**Name of journal: *World Journal of Clinical Oncology***

**ESPS Manuscript NO: 8135**

**Columns: TOPIC HIGHLIGHT**

WJCO 5th Anniversary Special Issues (2): Breast Cancer

**Main controversies in breast cancer**

Zervoudis S *et al.* Controversies in breast cancer

Stephane Zervoudis, George Iatrakis, Eirini Tomara, Anastasia Bothou, George Papadopoulos, George Tsakiris

**Stephane Zervoudis**, **George Iatrakis**, **George Papadopoulos**, **George Tsakiris**, Rea Hospital, 17564 Athens, Greece

**Stephane Zervoudis, George Iatrakis, Eirini Tomara, Anastasia Bothou, George Tsakiris,** Technological University of Athens, 12210 Athens, Greece

**Author contributions:** Zervoudis S andIatrakis G came up with the title and the format of the manuscript; Zervoudis S, Iatrakis G, Tomara E and Bothou A wrote the paper; Iatrakis G made the final corrections; Papadopoulos G and Tsakiris G help for the issues based on chemotherapy and radiotherapy consecutively.

**Correspondence to: Dr. Stephane Zervoudis,** Rea Hospital, 383-Suggrou Avenue, Palaio Faliro 17564 Athens, Greece. [szervoud@otenet.gr](mailto:szervoud@otenet.gr)

**Telephone:** +69-44-308777 **Fax:** +30-210-8981178

**Received:** December 17, 2013 **Revised:** April 7, 2014

**Accepted:** May 13, 2014

**Published online:**

**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 (FNA), core biopsy (CNB) 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.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**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 (MRI), fine needle aspiration (FNA) 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 (SWE), positron emission tomography–computed tomography (PET-CT), CT-scan and bone scintigraphy, hormonotherapy, bisphosphonates and SLNB.

Zervoudis S, Iatrakis G, Tomara E, Bothou A, Papadopoulos G, Tsakiris G. Main controversies in breast cancer. *World J Clin Oncol* 2014; In press

**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 UK 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 likehood 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 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. Polgar *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, numerous 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 Al 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 Al for 5 years, or with tamoxifen for 5 years followed by an Al for 5 years, or treatment with tamoxifen for 2 to 3 years followed by an Al 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, heterogenecity 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, Coleman *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]. Βased 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 ≥ 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”.

**REFERENCES**

1 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

2 **Forouzanfar MH**, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJ, Naghavi M. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet* 2011; **378**: 1461-1484 [PMID: 21924486 DOI: 10.1016/S0140-6736(11)61351-2]

3 Esserman L, Joe B. Clinical features, diagnosis, and staging of newly diagnosed breast cancer. UptoDate 2013

4 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

5 **Boughey JC**, Mittendorf EA, Solin LJ, Michael Dixon J, Tuttle TM, Beitsch PD, Cody HS, Leitch AM, Newman LA. Controversies in breast surgery. *Ann Surg Oncol* 2010; **17 Suppl 3**: 230-232 [PMID: 20853038 DOI: 10.1245/s10434-010-1264-0]

6 **Fletcher S**. Screening for breast cancer: Strategies and recommendations. UptoDate 2013

7 **US Preventive Services Task Force.** Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009; **151**: 716-26, W-236 [PMID: 19920272 DOI: 10.7326/0003-4819-151-10-200911170-00008]

8 **Nelson HD**, Tyne K, Naik A, Bougatsos C, Chan B, Nygren P, Humphrey L. Screening for Breast Cancer: Systematic Evidence Review Update for the US Preventive Services Task Force [Internet]. *Ann Intern Med* 2009; **151**: 727–W242 [PMID: 20722173 DOI: 10.1059/0003-4819-151-10-200911170-00009]

9 **Pace LE**, He Y, Keating NL. Trends in mammography screening rates after publication of the 2009 US Preventive Services Task Force recommendations. *Cancer* 2013; **119**: 2518-2523 [PMID: 23605683 DOI: 10.1002/cncr.28105]

10 American Cancer Society. Breast Cancer: Early Detection. http: //www.cancer.org/acs/groups/cid/documents/webcontent/003165-pdf.pdf. Jun 2013

11 **Lee CH**, Dershaw DD, Kopans D, Evans P, Monsees B, Monticciolo D, Brenner RJ, Bassett L, Berg W, Feig S, Hendrick E, Mendelson E, D'Orsi C, Sickles E, Burhenne LW. Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. *J Am Coll Radiol* 2010; **7**: 18-27 [PMID: 20129267 DOI: 10.1016/j.jacr.2009.09.022]

12 **Webb ML**, Cady B, Michaelson JS, Bush DM, Calvillo KZ, Kopans DB, Smith BL. A failure analysis of invasive breast cancer: Most deaths from disease occur in women not regularly screened. *Cancer* 2013 [PMID: 24018987 DOI: 10.1002/cncr.28199]

13 **Bastardis-Zakas K**, Iatrakis G, Navrozoglou I, Peitsidis P, Salakos N, Malakassis P, Zervoudis S. Maximizing the benefits of screening mammography for women 40-49 years old. *Clin Exp Obstet Gynecol* 2010; **37**: 278-282 [PMID: 21355457]

14 **Hellquist BN**, Duffy SW, Abdsaleh S, Björneld L, Bordás P, Tabár L, Viták B, Zackrisson S, Nyström L, Jonsson H. Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort. *Cancer* 2011; **117**: 714-722 [PMID: 20882563 DOI: 10.1002/cncr.25650]

15 Cancer Research UK. http: //www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/ incidence), 2013 May

16 **Alakhras M**, Bourne R, Rickard M, Ng KH, Pietrzyk M, Brennan PC. Digital tomosynthesis: a new future for breast imaging? *Clin Radiol* 2013; **68**: e225-e236 [PMID: 23465326 DOI: 10.1016/j.crad.2013.01.007]

17 **Freiherr G**. Tomosynthesis a new era in breast imaging, Medscape Ob/Gyn & Women’s Health Mar 2011

18 **Lei J**, Yang P, Zhang L, Wang Y, Yang K. Diagnostic accuracy of digital breast tomosynthesis versus digital mammography for benign and malignant lesions in breasts: a meta-analysis. *Eur Radiol* 2014; **24**: 595-602 [PMID: 24121712 DOI: 10.1007/s00330-013-3012-x]

