

The prognostic value of sentinel lymph node micrometastases in patients with invasive breast carcinoma



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AIM: *The prognostic value of sentinel lymph node micrometastases in invasive breast cancer patients is still widely debated. Even if, in the absence of unequivocal guidelines, the axillary lymphadenectomy is not still performed in the routine clinical care of these patients.*

METHOD: *We have retrospectively analyzed 746 patients with operable invasive breast cancer and clinically negative axillary lymph nodes. These patients underwent conservative surgery or total mastectomy with sentinel lymph node biopsy. Patients with micrometastases in the sentinel lymph node treated with axillary dissection have been checked and the involvement of the remaining lymph nodes analyzed. Patients with micrometastases in the SLN not followed by axillary dissection have been checked as well and the incidence of recurrences has been evaluated in both groups.*

RESULTS: *Micrometastases were found in 51 (6.83%) patients and isolated tumor cells in 8 (1.07%) patients at frozen section and confirmed at the final histopathologic examination. Fifteen of these patients underwent complete axillary dissection: two of them (13.33%) had metastatic involvement of other axillary lymph nodes. The other 44 patients didn't receive further surgical axillary procedure. No axillary recurrences in these patients were found during a median follow up of 65.3±9.65 months (range 42-78 months).*

CONCLUSION: *Based on the results and according to some recent randomized trials we can say that axillary lymphadenectomy can be avoided when micrometastases are found in sentinel lymph nodes. It should be performed anyway, depending on the analysis of the biomedical profile of the tumor.*

KEY WORDS: Breast carcinoma, Micrometastases, Sentinel lymph node

Introduction

Axillary nodal status has traditionally been the most important prognostic factor in staging breast cancer and determines, among other parameters, the need for sub-

sequent adjuvant treatment. Because of its high sensitivity and accuracy in predicting axillary lymph node status, sentinel lymph node biopsy (SLNB) for breast cancer is accepted as a standard procedure, which makes it possible to avoid unnecessary axillary node dissection (AD) ¹. The metastatic involvement of the sentinel lymph node (SLN) isn't always correlated to the metastatic involvement of the other lymph nodes. The metastatic involvement of the axillary non sentinel lymph nodes is due to varied factors, such as the size of the neoplastic cells cluster found in the SLN ²⁻³. Depending on its size, axillary lymph node metastases are classified as macrometastases (diameter >2 mm), micrometastases (diameter in between 0.2 and 2 mm) and isolated tumoral cells (ITC) (diameter ≤ 0.2 mm). It is estimated that only 40% of the patients with macrometastases and 18% of those with

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micrometastase and/or ITC in the SLN present metastatic involvement of the others axillary lymph nodes⁴. This implies that AD, in a greater extent of patients, especially in those with sentinel lymph node micrometastases, represents an overtreatment where those patients are exposed to prospective complications with no prognostic benefit.

Currently AD is still a valid procedure to perform on patients with SLN macrometastases, but it isn't suggested on patients with ITC in the SLN, the more that the TNM classify those patients as N0 (i+). Instead, it is still an open discussion about the prognostic meaning of micrometastases and the opportunity to perform AD on patients with it, even if, related to the low possibility of other axillary lymph nodes involvement, AD on those patients has been gradually abandoned in clinical practice.

In this study, patients with micrometastases in the SLN treated with AD have been checked and the involvement of the remaining LNs analyzed. Patients with micrometastases in the SLN not followed by AD have been checked as well, and the incidence of recurrences has been evaluated in both groups.

Materials and Methods

A retrospective study has been conducted on 746 patients with operable invasive breast carcinoma with clinically negative axillary lymph nodes that underwent conservative surgery or total mastectomy with SLNB at our Institution from January 2004 to December 2011. In all patients the diagnosis of infiltrating breast carcinoma was made by fine-needle aspiration cytology or by percutaneous core biopsy under stereotactic or ultrasound control. Evaluation of the axillary lymph nodes was done by clinical and ultrasound examinations of the axilla and fine needle aspiration cytology of the suspicious lymph node. The histological results of the needle biopsy was confirmed in all cases by the histological results of the operative specimen, proving an high diagnostic accuracy by this procedure in the preoperative diagnosis of breast cancer as well as demonstrated in our own experience⁵.

