

Breast cancer and sentinel lymph node micrometastases: indications for lymphadenectomy and literature review

G. ZANGHÌ, G. DI STEFANO, A. CAPONNETTO, R. VECCHIO, A. LANAIA,
A. LA TERRA, V. LEANZA, F. BASILE

SUMMARY: Breast cancer and sentinel lymph node micrometastases: indications for lymphadenectomy and literature review.

G. ZANGHÌ, G. DI STEFANO, A. CAPONNETTO, R. VECCHIO,
A. LANAIA, A. LA TERRA, V. LEANZA, F. BASILE

An increasingly early diagnosis for discovering breast cancer, an improvement of surgical procedures with refining techniques for research and study of sentinel node, currently allow a more conservative surgical approach. Association with suitable chemo-radiotherapy allows a good control of breast disease.

Our study, although modest, was carried out on 63 patients suffering from breast cancer, who underwent surgical treatment with assessment of sentinel lymph node.

Aim of study was to establish the most correct strategy in the presence of isolated tumor cells (ITC) and/or micro-metastases of sentinel lymph node. Many studies have been carried out to find which was the most appropriate treatment, nevertheless, in the absence of univocal guidelines, we prefer to proceed to axillary dissection, though the topic is very debated and controversial. Following this strategy we obtained quite satisfactory results.

KEY WORDS: Breast cancer - Sentinel node - Lymphadenectomy.

Introduction

The breast cancer is still the most common female malignant neoplasm in the Western population (1). Until twenty years ago it was treated by radical mastectomy with axillary emptying in order to obtain both a good loco-regional control and a comprehensive healing from disease. Thereafter the idea according which conservative treatment associated with adjuvant therapy could give statistically comparable results to radical treatment, regarding disease-free and overall survival, took place and became the main standard care (2).

In recent years, preventive measures, advanced diagnostics and timely treatment of breast cancer have led to a significant reduction in mortality. The marked tendency to lymphatic spread of breast cancer has long been

known, therefore the treatment of loco-regional lymphatic tissue always played an essential role. Lymph node metastases represent an important prognostic factor for predicting the outcome of tumor (3).

To assess axillary lymph nodes, usually the technique of sentinel lymph node biopsy (SLNB) has being used, simplifying the procedure and reducing complications of the axillary lymph node dissection (ALND) such as lymphedema, pain and paresthesia on the involved arm (4, 5). In addition, this also means reduction of surgical time, postoperative hospital stay, morbidity, and therefore an improving of the quality of life.

At the same time there is a suspicion that the SLNB may be insufficient; consequently the disease could be under-staged and under-treated. The serial sectioning and immunohistochemical staining cannot be applied to all axillary lymph nodes because it would be a process too laborious and too expensive for routine use; however, the technique of sentinel lymph node (SLN) enables pathologists to focus on a small number of lymph nodes removed, much more likely-containing tumor cells, due to their characteristic of being first filter drainage. After removing SLN, it is analyzed by pathologist to assess the presence or absence of neoplastic cells and

Department of Surgery, University of Catania, Catania, Italy

Corresponding Author: Guido Zanghi, e-mail: gzanghi@unicat.it

© Copyright 2014, CIC Edizioni Internazionali, Roma

classified in positive or negative lymph node. The management is standardized according to national and international guidelines (6, 7), which advise axillary lymphadenectomy in cases of SLN positivity. The detailed histology of these lymph nodes has led to an increased detection of micrometastases (clusters of tumor cells ranging between 0.2 and 2 mm) and Isolated Tumor Cell (ITC) not larger than 0.2 mm (8, 9).

The prognostic and therapeutic implications of micrometastasis in terms of local recurrence and long-term survival remains a matter of great debate.

Some studies report that the detection of micrometastases does not affect the prognosis (10-12); according to other authors (13, 14), however, it represents a negative prognostic factor associated with increased risk of non-sentinel lymph node involvement and distant metastases; others believe that the characteristics of tumor plays an import role, first of all the size, then the biological behavior, the presence of lymphovascular invasion and the grading too (11).