19 **Svane G**, Azavedo E, Lindman K, Urech M, Nilsson J, Weber N, Lindqvist L, Ullberg C. Clinical experience of photon counting breast tomosynthesis: comparison with traditional mammography. *Acta Radiol* 2011; **52**: 134-142 [PMID: 21498340 DOI: 10.1258/ar.2010.100262]

20 **Timberg P**, Baath M, Andersson I, Mattsson S, Tingberg A, Ruschin M. Visibility of microcalcification clusters and masses in breast tomosynthesis image volumes and digital mammography: a 4AFC human observer study. *Med Phys* 2012; **39**: 2431-2437 [PMID: 22559613 DOI: 10.1118/1.3694105]

21 **Ciatto S**, Houssami N, Bernardi D, Caumo F, Pellegrini M, Brunelli S, Tuttobene P, Bricolo P, Fantò C, Valentini M, Montemezzi S, Macaskill P. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. *Lancet Oncol* 2013; **14**: 583-589 [PMID: 23623721 DOI: 10.1016/S1470-2045(13)70134-7]

22 **Yang TL**, Liang HL, Chou CP, Huang JS, Pan HB. The adjunctive digital breast tomosynthesis in diagnosis of breast cancer. *Biomed Res Int* 2013; **2013**: 597253 [PMID: 23844366 DOI: 10.1155/2013/597253]

23 **Haas BM**, Kalra V, Geisel J, Raghu M, Durand M, Philpotts LE. Comparison of tomosynthesis plus digital mammography and digital mammography alone for breast cancer screening. *Radiology* 2013; **269**: 694-700 [PMID: 23901124 DOI: 10.1148/radiol.13130307]

24 **Drukteinis JS**, Mooney BP, Flowers CI, Gatenby RA. Beyond mammography: new frontiers in breast cancer screening. *Am J Med* 2013; **126**: 472-479 [PMID: 23561631 DOI: 10.1016/j.amjmed.2012.11.025]

25 **Venkataraman S**, Slanetz P. Breast imaging: Mammography and ultrasonography. UptoDate 2013

26 FDA. FDA approves first breast ultrasound imaging system for dense breast tissue. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm319867.htm (Accessed on September 19, 2012)

27 **Giuliano V**, Giuliano C. Improved breast cancer detection in asymptomatic women using 3D-automated breast ultrasound in mammographically dense breasts. *Clin Imaging* 2013; **37**: 480-486 [PMID: 23116728 DOI: 10.1016/j.clinimag.2012.09.018]

28 **Lander MR**, Tabár L. Automated 3-D breast ultrasound as a promising adjunctive screening tool for examining dense breast tissue. *Semin Roentgenol* 2011; **46**: 302-308 [PMID: 22035673 DOI: 10.1053/j.ro.2011.06.003]

29 **Hooley RJ**, Greenberg KL, Stackhouse RM, Geisel JL, Butler RS, Philpotts LE. Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. *Radiology* 2012; **265**: 59-69 [PMID: 22723501 DOI: 10.1148/radiol.12120621]

30 **Gartlehner G**, Thaler KJ, Chapman A, Kaminski A, Berzaczy D, Van Noord MG, Helbich TH. Adjunct ultrasonography for breast cancer screening in women at average risk: a systematic review. *Int J Evid Based Healthc* 2013; **11**: 87-93 [PMID: 23750571 DOI: 10.1111/1744-1609.12022]

31 **Gong X**, Xu Q, Xu Z, Xiong P, Yan W, Chen Y. Real-time elastography for the differentiation of benign and malignant breast lesions: a meta-analysis. *Breast Cancer Res Treat* 2011; **130**: 11-18 [PMID: 21870128 DOI: 10.1007/s10549-011-1745-2]

32 **Chang JM**, Moon WK, Cho N, Yi A, Koo HR, Han W, Noh DY, Moon HG, Kim SJ. Clinical application of shear wave elastography (SWE) in the diagnosis of benign and malignant breast diseases. *Breast Cancer Res Treat* 2011; **129**: 89-97 [PMID: 21681447 DOI: 10.1007/s10549-011-1627-7]

33 **Lee SH**, Chang JM, Kim WH, Bae MS, Cho N, Yi A, Koo HR, Kim SJ, Kim JY, Moon WK. Differentiation of benign from malignant solid breast masses: comparison of two-dimensional and three-dimensional shear-wave elastography. *Eur Radiol* 2013; **23**: 1015-1026 [PMID: 23085867 DOI: 10.1007/s00330-012-2686-9]

34 **Gweon HM**, Youk JH, Son EJ, Kim JA. Clinical application of qualitative assessment for breast masses in shear-wave elastography. *Eur J Radiol* 2013; **82**: e680-e685 [PMID: 23988689 DOI: 10.1016/j.ejrad.2013.08.004]

35 **Balleyguier C**, Ciolovan L, Ammari S, Canale S, Sethom S, Al Rouhbane R, Vielh P, Dromain C. Breast elastography: the technical process and its applications. *Diagn Interv Imaging* 2013; **94**: 503-513 [PMID: 23619293 DOI: 10.1016/j.diii.2013.02.006]

36 **Berg WA**, Cosgrove DO, Doré CJ, Schäfer FK, Svensson WE, Hooley RJ, Ohlinger R, Mendelson EB, Balu-Maestro C, Locatelli M, Tourasse C, Cavanaugh BC, Juhan V, Stavros AT, Tardivon A, Gay J, Henry JP, Cohen-Bacrie C. Shear-wave elastography improves the specificity of breast US: the BE1 multinational study of 939 masses. *Radiology* 2012; **262**: 435-449 [PMID: 22282182 DOI: 10.1148/radiol.11110640]

37 **Youk JH**, Gweon HM, Son EJ, Han KH, Kim JA. Diagnostic value of commercially available shear-wave elastography for breast cancers: integration into BI-RADS classification with subcategories of category 4. *Eur Radiol* 2013; **23**: 2695-2704 [PMID: 23652850 DOI: 10.1007/s00330-013-2873-3]

38 **Tamaki K**, Tamaki N, Kamada Y, Uehara K, Miyashita M, Sm Chan M, Ishida T, Ohuchi N, Sasano H. Non-invasive evaluation of axillary lymph node status in breast cancer patients using shear wave elastography. *Tohoku J Exp Med* 2013; **231**: 211-216 [PMID: 24213140 DOI: 10.1620/tjem.231.211]

39 **Kam JK**, Naidu P, Rose AK, Mann GB. Five-year analysis of magnetic resonance imaging as a screening tool in women at hereditary risk of breast cancer. *J Med Imaging Radiat Oncol* 2013; **57**: 400-406 [PMID: 23870334 DOI: 10.1111/1754-9485.12030]

