore, another meta-analysis and systematic review published in 2012, reports that the use of bisphosphonates did not reduce the incidence of BM when compared with placebo[147]. In contrast, a recent meta-analysis demonstrates that the use of ZOL improves overall survival (OS) compared with placebo (HR,0.81, 95%CI: 0.70-0.94)[148]. Moreover, there are three international randomized studies, Z-FAST, ZO-FAST, and E-ZO-FAST, which were performed to evaluate the bone-protective effects of ZOL[149]. After the analyses of the potential disease recurrence effects of ZOL, a significant activity in preventing bone loss during adjuvant AI therapy in postmenopausal women with EBC was noticed. However, heterogeneity between the trials for disease-free survival (DFS) and OS parameters resulted in statistically significant interaction P value, meaning that pooling of the data between studies would not be statistically valid[149]. Last but not least, according to recent presented studies in the San Antonio Breast Cancer Symposium, the use of bisphosphonates

remains controversial. Coleman *et al*[150], after selecting 11036 postmenopausal women, demonstrated that those who were on bisphosphonate therapy experienced distant recurrences in 18.4% while women who were not in 21.9% with high statistically significant difference ($P = 0.0003$) and distant bone metastases in 8.8% and 5.9% ($P < 0.0001$) respectively. In addition, Susman *et al*[151] reported that BC specific mortality was reduced by 3.1% from 18.3% in women who were not treated with bisphosphonates to 15.2% for those who were on treatment ($P = 0.004$)[150,151]. In contrast, in the other related to bisphosphonates presentation based on Neo-Adjuvant Trial Add-On (NATAN), von Minckwitz concluded that there was no difference in DFS and OS[152]. However, even if bisphosphonates are used as an adjuvant therapy, they should be in addition with nutritional (calcium 1000 mg and 400 international units vitamin D), physical and lifestyle modifications[153].

## OPTIMAL FOLLOW-UP IN BC SURVIVORS: WHAT SHOULD BE DONE, UNTIL WHEN?

The number of BC survivors has improved within the last decades due to earlier diagnosis and effective treatments in order to prevent recurrence[154,155]. In follow up guidelines, routine physical examination with a careful taking history has been the most valuable means of detecting BC recurrence[156,157]. The European Society for Medical Oncology (ESMO) recommends regular visits every 3 to 4 mo in the first 2 years, every 6 mo from years 3 to 5 and annually thereafter[72]. "In contrast", the American Society of Clinical Oncology (ASCO) recommendation for physical examinations is every 3 to 6 mo for the first 3 years, every 6 to 12 mo for years 4 and 5 and annually thereafter[73]. Based on the evidence, mammographic surveillance remains the principal examination in detecting curable recurrences and improving survival[158]. ESMO suggests ipsilateral (after breast-conservation surgery) and contralateral mammography every 1 or 2 years and ASCO recommends a post-treatment mammogram 1 year after the initial mammogram and at least 6 mo after completion of radiation therapy. According to ESMO, in the follow-up of patients on endocrine therapy, routine blood tests are usually indicated due to the potential side-effects of these drugs namely in the lipid profile. Furthermore, for patients on tamoxifen, an annual gynaecological examination (by an experienced gynaecologist) is recommended[72]. However, routine ultrasound assessment of endometrial thickness is not suggested[65]. Finally, for patients on aromatase inhibitors (AIs), regular bone density evaluation is advised[72]. According to ASCO, in asymptomatic patients, other laboratory or imaging tests (*e.g.*, blood counts, chemistry tests, chest X-rays, bone scans, magnetic resonance imaging, liver ultrasound exams, CT scans or any tumor markers) are not recommended for routine BC follow-up[73]. Last but not least, the follow up should not only focus in cancer surveillance but also in late-treatment complications such as psychosocial issues[157].

## ARE MARGINS FOR DCIS AS IMPORTANT AS WE THOUGHT?

Since the treatment decision for patients with DCIS was difficult, a prognostic tool has been created. In 1996, Silverstein *et al*[159] have been developed the Van Nuys Prognostic Index (VNPI) by combining three significant parameters (tumor size, margin width, pathologic classification). However, in 2003 the University of Southern California added the patient age as a fourth parameter. The score ranges for 4 to 12 and the final goal was the prediction of local recurrence[160]. The scores which were given to the four parameters range from 1 to 3. In case of margins, the score 1 is given for margin width $\geqslant$ 10 mm, the score 2 for 1 to 9 mm and the score 3 to less than 1 mm.

Even if this classification includes margins, it remains controversial the specific margin width which eliminates the risk of ipsilateral breast tumor recurrence (IBTR). Thus, the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) examined the relationship between margin width and IBTR after taking into consideration systematic review and metaanalysis of the literature by including 28162 patients[161]. They concluded that wider margin widths do not lower the risk for IBTR and consecutively wider negative margins, known as no ink on tumor, are not required. As a result, this new clinical recommendation has changed the way of thinking about negative margin widths. Even if, this was something new in clinical practice, for some others this was just a vindication[162]. An updated version of VNPI could be proposed without the margins as a graded parameter and/or the substitution of margins with the hormone receptors status [anecdotal proposal of profs G Iatrakis and S Zervoudis (co-researchers A. Bothou and E Tomara)].

## CONCLUSION

Clearly, there is much more evidence needed to clarify which answer is the correct one in the twenty-one aforementioned issues. The lack of recommended guidelines and reliable studies which include enough patients and give the possibility to generalize the results, are the main reasons why clinicians still have not consensus in clinical practice. Thus, multicentric studies and meta-analyses are required in order to clear up the less "acceptable" interventions and established the more "approved".

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