There are no univocal guidelines concerning the treatment of micrometastases in the sentinel lymph node because many studies in this field have not yet been concluded and the follow-up is ongoing. The aim of this study is to report our experience on the therapeutic approach regarding patients with micrometastases of SLN.

Patients and methods

From September 2008 to December 2010, 63 patients with breast cancer (mean age 52 years; range 37-80) were admitted to the General Surgery Unit of Catania Hospital "Policlinico-Vittorio Emanuele". 39 patients had the lesion on the right breast, the remaining 24 on the left breast. In 65% of cases, the lesion was located in the upper-outer, in 17% in the lower-outer, in 13% in the upper-inner and in 10% in the lower-inner quadrant. The patients aged more than 45 years underwent initially to mammography, in accordance with the guidelines, therefore all patients carried out ultrasounds of both breast and armpit. For locating sentinel node, we used the double contrast technique, that means the patients underwent preoperative axillary lymphoscintigraphy with mTc99, and then blue methylene perilesional injection during surgery. After identifying the sentinel node thanks to a probe absorbing radiation emitted by the radionuclide and under the vision of dye, the piece was removed and sent to pathologist for extemporaneous examination. All patients were informed of both benefits and possible risks regarding this method and signed a suitable informed consent. After surgery a six-month follow-up including clinical examination and axillary ultrasound in case of axillary lymphadenopathy was recommended.

Results

The final histological results of breast cancer were: invasive ductal carcinoma in 44, invasive lobular carcinoma in 13, in situ ductal carcinoma in 4, mixed invasive lobular and invasive ductal carcinoma in 2 patients, respectively. In 28 cases, the extemporaneous examination of SLN was positive and, among which, 10 had micrometastases. Both patients with macrometastases than those with micrometastases to the sentinel lymph node were treated in the same way with ALND. Histologically the diagnosis of sentinel lymph node micrometastasis was confirmed in 8 out 10 cases, in 1 case there was an over-staging of micrometastases to macrometastases and in 1 other case there was a under-staging from micrometastases to isolated cancer cells. The extemporaneous examination of the SLN on 2 patients was negative for metastasis detecting reactive hyperplasia, nevertheless final result showed micrometastases; so after ALND was carried out. The final histological examination of all axillary lymph nodes showed the exclusive involvement of the sentinel lymph node. All patients with micrometastases on sentinel lymph node undergoing ALND had no recurrence within 24 months. Among 18 patients with macrometastases to sentinel lymph node 14 had macrometastases in other axillary lymph nodes following axillary dissection. In one year follow-up, only one patient of this group died due to distant metastases.

Discussion

The last two decades have seen a radical change in the treatment of breast cancer. Late diagnosis, radical surgical treatment of both breast and axillary lymph nodes have been replaced by an effective program of screening and early detection allowing conservative treatment.

Currently, breast cancer is considered a systemic disease with disseminated micrometastases already present at the time of diagnosis (Fisher's theory) (15); the evidence that some patients developed distant metastases despite the axillary lymph nodes were negative on histological examination clearly was in discordance with Halsted theory; it was believed that tumor cells progressively permeated the lymphatic vessels to the regional lymph nodes, which was the main filter before at distance dissemination of the tumor via the blood. On the basis of the natural history of the disease, in the seventies, it was observed a gradual adoption of less radical surgery (16), while concerning axillary lymph node surgery, ALND was the gold standard until the end of the nineties, when the technique of sentinel lymph node was introduced (17). Thousands of studies evidenced the reliability of this technique, which is widely adopted in clinical prac-