40 **Sutcliffe JB**, Otto PM. Controversies in breast MRI. *Curr Probl Diagn Radiol* ; **42**: 149-163 [PMID: 23795994 DOI: 10.1067/j.cpradiol.2013.03.001]

41 American Cancer Society. Breast cancer. http: //www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf. Nov 2013

42 National Institute for Health and Care Excellence (NICE). Familial breast cancer. Classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. http: //www.nice.org.uk/nicemedia/live/14188/64202/64202.pdf. Jun 2013

43 **Sardanelli F**, Boetes C, Borisch B, Decker T, Federico M, Gilbert FJ, Helbich T, Heywang-Köbrunner SH, Kaiser WA, Kerin MJ, Mansel RE, Marotti L, Martincich L, Mauriac L, Meijers-Heijboer H, Orecchia R, Panizza P, Ponti A, Purushotham AD, Regitnig P, Del Turco MR, Thibault F, Wilson R. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. *Eur J Cancer* 2010; **46**: 1296-316

44 **Evans DG**. Li-Fraumeni syndrome. UptoDate 2013

45 **Stanich P**, Lindor N, Patnaik M. PTEN hamartoma tumor syndrome, including Cowden syndrome. UptoDate 2013

46 **Sardanelli F**, Podo F, Santoro F, Manoukian S, Bergonzi S, Trecate G, Vergnaghi D, Federico M, Cortesi L, Corcione S, Morassut S, Di Maggio C, Cilotti A, Martincich L, Calabrese M, Zuiani C, Preda L, Bonanni B, Carbonaro LA, Contegiacomo A, Panizza P, Di Cesare E, Savarese A, Crecco M, Turchetti D, Tonutti M, Belli P, Maschio AD. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results. *Invest Radiol* 2011; **46**: 94-105 [PMID: 21139507 DOI: 10.1097/RLI.0b013e3181f3fcdf]

47 **Saadatmand S**, Tilanus-Linthorst MM, Rutgers EJ, Hoogerbrugge N, Oosterwijk JC, Tollenaar RA, Hooning M, Loo CE, Obdeijn IM, Heijnsdijk EA, de Koning HJ. Cost-effectiveness of screening women with familial risk for breast cancer with magnetic resonance imaging. *J Natl Cancer Inst* 2013; **105**: 1314-1321 [PMID: 23940285 DOI: 10.1093/jnci/djt203]

48 **Slanetz P**. MRI of the breast and emerging technologies. UptoDate 2013

49 **Parsyan A**, Alqahtani A, Mesurolle B, Meterissian S. Impact of preoperative breast MRI on surgical decision making and clinical outcomes: a systematic review. *World J Surg* 2013; **37**: 2134-2139 [PMID: 23661259 DOI: 10.1007/s00268-013-2077-7]

50 **Taneja S**, Jena A, Zaidi SM, Khurana A. MRI evaluation of the contralateral breast in patients with recently diagnosed breast cancer. *Indian J Radiol Imaging* 2012; **22**: 69-73 [PMID: 22623820 DOI: 10.4103/0971-3026.95408]

51 **Pediconi F**, Miglio E, Telesca M, Luciani ML, Kirchin MA, Passariello R, Catalano C. Effect of preoperative breast magnetic resonance imaging on surgical decision making and cancer recurrence rates. *Invest Radiol* 2012; **47**: 128-135 [PMID: 21934515 DOI: 10.1097/RLI.0b013e318230061c]

52 **Killelea BK**, Grube BJ, Rishi M, Philpotts L, Tran EJ, Lannin DR. Is the use of preoperative breast MRI predictive of mastectomy? *World J Surg Oncol* 2013; **11**: 154 [PMID: 23849218 DOI: 10.1186/1477-7819-11-154]

53 **Esserman L**, Joe B. Diagnostic evaluation of women with suspected breast cancer. UptoDate 2013

54 **Houssami N**, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. *Ann Surg* 2013; **257**: 249-255 [PMID: 23187751 DOI: 10.1097/SLA.0b013e31827a8d17]

55 **Turnbull L**, Brown S, Harvey I, Olivier C, Drew P, Napp V, Hanby A, Brown J. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *Lancet* 2010; **375**: 563-571 [PMID: 20159292 DOI: 10.1016/S0140-6736(09)62070-5]

56 **Esserman L**, Joe B. Breast biopsy. UptoDate 2013

57 **Zervoudis S**. A simple tool complementary for the diagnosis of breast diseases: the mammary pump. *Breast J* 2003; **9**: 445-447 [PMID: 12968976 DOI: 10.1046/j.1524-4741.2003.09524.x]

58 **Nassar A**. Core needle biopsy versus fine needle aspiration biopsy in breast--a historical perspective and opportunities in the modern era. *Diagn Cytopathol* 2011; **39**: 380-388 [PMID: 20949457 DOI: 10.1002/dc.21433]

59 **Willems SM**, van Deurzen CH, van Diest PJ. Diagnosis of breast lesions: fine-needle aspiration cytology or core needle biopsy? A review. *J Clin Pathol* 2012; **65**: 287-292 [PMID: 22039282 DOI: 10.1136/jclinpath-2011-200410]

60 **Garbar C**, Curé H. Fine-needle aspiration cytology can play a role in neoadjuvant chemotherapy in operable breast cancer. *ISRN Oncol* 2013; **2013**: 935796 [PMID: 23936675 DOI: 10.1155/2013/935796]

61 **Tse G**, Tan PH, Schmitt F. Fine Needle Aspiration Cytology of the Breast. Comparison of Aspiration and Core Needle Biopsy. Springer 2013

62 **Masood S**. Core needle biopsy versus fine needle aspiration biopsy: are there similar sampling and diagnostic issues? *Clin Lab Med* 2005; **25**: 679-88, vi [PMID: 16308086 DOI: 10.1016/j.cll.2005.08.006]

63 **He Q**, Fan X, Yuan T, Kong L, Du X, Zhuang D, Fan Z. Eleven years of experience reveals that fine-needle aspiration cytology is still a useful method for preoperative diagnosis of breast carcinoma. *Breast* 2007; **16**: 303-306 [PMID: 17287118 DOI: 10.1016/j.breast.2006.12.006]

64 **Nagar S**, Iacco A, Riggs T, Kestenberg W, Keidan R. An analysis of fine needle aspiration versus core needle biopsy in clinically palpable breast lesions: a report on the predictive values and a cost comparison. *Am J Surg* 2012; **204**: 193-198 [PMID: 22464444 DOI: 10.1016/j.amjsurg.2011.10.018]