LYMPH NODE MAPPING AND OPERATIVE TECHNIQUE FOR SLNB.

The day before surgery, all patients underwent lymphoscintigraphy by injection of ⁹⁹Tc-labeled human albumin colloid (10-12 MBq of Tc-99m in 0.2 ml of albumin colloid). The periareolar subdermal injection of the radiotracer was preferred because of the high level of accuracy⁶. The SLN was identified by acquiring a double projection of the scintigraphic images 15, 30, and 180 minutes after the injection of the radiotracer. A cobalt pen was used to locate the cutaneous projection

of the SLN. For the intraoperative identification of the SLN, we used a radio-guided surgical probe (neo2000 Gamma Detection Systems®) about 10 min before the beginning of surgery detection. In a few cases, when the radio-guided surgical probe recorded a weak radiotracer signal, a subareolar injection of 0.5-0.8 ml of vital stain (1% lymphazurin) was performed about 10 min before the beginning of surgery as well. The hot and/or blue lymph nodes were removed, their radioactivity was verified out of the operating field by the same probe, and then they were immediately submitted to frozen section (FS).

PATHOLOGICAL EXAMINATION

SLNs with a diameter of less than 5 mm were frozen intact, whereas nodes with a diameter greater than 5 mm were bisected longitudinally and frozen. Two 4 µm frozen sections were taken from the optimal cross-sectional surface of one half of the lymph node and stained with hematoxylin and eosin (H&E) for intraoperative examination. For definitive histopathological examination, all the remaining tissue was formalin-fixed and paraffin-embedded. Two serial sections, 4 µm thick, were obtained for each block at a cutting interval of 50 µm throughout the whole lymph node. For each step, the first section obtained was stained with H&E. When neoplastic cells were not observed or when the result was ambiguous on H&E sections at each step, the remaining sections were stained with the use of the monoclonal antibody for pancytokeratins AE1/AE3 (Dako). Immunohistochemical analysis was performed using the avidin biotin peroxidase complex method. Brief counterstaining in Mayer's hematoxylin followed immunostaining. If more than one SLN was obtained from a patient, all the nodes designated as SLN were examined in this way.

Metastases were classified as micrometastases (diameter ≤2 mm) or macrometastases (diameter ≥2 mm); single tumor cells or small clusters of cells (diameter <0.2 mm) were defined as isolated tumor cells (ITC).

SURGICAL PROCEDURE

All the patients underwent synchronous excision of the breast cancer either by conservative surgery or total mastectomy and SLN biopsy. In cases of non palpable breast lesions, a guided wire was placed in the tumor site under either stereotactic or ultrasonographic guidance. All patients with SLN macrometastases in FS underwent immediate completion AD. If the SLN was negative at FS but was found to contain macrometastases in the final histopathology, patients underwent delayed completion of total AD.

In case of SLN micrometastases at FS confirmed at final histopathology the patients underwent immediate or

delayed completion AD until 2008, then since the early months of 2009 completion AD was not performed and these patients, as well as those with negative SLN, received clinical and ultrasonographic examination of the axilla every six months to detect possible axillary lymph node recurrences.

Then, in the group of patients with SLN micrometastases that underwent AD, we analyzed the incidence of non sentinel axillary lymph node metastases at final histological examination. In the group of patients with SLN micrometastases that didn't undergo AD, we analyzed the incidence of axillary lymph node recurrences.

Results

The mean age of the 746 patients was 58.44 ± 11.27 years (range 29-87 years). The mean tumor diameter (histopathological measurement) was 19.03 ± 11.10 mm (range 30-80 mm). Regarding the histological type of the tumors, 622 (83.38%) were ductal infiltrating carcinoma, 57 (7.64%) were lobular infiltrating carcinoma, 10 (1.34%) were mixed histotype (ductal infiltrating + lobular infiltrating) and 57 (7.64%) were other histotypes (as medullary carcinoma, tubular carcinoma, gelatinous carcinoma etc.). Regarding the histological grade of the tumors, 108 (14.48%) were G1, 459 (61.53%) G2 and 179 (23.99%) G3. The receptors for the estrogens were expressed in 668 cases (89.54%) and the receptors for the progesterone were expressed in 618 cases (82.84%). Multifocality was registered in 87 cases (11.66%) (Table I).