tice (18, 19). The identification of the SLN takes place through preoperative lymphoscintigraphy, injection of vital dye or both techniques together. During surgery SLN identified and removed is evaluated intraoperatively by pathologist with smear slide and/or frozen section. Axillary dissection is performed in case of positive SLN otherwise the definitive histological examination after extensive sampling of the lymph node will lead the appropriate treatment. Currently, patients with negative SLN do not undergo ALND, while this procedure is indicated in those with a positive SLN. The so exposed speech appears straightforward and easy to treat in clinical practice, however, the surgeon in the management of the disease often has to deal with a lot of nuances, many risk classes, variants, each with a prognosis more influenced by multiple factors (depending on the characteristics of the tumor, lymph nodes, patient intrinsic factors). Perhaps the most controversial argument and object of many clinical trials in recent years is the presence of micrometastases in SLN and the subsequent clinical management. Micrometastases appear to have a negative influence on survival in some studies but not in others. In order to define the proper predictive value of these nodal locations it should be necessary to standardize the methods of histological preparation of SLN by means of an homogeneous preparation of material, diagnostic technique and methods of reporting (20).

According to American Society of Clinical Oncology (ASCO) (21) until further clinical studies on the importance of the ITC or micro metastases will not be finalized, the guidelines recommend the axillary dissection for patients with micrometastases in SLN, whereas there are no indications for the treatment of ITC. Several studies were carried out in recent years, however, a certain category of patients through a single feature which would show a risk of metastasis to nLS <10% has not yet been identified so as to avoid axillary dissection. Regarding the question of which patients with positive sentinel lymph node should be appropriately treated with radiation therapy and which should undergo ALND to complete the treatment, many studies have included follow-up of short duration and no results are yet available. So we conclude there are no sufficient data to give a clear answer to this question (21).

IBCSG 23-01 trial (22), carried from 2001 to 2010 at the European Institute of Oncology (IEO), included patients with T <5cm and not clinically suspicious axillary lymph nodes, they were treated surgically after selecting those with micrometastatic SLN or with ITC. The latter were divided randomly into two groups: a group ALND was performed either in case of micrometastases or ITC in the SLN, whereas in the another ALND was not carried out.

The patients underwent a 5 years follow-up, resulting in a low (<1%) final local recurrence rate in group

without ALND and, finally, no statistically significant difference in survival between the two groups was observed. Although these results were promising, in the group treated with ALND was found an involvement of non-SLN in 13% of cases. The study was limited by the small number of patients due to selection criteria. The data obtained led the St Gallen Consensus Conference of 2011 to amend the recommendations in this direction, advising people to avoid ALND for patients with SLN micro-metastases.

By the same authors in Milan we receive more data from a retrospective study carried out at the same Institution (IEO) (23). 377 patients with micrometastases to SLN between 1999 and 2007 were treated for breast cancer without ALND for any reason (most frequently for patient refusal or because they were included in the trial IBCSG). The 5-year survival was 97.3%, the cumulative incidence of local recurrences was 1.6% and it seems that the tumor size and histological grade may have a important role. The authors (Galimberti et al.) concluded that in accordance with results of this trial it is reasonable to discuss with the patient the chance to refuse any additional treatments when micrometastases in SLN are found, particularly for patients with small tumor (<2cm), low histological grade, particularly for the low risk of local recurrence.

In Spain, Solà et al. (24) undertook another prospective randomized study, the AATRM 048/13/2000. Patients with newly diagnosed breast cancer at an early stage (T <3.5 cm, N0 and Clinical M0) with micrometastases to the SLN were included and treated with surgical excision (mastectomy or conservative treatment) as a first approach; differently from Milan study patients with ITC were excluded. The patients were divided randomly into two groups, on the former group patients were subjected to a complete ALND while in the latter, experimental group, a clinical evaluation with a clinical follow-up without ALND was carried out. In conclusion Solà et al. suggest that the patients with early-stage breast cancer and micrometastases in the SLN, the SLN selective lymphadenectomy is sufficient for regional and at distance control of the disease, without significant deleterious consequences for survival. In this trial the main limitation was the small number of patients (247) included. In this regard, the authors report that further extension of the study could have introduced bias regarding the interpretation of data, as well as the progress of diagnostic techniques and treatment with possible changes in systemic therapy; for the analysis results were carried out only on the initial sample. However, in order to demonstrate the negative impact on prognosis and on the incidence of local recurrence of the ITC and micrometastases in comparison with N0, we report two studies in the Netherlands.