65 **Iatrakis G**. Gynaecological Oncology (prefaced by Zervoudis S). “Desmos” Publications, Athens 2013; http: //service.eudoxus.gr/search/#a/id: 33134040/0

66 **Xu G**, Zhao L, He Z. Performance of whole-body PET/CT for the detection of distant malignancies in various cancers: a systematic review and meta-analysis. *J Nucl Med* 2012; **53**: 1847-1854 [PMID: 23073605 DOI: 10.2967/jnumed.112.105049]

67 **Liu NB**, Zhu L, Li MH, Sun XR, Hu M, Huo ZW, Xu WG, Yu JM. Diagnostic value of 18F-FDG PET/CT in comparison to bone scintigraphy, CT and 18F-FDG PET for the detection of bone metastasis. *Asian Pac J Cancer Prev* 2013; **14**: 3647-3652 [PMID: 23886160 DOI: 10.7314/APJCP.2013.14.6.3647]

68 **Rong J**, Wang S, Ding Q, Yun M, Zheng Z, Ye S. Comparison of 18 FDG PET-CT and bone scintigraphy for detection of bone metastases in breast cancer patients. A meta-analysis. *Surg Oncol* 2013; **22**: 86-91 [PMID: 23726506 DOI: 10.1016/j.suronc.2013.01.002]

69 **Emad-Eldin S**, Abdelaziz O, Harth M, Hussein M, Nour-Eldin N, Vogl T. The clinical utility of FDG-PET/CT in follow up and restaging of breast cancer patients. *EJRNM* 2013: 937–943 [DOI: 10.1016/j.ejrnm.2013.07.002]

70 **Balci A**, Koc P, Komek H. Bone Scan or 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography; Which Modality Better Shows Bone Metastases of Breast Cancer? *Breast Care* 2012; **7**: 389–393 [DOI: 10.1159/000341559]

71 **Kalinyak JE**, Berg WA, Schilling K, Madsen KS, Narayanan D, Tartar M. Breast cancer detection using high-resolution breast PET compared to whole-body PET or PET/CT. *Eur J Nucl Med Mol Imaging* 2014; **41**: 260-275 [PMID: 24085500 DOI: 10.1007/s00259-013-2553-1]

72 **Senkus E**, Kyriakides S, Penault-Llorca F, Poortmans P, Thompson A, Zackrisson S, Cardoso F. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24 Suppl 6**: vi7-v23 [PMID: 23970019 DOI: 10.1093/annonc/mdt284]

73 **Khatcheressian JL**, Hurley P, Bantug E, Esserman LJ, Grunfeld E, Halberg F, Hantel A, Henry NL, Muss HB, Smith TJ, Vogel VG, Wolff AC, Somerfield MR, Davidson NE. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013; **31**: 961-965 [PMID: 23129741 DOI: 10.1200/JCO.2012.45.9859]

74 **Iatrakis G**. Surveillance après cancer du sein. Diplôme Supérieur de Mastologie (MANOSMED [President Zervoudis S]). Marrakech 26-28 Octobre 2011

75 **Galimberti V**, Botteri E, Chifu C, Gentilini O, Luini A, Intra M, Baratella P, Sargenti M, Zurrida S, Veronesi P, Rotmensz N, Viale G, Sonzogni A, Colleoni M, Veronesi U. Can we avoid axillary dissection in the micrometastatic sentinel node in breast cancer? *Breast Cancer Res Treat* 2012; **131**: 819-825 [PMID: 21468637 DOI: 10.1007/s10549-011-1486-2]

76 **Giuliano AE**, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Hunt KK, Morrow M, Ballman K. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 2010; **252**: 426-32; discussion 432-3 [PMID: 20739842 DOI: 10.1097/SLA.0b013e3181f08f32]

77 **Galimberti V**, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M, Gentilini O, Mastropasqua MG, Mazzarol G, Massarut S, Garbay JR, Zgajnar J, Galatius H, Recalcati A, Littlejohn D, Bamert M, Colleoni M, Price KN, Regan MM, Goldhirsch A, Coates AS, Gelber RD, Veronesi U. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* 2013; **14**: 297-305 [PMID: 23491275 DOI: 10.1016/S1470-2045(13)70035-4]

78 **AMAROS**. The EORTC 10981-22023 AMAROS trial. http: //research.nki.nl/amaros/

79 **Harbeck N**, Thomssen C, Gnant M. St. Gallen 2013: brief preliminary summary of the consensus discussion. *Breast Care (Basel)* 2013; **8**: 102-109 [PMID: 24000280 DOI: 10.1159/000351193]

80 **Pepels MJ**, de Boer M, Bult P, van Dijck JA, van Deurzen CH, Menke-Pluymers MB, van Diest PJ, Borm GF, Tjan-Heijnen VC. Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. *Ann Surg* 2012; **255**: 116-121 [PMID: 22183034 DOI: 10.1097/SLA.0b013e31823dc616]

81 **Rao R**, Euhus D, Mayo HG, Balch C. Axillary node interventions in breast cancer: a systematic review. *JAMA* 2013; **310**: 1385-1394 [PMID: 24084924 DOI: 10.1001/jama.2013.277804]

82 **Harlow SP**, Weaver DL. Sentinel lymph node dissection for breast cancer: Indications and outcomes. UpToDate 2013

83 **Gobardhan PD**, Elias SG, Madsen EV, van Wely B, van den Wildenberg F, Theunissen EB, Ernst MF, Kokke MC, van der Pol C, Borel Rinkes IH, Wijsman JH, Bongers V, van Gorp J, van Dalen T. Prognostic value of lymph node micrometastases in breast cancer: a multicenter cohort study. *Ann Surg Oncol* 2011; **18**: 1657-1664 [PMID: 21153885 DOI: 10.1245/s10434-010-1451-z]

84 **Hansen NM**, Grube B, Ye X, Turner RR, Brenner RJ, Sim MS, Giuliano AE. Impact of micrometastases in the sentinel node of patients with invasive breast cancer. *J Clin Oncol* 2009; **27**: 4679-4684 [PMID: 19720928 DOI: 10.1200/JCO.2008.19.0686]