Seven hundred eleven (95.31%) patients underwent conservative surgery, and 35 (4.69%) underwent total mastectomy. In 740 cases (99.2%) the SLN was accurately detected intraoperatively, the mean number of them was 1.93 (range 1-8). Only in 6 (0.80%) cases, although identified by the preoperative lymphoscintigraphy, they weren't detected intraoperatively. In these cases immediate AD was performed but only 2 of them were LNs positive at the histopathological examination.

At FS histopathological examination SLN were negative in 572 (76.88%) patients, macrometastases were found in 166 (22.25%) patients and micrometastases and/or ITC only in 4 (0.54%) cases. Only in 3 cases (0.40%) the pathologist postponed the diagnosis at the definitive examination of the SLN. In one case the SLN was negative; in 2 cases micrometastases were found. Although it has high diagnostic accuracy, FS of SLN is burdened by a low rate of false negative diagnosis⁷. Indeed in 72 (12.59%) patients with negative SLN at FS the final histopathological examination found macrometastases in 20 case, micrometastases in 46 cases and ITC in 6 cases. The 20 patients with macrometastases underwent completion AD. The patients with micrometastases and ITC didn't.

In total 51 (6.83%) patients with micrometastases and 8 (1.07%) with ITC were both found at FS and at final

TABLE I - Patients and tumour features.

	Number	%
Age		
≤ 50 years	190	25.47%
> 50 years	556	74.53%
Surgery		
Conservative surgery	711	95.31%
Total mastectomy	35	4.69%
Histologic type		
Ductal Infiltrating	622	83.38%
Lobular Infiltrating	57	7.64%
Ductal+Lobular Infiltrating	10	1.34%
Other	57	7.64%
Tumor size		
pT1 (≤ 2 cm)	478	64.07%
p T2 (> 2 cm e ≤ 5 cm)	254	34.05%
p T3 (> 5 cm)	14	1.88%
Grading		
G1	108	14.48%
G2	459	61.53%
G3	179	23.99%
Estrogen Receptors		
positive	668	89.54%
negative	78	10.46%
Progesterone Receptors		
positive	618	82.84%
negative	128	17.16%
HER-2/neu overexpression		
Yes	416	55.76%
No	330	44.24%
Multifocality	87	11.66%

histopathological examination. The characteristics of these patients are summarized in Table II. Fourteen (27.45%) patients with micrometastases and 1 (12.5%) patient with ITC received completion AD, while 37 (72.55%) patients with micrometastases and 7 (87.5%) patients with ITC didn't receive any additional surgery in the axilla. Furthermore, in 12 of these patients, in addition to SLNB, a sampling of palpable non-sentinel lymph node was performed⁸ but in no case were found metastases at final histopathological examination of them.

Regarding the 15 patients with SLN micrometastases or ITC that underwent completion AD, only 2 (13.33%) cases had metastatic involvement of the other axillary lymph nodes. In both cases the primary breast carcinoma had unfavorable features as a high grade differentiation (G3), a high cellular proliferation index, multifocality and high score of HER-2/neu receptors.

TABLE II - Tumour features in cases with micrometastases and ITC in SLN.

Tumor size (mm)	Micrometastases 21.72 (range 4-55)	ITC 19 (range 9-32)
Histologic type		
Ductal Infiltrating	45 (88.24%)	7 (87.50%)
Lobular Infiltrating	3 (5.88%)	1 (12.50%)
Ductal+Lobular Infiltrating	2 (3.92%)	0
Other	1 (1.96%)	
Grading		
G1	4 (7.84%)	2 (25.00%)
G2	32 (62.74%)	5 (62.50%)
G3	15 (29.42%)	1 (12.50%)
Estrogen Receptors		
positive	49 (96.08%)	7 (87.50%)
negative	2 (3.92%)	1 (12.50%)
Progesterone Receptors		
positive	46 (90.20%)	6 (75.00%)
negative	5 (9.80%)	2 (25.00%)
HER-2/neu overexpression		
Yes	30 (58.82%)	3 (37.50%)
No	21 (41.18%)	5 (62.50%)
Multifocality	7 (13.72%)	1 (12.50%)

TABLE III - Treatment of the axilla in micrometastases and ITC patients.