MIRROR study (25, 26) is a cohort study of 2009

which had as its objective the evaluation of the impact of ITC and micrometastases on disease-free survival at 5 years in patients who underwent SLNB. In the study the patients were divided into 3 groups according to the final result of the lymph nodes via SLNB and/or ALND. Group 1 included patients who did not have lymph node metastases and did not perform adjuvant systemic therapies; group 2 patients with ITC or SLN micrometastases who did not undergo adjuvant systemic therapy and group 3, finally, patients with ITC or micrometastases treated with postoperative systemic therapy.

The first objective of the study was to determine whether there was a difference between the ITC or micrometastases and the evolution of the disease by comparing the disease-free survival (DFS) between groups 1 and 2. The 5-year DFS in group 2 was significantly worse than the first group (75.6 vs. 85.7%). The negative impact of ITC was equal to that of micrometastases. Second endpoint of the trial was to verify whether adjuvant systemic therapy would change the course of disease in patients with micrometastatic SLN or ITC, comparing the DFS between group 2 and 3. The DFS in the 5 years was significant. The disease-free survival in the 5 years was significantly worse in the second group compared to the third group (76.5 vs. 86.2%). They were no differences in efficacy of adjuvant therapy among patients with ITC and those with micrometastases. From these observations, the authors concluded that the management of the metastatic axilla must still be considered just like that of the primary tumor, even in the presence of minimal involvement of the lymph nodes, stating that ALND should not be seen as a process that belongs to the past but it must still be considered the next logical step in the treatment of advanced cancers.

Netherlands study (25-27), was a trial carried out in 2012 in which an attempt was made to assess the incidence of local recurrences in patients with ITC and micrometastases. Patients with invasive breast cancer were divided into 3 groups: A group with negative SLN, B group with ITC on SLN and finally C group the patients with micrometastatic SLN. In the absence of ALND the incidence of local recurrence at 5 years was 2.3; 2 and 5.6% respectively. The authors found a high rate of local recurrences in patients with ITC or micrometastases in SLN who had not performed the axillary dissection, for which they assert the importance of ALND, which should be recommended as standard treatment for these women.

Therefore conflicting opinions in the axillary management in patients with ITC and/or micrometastases in the SLN are continuing. Further results are expected from clinical trials with a longer follow-up and with a more careful selection of treatment parameters and inclusion in the comparison groups.

Recent retrospective studies of patients selected for having had micrometastases without performing ALND suggest that this subclass of patients do not have increased risk of developing locoregional recurrences. Some authors have studied the prognosis of these patients without ALND such as Fan et al. (28) they saw that a patient out of 27 with a micrometastasis, for not having done ALND, has a risk to develop local and systemic recurrence 17 months after surgery (mastectomy).

The modern surgical treatment has the purpose to locally control the disease and does not aim to systemic treatment, which is delegated to the radio-chemotherapy. In fact, several studies have shown that in more than 60% of the samples of mastectomy were highlighted additional foci of carcinoma and, in these cases, the conservative treatment of breast associated with adjuvant radiotherapy has been related to a therapeutic success. In addition, radiation therapy allows an effective local-regional control and is able to cover the lymph nodes of the first level. The subsequent adjuvant systemic chemotherapy could eradicate any non-SLN macrometastases in lymph nodes and reduce the risk of local recurrence. These therapies have as an objective the treatment of micrometastatic disease and thus improve the long-term survival.

There are many ongoing multicenter studies, among them AMAROS, in which patients with a positive SLN are assigned randomly to the group to perform either ALND or axillary radiotherapy. In this study it was hypothesized that both methods can guarantee a good regional control and survival (29). Until the end of the trial, however, ALND remains the only treatment indicated, as we have already expressed previously, according to the most recent reports.