85 **Maaskant-Braat AJ**, van de Poll-Franse LV, Voogd AC, Coebergh JW, Roumen RM, Nolthenius-Puylaert MC, Nieuwenhuijzen GA. Sentinel node micrometastases in breast cancer do not affect prognosis: a population-based study. *Breast Cancer Res Treat* 2011; **127**: 195-203 [PMID: 20680679 DOI: 10.1007/s10549-010-1086-6]

86 **Cox CE**, Kiluk JV, Riker AI, Cox JM, Allred N, Ramos DC, Dupont EL, Vrcel V, Diaz N, Boulware D. Significance of sentinel lymph node micrometastases in human breast cancer. *J Am Coll Surg* 2008; **206**: 261-268 [PMID: 18222378 DOI: 10.1016/j.jamcollsurg.2007.08.024]

87 **Hindié E**, Groheux D, Brenot-Rossi I, Rubello D, Moretti JL, Espié M. The sentinel node procedure in breast cancer: nuclear medicine as the starting point. *J Nucl Med* 2011; **52**: 405-414 [PMID: 21321267 DOI: 10.2967/jnumed.110.081711]

88 **Sikov WM**. Neoadjuvant systemic therapy for breast cancer: Response, subsequent treatment, and prognosis. UptoDate 2013

89 **Boughey JC**, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, Leitch AM, Kuerer HM, Bowling M, Flippo-Morton TS, Byrd DR, Ollila DW, Julian TB, McLaughlin SA, McCall L, Symmans WF, Le-Petross HT, Haffty BG, Buchholz TA, Nelson H, Hunt KK. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 2013; **310**: 1455-1461 [PMID: 24101169 DOI: 10.1001/jama.2013.278932]

90 **Kuehn T**, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, Lebeau A, Liedtke C, von Minckwitz G, Nekljudova V, Schmatloch S, Schrenk P, Staebler A, Untch M. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol* 2013; **14**: 609-618 [PMID: 23683750]

91 **Morrow M**, Dang CT. Sentinel node biopsy after neoadjuvant chemotherapy: a new standard for patients with axillary metastases? *JAMA* 2013; **310**: 1449-1450 [PMID: 24100931 DOI: 10.1016/S1470-2045(13)70166-9]

92 **van Deurzen CH**, Vriens BE, Tjan-Heijnen VC, van der Wall E, Albregts M, van Hilligersberg R, Monninkhof EM, van Diest PJ. Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer patients: a systematic review. *Eur J Cancer* 2009; **45**: 3124-3130 [PMID: 19716287 DOI: 10.1016/j.ejca.2009.08.001]

93 **Ho AY**, Cody HS. Which patients with sentinel node-positive breast cancer can avoid axillary dissection? *Am Soc Clin Oncol Educ Book* 2013: 61-65 [PMID: 23714457 DOI: E10.1200/EdBook\_AM.2013.33.61]

94 **Rebollo-Aguirre AC**, Gallego-Peinado M, Sánchez-Sánchez R, Pastor-Pons E, García-García J, Chamorro-Santos CE, Menjón-Beltrán S. Sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with operable breast cancer and positive axillary nodes at initial diagnosis. *Rev Esp Med Nucl Imagen Mol* 2013; **32**: 240-245 [PMID: 23684711 DOI: 10.1016/j.remn.2013.03.006]

95 **Zhang GC**, Liao N, Guo ZB, Qian XK, Ren CY, Yao M, Li XR, Wang K, Zu J. Accuracy and axilla sparing potentials of sentinel lymph node biopsy with methylene blue alone performed before versus after neoadjuvant chemotherapy in breast cancer: a single institution experience. *Clin Transl Oncol* 2013; **15**: 79-84 [PMID: 22926944 DOI: 10.1007/s12094-012-0885-0]

96 **Kontos M**, Roy P, Rizos D, Hamed H. An evidence based strategy for follow up after breast conserving treatment for breast cancer. *J Surg Oncol* 2011; **104**: 223-227 [PMID: 21370233 DOI: 10.1002/jso.21747]

97 **Wapnir IL**, Anderson SJ, Mamounas EP, Geyer CE, Jeong JH, Tan-Chiu E, Fisher B, Wolmark N. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. *J Clin Oncol* 2006; **24**: 2028-2037 [PMID: 16648502 DOI: 10.1200/JCO.2005.04.3273]

98 **Maaskant-Braat AJ**, Voogd AC, Roumen RM, Nieuwenhuijzen GA. Repeat sentinel node biopsy in patients with locally recurrent breast cancer: a systematic review and meta-analysis of the literature. *Breast Cancer Res Treat* 2013; **138**: 13-20 [PMID: 23340861 DOI: 10.1007/s10549-013-2409-1]

99 **Maaskant-Braat AJ**, Roumen RM, Voogd AC, Pijpers R, Luiten EJ, Rutgers EJ, Nieuwenhuijzen GA. Sentinel Node and Recurrent Breast Cancer (SNARB): results of a nationwide registration study. *Ann Surg Oncol* 2013; **20**: 620-626 [PMID: 22941173 DOI: 10.1245/s10434-012-2625-7]

100 **Taback B**, Nguyen P, Hansen N, Edwards GK, Conway K, Giuliano AE. Sentinel lymph node biopsy for local recurrence of breast cancer after breast-conserving therapy. *Ann Surg Oncol* 2006; **13**: 1099-1104 [PMID: 16791446 DOI: 10.1245/ASO.2006.08.026]

101 **Roumen RM**, Kuijt GP, Liem IH. Lymphatic mapping and sentinel node harvesting in patients with recurrent breast cancer. *Eur J Surg Oncol* 2006; **32**: 1076-1081 [PMID: 16996237 DOI: 10.1016/j.ejso.2006.08.007]

102 **Maráz R**, Boross G, Pap-Szekeres J, Rajtár M, Ambrózay E, Cserni G. Internal Mammary Sentinel Node Biopsy in Breast Cancer. Is it Indicated? *Pathol Oncol Res* 2014; **20**: 169-177 [PMID: 23934505 DOI: 10.1007/s12253-013-9680-7]

103 **Paredes P**, Vidal-Sicart S, Zanón G, Pahisa J, Fernández PL, Velasco M, Santamaría G, Ortín J, Duch J, Pons F. Clinical relevance of sentinel lymph nodes in the internal mammary chain in breast cancer patients. *Eur J Nucl Med Mol Imaging* 2005; **32**: 1283-1287 [PMID: 16007422 DOI: 10.1007/s00259-005-1867-z]

104 **Cserni G**, Szekeres JP. Internal mammary lymph nodes and sentinel node biopsy in breast cancer. *Surg Oncol* 2001; **10**: 25-33 [PMID: 11719026 DOI: 10.1016/S0960-7404(01)00017-2]