	Micrometastases	ITC	Total	Axillary recurrences
Axillary dissection	14	1	15	0
Positive lymph nodes	1	1	2 (13.33%)	
Negative lymph nodes	13	0	13 (86.66%)	
No Axillary dissection	37	7	44	0

The median follow-up of the patients with SLN micrometastases and ITC that didn't undergo complete AD was of 65.3±9.65 months (range 42-78 months). Neither axillary recurrences nor distant metastases were found in this period in all patients.

Discussion

The staging of the axilla obtained through the study of SNL is considered a highly effective and accurate method, burdened with a very low incidence of false

negatives^{4,9}. The current guidelines recommend performing AD exclusively in patients with positive SLN, although it is estimated that only in 40% of cases with positive SLN metastases occur in other axillar nodes⁴. No additional surgery is now unanimously indicated for ITC in the SLN, considered absolutely irrelevant in terms of adverse prognosis¹⁰.

However, the indication to perform the AD in the presence of micrometastases in the SLN is still widely debated. Unlike macrometastases, they have an uncertain prognostic significance and the guidelines aren't unanimous on the behavior the surgeon must keep in their presence.

Over the last few years we have conducted several clinical trials in order to clarify what the optimal choice of therapy in case of micrometastases in the SLN was. The results obtained in the first studies on the subject recommend to perform a complete AD in these patients, as sentinel lymph node micrometastases were associated with high rates of additional lymph node metastases and recurrences¹⁰. Subsequently the prospective randomized trial AATRM has instead shown how the removal of only the sentinel lymph node represents, together with a valid adjuvant therapy, an effective means of locoregional control of the disease avoiding, in these patients, the AD¹¹. Similar results were also obtained from the trial IBCSG 23-01¹², which showed that there is absolute uniformity in terms of overall survival and disease-free survival at 5 years among patients with micrometastases in SLN subject to completion AD and those in which there has been no additional surgical treatment of the axilla. The fact that the surgical excision of the primary tumor is always followed by adjuvant therapy (radiotherapy, hormonal therapy or systemic therapy) when deemed appropriate for the type of surgical treatment carried out and the cancer's biological and histopathological characteristics.

These conclusions correspond to our experience. The incidence of metastases in other axillar nodes in cases of micrometastases and / or ITC in the sentinel node was 13.33%, only two cases in which the primary tumor biological characteristics were also particularly unfavorable.

Currently, the theory that the main factors predisposing to axillary recurrence are genetic characteristics and histopathological of the primary tumors such as size, histological grade and¹³ the pattern of gene expression of the tumor seems to prevail¹⁴. Only in such cases the AD may be indicated even with minimal metastatic involvement of SLN.

In our experience, the indication for AD in the presence of micrometastases and / or ITC in the SLN has been modified over the years. Completion AD was performed in patients with micrometastases and / or ITC in SLN until 2008. Since 2009, on the basis of the preliminary results of the mentioned randomized trials in which more precisely defined the prognostic significance