Today the SLNB is used exclusively as a suitable procedure to stage the disease and to lead towards lymphadenectomy or radiotherapy.

Advances in molecular biology and immunohistochemistry have been increasing the detection of micrometastases in the SLN.

The fundamental question arises as to why we should consider treatment of micrometastases in the SLN in a different way to elsewhere. It should be based on a rational adjuvant systemic treatment to perform on armpit and other parties involved, considering micrometastases an suitable indication for systemic therapy.

In fact, several authors compared the risk of developing metastases in women with SLN micrometastases and women with negative SLN. The results show that the presence of micrometastases worsens the prognosis bringing from N0 and N1 (30). A retrospective study involving 10,000 patients showed that patients with SLN micro-metastases have a worse prognosis than those with negative SLN, but the difference is statistically significant in the group that does not carry out adjuvant treat-

ment. Patients with micrometastases who do not receive adjuvant systemic therapy have a prognosis comparable to patients with single macro metastasis (31). Lymph node dissection or axillary radiotherapy may reduce recurrence in patients with locally regional SLN micrometastases due to the increased risk of metastases in non SLN.

Considering the evidence against axillary lymphadenectomy for micrometastases, Tjan-Heijen in a review of eight studies (10) each with at least 100 patients at 5 years follow-up, concluded that there was insufficient evidence to confirm that micrometastases were of prognostic utility. Other authors in a prospective study of 150 patients who underwent only a biopsy of the sentinel node did not find differences in the development of recurrence in the armpit between those with and without micrometastases after a 42 months mean follow-up (32).

Conclusions

At present, patients with negative SLN do not perform axillary dissection, while this procedure is indicated in case of positive SLN. However, the debate is about the opportunity to practice the axillary lymph node dissection in all patients with positive SLN. In fact, patients with axillary metastases do not always develop axillary recurrences, even if they are not treated. The use of axillary dissection in patients with micrometastases is still actually controversial, however, it is an indication to follow.

Local and systemic recurrences associated with residual disease in patients with positive SLN eligible to have no further surgical treatments have not been seen in a

long follow-up. Therefore, the ALND may be omitted in case of micrometastases to the low prevalence of non-sentinel lymph node micrometastases. For some authors, the surgical removal of subclinical nodal disease is associated with a benefit in terms of survival minimum, but still greater than zero, while for others the adjuvant systemic therapy and/or radiation would be opportune to treat these patients adequately.

Micrometastases probably interfere with the prognosis and management of breast cancer. Although the future also offer the most daring hypotheses such as the replacement of the sentinel lymph node biopsy with an pre-operative ultrasound-guided fine needle aspiration cytology (FNAC) (33) anyway to eliminate any lingering doubts about the treatment of SLN micrometastases results of randomized clinical trials are still expecting.

In the absence of guidelines for level 1 with respect to the treatment of patients with micrometastases in the SLN, each case requires careful study on the tumor and the patient-related factors in the context of a multidisciplinary team.

If the outcomes of current trials do not provide for the formulation of guidelines could at least provide a clinical and ethical justification for randomized trials to assess the prognostic significance and optimal treatment for each category of neoplastic involvement of the SLN. The identification of micrometastases remains highly dependent on the analytical technique used, and there exists the potential to stage the disease and to determine the suitable treatment.

In addition, since breast cancer affects women's identities, studying quality of life in women who lose their breasts is vital (34-36).