105 **Chen RC**, Lin NU, Golshan M, Harris JR, Bellon JR. Internal mammary nodes in breast cancer: diagnosis and implications for patient management -- a systematic review. *J Clin Oncol* 2008; **26**: 4981-4989 [PMID: 18711171 DOI: 10.1200/JCO.2008.17.4862]

106 **Ramsay SC**, Cassidy N, Meade S. Clinically node-negative breast cancer, internal mammary lymph nodes, and sentinel lymph node biopsy. *Clin Nucl Med* 2008; **33**: 391-393 [PMID: 18496443 DOI: 10.1097/RLU.0b013e318170d569]

107 **Veronesi U**, Marubini E, Mariani L, Valagussa P, Zucali R. The dissection of internal mammary nodes does not improve the survival of breast cancer patients. 30-year results of a randomised trial. *Eur J Cancer* 1999; **35**: 1320-1325 [PMID: 10658521 DOI: 10.1016/S0959-8049(99)00133-1]

108 **Morimoto T**, Monden Y, Takashima S, Itoh S, Kimura T, Yamamoto H, Kitamura M, Inui K, Tanaka N, Nagano T. Five-year results of a randomized clinical trial comparing modified radical mastectomy and extended radical mastectomy for stage II breast cancer. *Surg Today* 1994; **24**: 210-214 [PMID: 8003862 DOI: 10.1007/BF02032889]

109 **Vrana D**, Gatek J, Cwiertka K, Lukesova L, Koranda P. Internal mammary node management in breast cancer. A review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2013; **157**: 261-265 [PMID: 24042333 DOI: 10.5507/bp.2013.068]

110 **Postma EL**, van Wieringen S, Hobbelink MG, Verkooijen HM, van den Bongard HJ, Borel Rinkes IH, Witkamp AJ. Sentinel lymph node biopsy of the internal mammary chain in breast cancer. *Breast Cancer Res Treat* 2012; **134**: 735-741 [PMID: 22678155 DOI: 10.1007/s10549-012-2086-5]

111 **Pierce LJ.** Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer. UptoDate 2013

112 American Society of Breast Surgeons, Consensus statement for Accelerated Partial Irradiation, www.breastsurgeons.org (Revised August 15, 2011)

113 **Shah C**, Vicini F, Wazer DE, Arthur D, Patel RR. The American Brachytherapy Society consensus statement for accelerated partial breast irradiation. *Brachytherapy* 2013; **12**: 267-277 [PMID: 23619524 DOI: 10.1016/j.brachy.2013.02.001]

114 [**Smith BD**](http://www.ncbi.nlm.nih.gov/pubmed?term=Smith%20BD%5BAuthor%5D&cauthor=true&cauthor_uid=19545784), Arthur DW, [Buchholz TA](http://www.ncbi.nlm.nih.gov/pubmed?term=Buchholz%20TA%5BAuthor%5D&cauthor=true&cauthor_uid=19545784), [Haffty BG](http://www.ncbi.nlm.nih.gov/pubmed?term=Haffty%20BG%5BAuthor%5D&cauthor=true&cauthor_uid=19545784), [Hahn CA](http://www.ncbi.nlm.nih.gov/pubmed?term=Hahn%20CA%5BAuthor%5D&cauthor=true&cauthor_uid=19545784), [Hardenbergh PH](http://www.ncbi.nlm.nih.gov/pubmed?term=Hardenbergh%20PH%5BAuthor%5D&cauthor=true&cauthor_uid=19545784), Julian TB, Marks LB, [Todor DA](http://www.ncbi.nlm.nih.gov/pubmed?term=Todor%20DA%5BAuthor%5D&cauthor=true&cauthor_uid=19545784), [Vicini FA](http://www.ncbi.nlm.nih.gov/pubmed?term=Vicini%20FA%5BAuthor%5D&cauthor=true&cauthor_uid=19545784), Whelan TJ, [White J](http://www.ncbi.nlm.nih.gov/pubmed?term=White%20J%5BAuthor%5D&cauthor=true&cauthor_uid=19545784), [Wo JY](http://www.ncbi.nlm.nih.gov/pubmed?term=Wo%20JY%5BAuthor%5D&cauthor=true&cauthor_uid=19545784), Harris JR. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 2009; **74**: 987-1001 [PMID: 19545784 DOI: 10.1016/j.ijrobp.2009.02.031]

115 **Polgár C**, Van Limbergen E, Pötter R, Kovács G, Polo A, Lyczek J, Hildebrandt G, Niehoff P, Guinot JL, Guedea F, Johansson B, Ott OJ, Major T, Strnad V. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). *Radiother Oncol* 2010; **94**: 264-273 [PMID: 20181402 DOI: 10.1016/j.radonc.2010.01.014]

116 **Njeh CF**, Saunders MW, Langton CM. Accelerated Partial Breast Irradiation (APBI): A review of available techniques. *Radiat Oncol* 2010; **5**: 90 [PMID: 20920346 DOI: 10.1186/1748-717X-5-90]

117 **Gieni M**, Avram R, Dickson L, Farrokhyar F, Lovrics P, Faidi S, Sne N. Local breast cancer recurrence after mastectomy and immediate breast reconstruction for invasive cancer: a meta-analysis. *Breast* 2012; **21**: 230-236 [PMID: 22225710 DOI: 10.1016/j.breast.2011.12.013]

118 **van Mierlo DR**, Lopez Penha TR, Schipper RJ, Martens MH, Serroyen J, Lobbes MB, Heuts EM, Tuinder S, Smidt ML. No increase of local recurrence rate in breast cancer patients treated with skin-sparing mastectomy followed by immediate breast reconstruction. *Breast* 2013; **22**: 1166-1170 [PMID: 24025989 DOI: 10.1016/j.breast.2013.08.002]

119 **Lindford AJ**, Siponen ET, Jahkola TA, Leidenius MH. Effect of delayed autologous breast reconstruction on breast cancer recurrence and survival. *World J Surg* 2013; **37**: 2872-2882 [PMID: 24045967 DOI: 10.1007/s00268-013-2212-5]

120 **Nahabedian M**. Breast reconstruction in women with breast cancer. UptoDate 2013

121 **Nahabedian MY**, Momen B. The impact of breast reconstruction on the oncologic efficacy of radiation therapy: a retrospective analysis. *Ann Plast Surg* 2008; **60**: 244-250 [PMID: 18443503 DOI: 10.1097/SAP.0b013e31811ff91b]