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics. *CA Cancer J Clin.* 2008;58:71-96.
2. Song XY, Yuan XM, Chen WJ, Pan T, Xie SD, Qin C, Lou C, Jin M, Wang LB, Wu JM. Different criteria for radioactive sentinel lymph nodes has different impact on sentinel node biopsy in breast cancer patients. *J Surg Oncol.* 2007;15:635-9.
3. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24, 740 breast cancer cases. *Cancer.* 1989;63:181-187.
4. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, Aguilar M, Marubini E: Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347:1227-32.
5. Veronesi U, Paganelli G, Viale G, Luini A, Zurrada S, Galimberti V, Intra M, Veronesi P, Robertson C, Maisonneuve P, Renne G, De Cicco C, De Lucia F, Gennai R. A randomized comparison of sentinel node biopsy with routine axillary dissection in breast cancer. *N Engl J Med.* 2003;349:546-53.
6. Lyman GH, Giuliano AE, et al. American Society of Clinical Oncology Guideline Recommendations for Sentinel Lymph Node Biopsy in Early-Stage Breast Cancer. *J Clin Oncol.* 2005;23:7703-7720.
7. Veronesi U. Forza Operativa Nazionale sul Carcinoma Mammario. Linee Guida biopsia del linfonodo sentinella. 2012 <http://www.senologia.it/index.php/f-o-n-ca>.
8. International Agency for Research on Cancer (IARC): WHO histological classification of tumours of the breast. In: Tavassoli FA, Devilee P (eds). World health organization classification of tumours, pathology & genetics tumours of the breast and female genital organs. IARC Press. 2003 Lyon:10-12.
9. Greene FL, Page DL, Fleming ID, Fritz A, Balch CM, et al (eds). 2002 AJCC Cancer Staging Manual, 6th edn.
10. Tjan-Heijen VCG, Bult P, de Widt-Levert LM, Ruers TJ, Beex LVAM. Micro-metastases in axillary lymph nodes: an increasing classification and treatment dilemma in breast cancer due to the

- introduction of the sentinel lymph node procedure. *Breast Cancer Res Treat.* 2001;70:81-88.
11. Rutledge H, Davis J, Chiu R, Cibull M, Brill Y, McGrath P, Samayoa L. Sentinel node micrometastasis in breast carcinoma may not be an indication for complete axillary dissection. *Mod Pathol.* 2005;18(6):762-768.
 12. Nagashima T, Sakakibara M, Nakano S, Tanabe N, Nakamura R, Nakatani Y, Nagai Y, Koda K, Miyazaki M. Sentinel node micrometastasis and distant failure in breast cancer patients. *Breast Cancer.* 2006;13(2):186-191.
 13. Houvenaeghel G, Nos C, Mignotte H, Classe JM, Giard S, Rouanet P, Lorca FP, Jacquemier J, Bardou: Groupe des Chirurgiens de la Federation des Centres de Lutte Contre le Cancer. Micrometastases in sentinel lymph node in a multicentric study: predictive factors of nonsentinel lymph node involvement - Groupe des Chirurgiens de la Federation des Centres de Lutte Contre le Cancer. *J Clin Oncol.* 2006;24(12):1814-1822.
 14. Viale G, Maiorano E, Mazzarol G, Zurrida S, Galimberti V, Luni A, et al. Histologic detection and clinical implications of micrometastases in axillary sentinel lymph nodes for patients with breast carcinoma. *Cancer.* 2001;92:1378-1384.
 15. Fisher B, Wolmark N, Bauer M, Redmond C, Gebhardt M. The accuracy of clinical node staging and limited axillary dissection as a determinant of histology nodal status in carcinoma of the breast. *Surg Gynecol Obstet.* 1981;152:765-72.
 16. Huvos AG, Hutter RV, Berg JW. Significance of axillary macrometastases and micrometastases in mammary cancer. *Ann Surg.* 1971;173:44-46.
 17. Cox CE, Pendas S, Cox JM, Joseph E, Shons AR, Yeatman T, Ku NN, Lyman GH, Berman C, Haddad F, Reintgen DS. Guidelines for sentinel node biopsy and lymphatic mapping of patients with breast cancer. *Ann Surg.* 1998;227(5):645-653.
 18. Giuliano AE. Lymphatic mapping and sentinel node biopsy in breast cancer. *JAMA.* 1997;277(10):791-792.
 19. Zanghì G, Di Stefano G, Furci M, Biondi A, Catalano F, Benfatto G, Basile F. Studio del linfonodo sentinella nel carcinoma della mammella: nostra esperienza. *Ann Ital Chir.* 2004;75(3):325-330.
 20. Cserni G, Bianchi S, Boecker W, Decker T, Lacerda M, Rank F, Wells CA; European Working Group for Breast Screening Pathology. Improving the reproducibility of diagnosing micrometastases and isolated tumor cells. *Cancer.* 2005;103(2):358-67.
 21. Gary H, Lyman, Armando E, Giuliano, Mark R, Somerfield, Al B, Benson III, Diane C, Bodurka, Harold J, et al. American Society of Clinical Oncology Guideline Recommendations for Sentinel Lymph Node Biopsy in Early-Stage Breast Cancer *J Clin Oncol.* 2005;23:7703-7720.
 22. Galimberti V, Cole BF, et al. Axillary dissection vs no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncology.* 2013;14:297-305.
 23. Galimberti V, Botteri E, et al. Can we avoid axillary dissection in the micrometastatic sentinel node in breast cancer? *Breast Cancer Research and Treatment.* 2011. 10.1007/s10549-011-1486-2
 24. Solà M, Alberro JA, et al. Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multi center clinical trial AATRM: 048/13/2000” 2012 10.1245.
 25. Gatzemeier W, Mann GB, et al. Which sentinel lymph node (SLN) positive breast cancer patient needs an axillary lymph-node dissection (ALND)-ACOSOG Z0011 results and beyond. *The breast* 2013. 10.1016.
 26. Giuliano AE, Morrow M, et al. Should ACOSOG Z0011 change practice with respect to axillary lymph node dissection for a positive sentinel lymph node biopsy in breast cancer? *Clin & Exper Met Off Journal.* 2012. 10.1007.
 27. Shan-Khan M, Boughey C. Evolution of axillary nodal staging in breast cancer: clinical implications of ACOSOG Z0011 trial. *Cancer Control.* 2012;Vol 19 N.4.
 28. Fan YG, Tan YY, Wu CT, et al. The effect of sentinel node tumor burden on non-sentinel node status and recurrence rates in breast cancer. *Ann Surg Oncol.* 2005;12:705-11.
 29. Straver ME, Meijnen P, Tienhoven G, Van de Velde CJ, Mansel RE, Bogaerts J, Demonty G, Duez N, Rutgers EJ. Patterns of care in the EORTC AMAROS sentinel node trial. Poster presentation at The Breast Cancer Symposium, Washington, U.S.A., September 5-7, 2008.
 30. Chen SL, Hoehne FM, Giuliano AE. The prognostic significance of micrometastases in breast cancer: a SEER population-based analysis. *Ann Surg Oncol.* 2007;14:3378-3384.
 31. Kuijt GP, Voogd AC, van de Poll-Franse LV, Scheijmans LJ, van Beck MW, Roumen RM. The prognostic significance of axillary lymph-node micrometastases in breast cancer patients. *Eur J Surg Oncol.* 2005;31(5):500-505.
 32. Langer I, Marti WR, Guller U, et al. Axillary recurrence rate in breast cancer patients with negative sentinel lymph node (SLN) or SLN micrometastases. *Ann Surg.* 2005;241:152-158.
 33. Gentilini O, Veronesi U, et al. Abandoning sentinel lymph node biopsy in breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs Observation after axillary UltraSound). *The Breast.* 2012;21:678-681.
 34. Benfatto G, Zanghì G, Catalano F, Di Stefano G, Fancello R, Mugavero F, Giovinetto A. La day-surgery del carcinoma della mammella senile. *G. Chir.* 2006;27:49-52.
 35. Passanisi A, Leanza V, Leanza G. The impact of sexually transmitted diseases on quality of life: application of three validated measures. *Giornale Italiano di Ostetricia e Ginecologia.* 2013;35(6):722-727.
 36. Leanza V, Passanisi A, Leanza G. Urinary incontinence: quality of life and psychological aspects. *Urogynaecol Int J.* 2013;27:e3.