122 **Wright JL**, Cordeiro PG, Ben-Porat L, Van Zee KJ, Hudis C, Beal K, McCormick B. Mastectomy with immediate expander-implant reconstruction, adjuvant chemotherapy, and radiation for stage II-III breast cancer: treatment intervals and clinical outcomes. *Int J Radiat Oncol Biol Phys* 2008; **70**: 43-50 [PMID: 17855006 DOI: 10.1016/j.ijrobp.2007.05.032]

123 **Hickey BE**, Francis DP, Lehman M. Sequencing of chemotherapy and radiotherapy for early breast cancer. *Cochrane Database Syst Rev* 2013; **4**: CD005212 [PMID: 23633328 DOI: 10.1002/14651858.CD005212]

124 **Isaac N**, Panzarella T, Lau A, Mayers C, Kirkbride P, Tannock IF, Vallis KA. Concurrent cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy and radiotherapy for breast carcinoma: a well tolerated adjuvant regimen. *Cancer* 2002; **95**: 696-703 [PMID: 12209711 DOI: 10.1002/cncr.10744]

125 **Kim K**, Chie EK, Han W, Noh DY, Oh DY, Im SA, Kim TY, Bang YJ, Ha SW. Concurrent versus sequential administration of CMF chemotherapy and radiotherapy after breast-conserving surgery in early breast cancer. *Tumori* 2011; **97**: 280-285 [PMID: 21789003 DOI: 10.1700/912.10022]

126 **Burstein H**. Adjuvant chemotherapy for hormone receptor-positive or negative, HER2-negative breast cancer. UptoDate 2013

127 **Abbas H**, Elyamany A, Salem M, Salem A, Binziad S, Gamal B. The optimal sequence of radiotherapy and chemotherapy in adjuvant treatment of breast cancer. *Int Arch Med* 2011; **4**: 35 [PMID: 21999819 DOI: 10.1186/1755-7682-4-35]

128 **Fernando IN**, Bowden SJ, Brookes CL, Grieve R, Spooner D, Agrawal RK, Brunt AM. Synchronous chemo-radiation can reduce local recurrence in early stage breast cancer: results of the SECRAB trial. 2011 European Multi-Disciplinary Cancer Conference, Stockholm, Sweden. September 2011

129 **Tsoutsou PG**, Belkacemi Y, Gligorov J, Kuten A, Boussen H, Bese N, Koukourakis MI. Optimal sequence of implied modalities in the adjuvant setting of breast cancer treatment: an update on issues to consider. *Oncologist* 2010; **15**: 1169-1178 [PMID: 21041378 DOI: 10.1634/theoncologist.2010-0187]

130 **Regan MM**, Neven P, Giobbie-Hurder A, Goldhirsch A, Ejlertsen B, Mauriac L, Forbes JF, Smith I, Láng I, Wardley A, Rabaglio M, Price KN, Gelber RD, Coates AS, Thürlimann B. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8·1 years median follow-up. *Lancet Oncol* 2011; **12**: 1101-1108 [PMID: 22018631 DOI: 10.1016/S1470-2045(11)70270-4]

131 **Dowsett M**, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, Buyse M, Baum M, Buzdar A, Colleoni M, Coombes C, Snowdon C, Gnant M, Jakesz R, Kaufmann M, Boccardo F, Godwin J, Davies C, Peto R. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010; **28**: 509-518 [PMID: 19949017 DOI: 10.1200/JCO.2009.23.1274]

132 **Pritchard K**. Adjuvant endocrine therapy for non-metastatic, hormone receptor-positive breast cancer. UptoDate 2013

133 **Davies C**, Pan H, Godwin J, Gray R, Arriagada R, Raina V, Abraham M, Medeiros Alencar VH, Badran A, Bonfill X, Bradbury J, Clarke M, Collins R, Davis SR, Delmestri A, Forbes JF, Haddad P, Hou MF, Inbar M, Khaled H, Kielanowska J, Kwan WH, Mathew BS, Mittra I, Müller B, Nicolucci A, Peralta O, Pernas F, Petruzelka L, Pienkowski T, Radhika R, Rajan B, Rubach MT, Tort S, Urrútia G, Valentini M, Wang Y, Peto R. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013; **381**: 805-816 [PMID: 23219286 DOI: 10.1016/S0140-6736(12)61963-1]

134 **Goss PE**, Ingle JN, Pritchard KI, Ellis MJ, Sledge GW, Budd GT, Rabaglio M, Ansari RH, Johnson DB, Tozer R, D'Souza DP, Chalchal H, Spadafora S, Stearns V, Perez EA, Liedke PE, Lang I, Elliott C, Gelmon KA, Chapman JA, Shepherd LE. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial. *J Clin Oncol* 2013; **31**: 1398-1404 [PMID: 23358971 DOI: 10.1200/JCO.2012.44.7805]

135 **Vogel VG**, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon ER, Wade JL, Robidoux A, Margolese RG, James J, Runowicz CD, Ganz PA, Reis SE, McCaskill-Stevens W, Ford LG, Jordan VC, Wolmark N. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. *Cancer Prev Res (Phila)* 2010; **3**: 696-706 [PMID: 20404000 DOI: 10.1158/1940-6207]

136 **Cummings SR**, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A, Jordan VC. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA* 1999; **281**: 2189-2197 [PMID: 10376571 DOI: 10.1001/jama.281.23.2189]

137 **Martino S**, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D, Secrest RJ, Cummings SR. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst* 2004; **96**: 1751-1761 [PMID: 15572757 DOI: 10.1093/jnci/djh319]

138 **Grady D**, Cauley JA, Geiger MJ, Kornitzer M, Mosca L, Collins P, Wenger NK, Song J, Mershon J, Barrett-Connor E. Reduced incidence of invasive breast cancer with raloxifene among women at increased coronary risk. *J Natl Cancer Inst* 2008; **100**: 854-861 [PMID: 18544744 DOI: 10.1093/jnci/djn153]

139 **Cuzick J**, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A. Long-term results of tamoxifen prophylaxis for breast cancer--96-month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 2007; **99**: 272-282 [PMID: 17312304 DOI: 10.1093/jnci/djk049]

140 **Veronesi U**, Maisonneuve P, Rotmensz N, Bonanni B, Boyle P, Viale G, Costa A, Sacchini V, Travaglini R, D'Aiuto G, Oliviero P, Lovison F, Gucciardo G, del Turco MR, Muraca MG, Pizzichetta MA, Conforti S, Decensi A. Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. *J Natl Cancer Inst* 2007; **99**: 727-737 [PMID: 17470740 DOI: 10.1093/jnci/djk154]

141 **Powles T**, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, Tidy A, Viggers J, Davey J. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet* 1998; **352**: 98-101 [PMID: 9672274]

142 **den Hollander P**, Savage MI, Brown PH. Targeted Therapy for Breast Cancer Prevention. *Front Oncol* 2013; **3**: 250 [PMID: 24069582 DOI: 10.3389/fonc.2013.00250]

143 **Cuzick J**, Sestak I, Forbes JF, Dowsett M, Knox J, Cawthorn S, Saunders C, Roche N, Mansel RE, von Minckwitz G, Bonanni B, Palva T, Howell A. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* 2013 (early online publication) [DOI: 10.1016/S0140-6736(13)62292-8]

144 **Moyer VA.** Medications for Risk Reduction of Primary Breast Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 2013159: 698-708 [PMID: 24061472 DOI: 10.7326/0003-4819-159-10-201311190-00718]

145 **Ben-Aharon I**, Vidal L, Rizel S, Yerushalmi R, Shpilberg O, Sulkes A, Stemmer SM. Bisphosphonates in the adjuvant setting of breast cancer therapy--effect on survival: a systematic review and meta-analysis. *PLoS One* 2013; **8**: e70044 [PMID: 23990894 DOI: 10.1371/journal.pone.0070044]

146 **Mauri D**, Valachis A, Polyzos NP, Tsali L, Mavroudis D, Georgoulias V, Casazza G. Does adjuvant bisphosphonate in early breast cancer modify the natural course of the disease? A meta-analysis of randomized controlled trials. *J Natl Compr Canc Netw* 2010; **8**: 279

147 **Wong MH**, Stockler MR, Pavlakis N. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst Rev* 2012; **2**: CD003474 [PMID: 22336790 DOI: 10.1002/14651858.CD003474]

148 **Valachis A**, Polyzos NP, Coleman RE, Gnant M, Eidtmann H, Brufsky AM, Aft R, Tevaarwerk AJ, Swenson K, Lind P, Mauri D. Adjuvant therapy with zoledronic acid in patients with breast cancer: a systematic review and meta-analysis. *Oncologist* 2013; **18**: 353-361 [PMID: 23404816 DOI: 10.1634/theoncologist.2012-0261]

149 **Coleman R**, Bundred N, de Boer R, Llombart A, Campbell I, Neven P, Barrios C, Miller J, Dias R, Brufsky A. Impact of zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: Z-FAST, ZOFAST, and E-ZO-FAST. Presented at: 32nd Annual San Antonio Breast Cancer Symposium, December 9–13, 2009, San Antonio, TX, abstract 4082

150 **Coleman R**, Gnant M, Paterson A, Powles T, von Minckwitz G, Pritchard K, Bergh J, Evans V, Pan H, Bradley R, Davies C, Gray R; on behalf of the Early Breast Cancer Clinical Trials Collaborative Group (EBCTCG)’s Bisphosphonate Working Group. "Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer: A meta-analysis of individual patient data from randomised trials" SABCS2013; Abstract S4-07

151 **Susman E.** Bisphosphonates useful in older women with breast cancer. Medpage Today; 2013; http: //www.medpagetoday.com/MeetingCoverage/SABCS/43435

152 **von Minckwitz G**, Rezai M, Eidtmann H, Tesch H, Huober J, Gerber B, Zahn DM, Costa S, Gnant M, Blohmer JU, Denkert C, Hanusch C, Jackisch C, Kümmel S, Fasching PA, Schneeweiss A, Paepke S, Untch M, Nekljudova V, Mehta K, Loibl S. "Postneoadjuvant treatment with zoledronate in patients with tumor residuals after anthracyclines-taxane-based chemotherapy for primary breast cancer – The phase III NATAN study (GBG 36/ABCSG XX)" SABCS 2013; Abstract S5-05 <http://www.sabcs.org/PressReleases/Documents/2013/a4bcd1f80d490a65.pdf>

153 **Van Poznak C**. Overview of the use of osteoclast inhibitors in early breast cancer. Uptodate 2013

154 **Coleman MP**, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, E Silva GA, Francisci S, Santaquilani M, Verdecchia A, Storm HH, Young JL. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008; **9**: 730-756 [PMID: 18639491 DOI: 10.1016/S1470-2045(08)70179-7]

155 **Peto R**, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. *Lancet* 2000; **355**: 1822 [PMID: 10832853 DOI: 10.1016/S0140-6736(00)02277-7]

156 **Lu W**, de Bock GH, Schaapveld M, Baas PC, Wiggers T, Jansen L. The value of routine physical examination in the follow up of women with a history of early breast cancer. *Eur J Cancer* 2011; **47**: 676-682 [PMID: 21130643 DOI: 10.1016/j.ejca.2010.11.006]

157 **Ruddy KJ**, Partridge AH. Approach to the patient following treatment for breast cancer. UptoDate 2013

158 **Taggart F**, Donnelly P, Dunn J. Options for early breast cancer follow-up in primary and secondary care - a systematic review. *BMC Cancer* 2012; **12**: 238 [PMID: 22695275 DOI: 10.1186/1471-2407-12-238]

159 **Silverstein MJ**, Lagios MD, Craig PH, Waisman JR, Lewinsky BS, Colburn WJ, Poller DN. A prognostic index for ductal carcinoma in situ of the breast. *Cancer* 1996; **77**: 2267-2274 [PMID: 8635094 DOI: 10.1002/(SICI)1097-0142(19960601)77: 11<2267: : AID-CNCR13>3.0.CO; 2-V]

160 **Silverstein MJ**. The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. *Am J Surg* 2003; **186**: 337-343 [PMID: 14553846 DOI: 10.1016/S0002-9610(03)00265-4]

161 **Moran M**, Schnitt S, Giuliano A, Harris J, Khan S, Horton J, Klimberg S, Chavez-MacGregor M, Freedman G, Houssami N, Johnson P, Morrow M. Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer. *Int J Radiation Oncol Biol Phys* 2014 [DOI:10.1016/j.ijrobp.2013.11.012]

162 **Collins LC**, Laronga C, Wong JS. Ductal carcinoma in situ: Treatment and prognosis. UptoDate 2014

**P-Reviewer:** Georgoulias V **S-Editor:** Ji FF **L-Editor: E-Editor:**

**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.