of micrometastases in SLN, the complete AD is no longer performed. In addition, more recently, we evaluated the choice to execute the AD relying also on biomorphologic characteristics of the primary tumor, considering as important risk factors for axillary recurrence some parameters such as multifocality, the absence of hormone receptors, the high histological degree and the over expression of HER2 / neu. It seems, in fact, that the multifocal or multicentric cancers are associated with the presence of metastasis to axillary lymph nodes more frequently than monofocal tumors¹⁵. Similarly, the gene expression pattern of the primary tumor is related to the probability of axillar metastases, as well as to locoregional recurrences¹⁶. It was shown that the molecular subtypes "triple negative" and HER2 / neu-positive are those at greatest risk of positive axillar lymph nodes, as well as a worse prognosis^{17, 18}. Although, to date, guidelines on surgical treatment of the axilla aren't unanimous, based on the results of various studies it must be considered absolutely the choice of not performing the AD in the presence of micrometastases in SLN. In these patients, however, postoperative adjuvant therapies are absolutely valid instruments of control for both the locoregional metastasis that for the distant metastases. In our experience, in the group of patients with SLN micrometastases and ITC followed by no additional AD there were no recurrences to axillary lymph nodes nor to distant metastases. Considering furthermore that the risk of cancer recurrence is greater in the first two years after surgery¹⁹, and that the patients we studied have received a minimum of 42 months follow-up, we can conclude that, in our experience, prognosis of patients with SLN micrometastases and ITC followed by no additional AD is comparable to that of patients with negative SLN.

Notwithstanding the importance of postoperative adjuvant therapy, particularly chemotherapy²⁰, it can be concluded that in patients with SLN micrometastases AD does not improve the prognosis and that the AD does not have any absolute indication. While waiting for more precise and shared guidelines we believe that AD must be carefully assessed case by case, particularly taking into account the high bio-morphological characteristics of the primary tumor.

Riassunto

Il significato prognostico delle micrometastasi nel linfonodo sentinella nelle pazienti affette da carcinoma della mammella è ancora ampiamente dibattuto. Anche se, in assenza di univoche linee guida, nella pratica clinica la linfadenectomia ascellare in queste pazienti non viene più eseguita di routine.

Abbiamo condotto uno studio retrospettivo su 746 pazienti affette da carcinoma invasivo della mammella

con linfonodi ascellari negativi, sottoposte a chirurgia conservativa o a mastectomia totale con biopsia del linfonodo sentinella. Le pazienti in cui è stata diagnostica la presenza di micrometastasi del linfonodo sentinella sono state considerate in due diversi gruppi. In un primo gruppo, trattato con linfadenectomia ascellare totale è stata valutata l'incidenza di metastasi a carico dei rimanenti linfonodi ascellari. Un secondo gruppo non ha ricevuto alcun trattamento aggiuntivo dell'ascella e le pazienti sono state seguite con controlli periodici clinico strumentali. In entrambi i gruppi è stata valutata l'incidenza di eventuali recidive ascellari.

All'esame istologico estemporaneo ed al successivo esame istologico definitivo del linfonodo sentinella, in 51 pazienti (6,83%) sono state evidenziate micrometastasi, in 8 pazienti (1,07%) erano presenti cellule tumorali isolate. Quindici di queste pazienti sono state sottoposte a linfadenectomia ascellare totale. Solo in 2 casi (13,33%) sono state ritrovate metastasi a carico dei rimanenti linfonodi ascellari. Quarantaquattro pazienti non hanno ricevuto alcun trattamento aggiuntivo dell'ascella. In queste pazienti nessuna recidiva ascellare è stata registrata durante un follow-up medio di 65,3±9,65 mesi (range 42-78 mesi).

Sulla base dei risultati ottenuti in questo studio ed in linea con alcuni recenti trials randomizzati si ci sentiamo di concludere che la linfadenectomia ascellare può essere evitata nei casi con micrometastasi nel linfonodo sentinella. Una sua eventuale indicazione può essere valutata caso per caso considerando come fattori di rischio per la recidiva ascellare alcune caratteristiche biomorfologiche del tumore primitivo.

References

1. Lyman GH, Giuliano AE, Somerfield M., Benson III AB, Bodurka DC, Burstein HJ, Cochran AJ, Cody III HS, Edge SB, Galper S, Hayman JA, Kim TY, Perkins CH, Podoloff DA, Sivasubramaniam VH, Turner RR, Wahl R, Weaver DL, Wolff AC, Winer EP: *American society of clinical oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer*. J Clin Oncol, 2005; 23:7703-720.
2. Scomersi S, Da Pozzo F, Torelli L, Zanconati F, Tonutti M, Dore F, Bortul M: *Clinicopathologic factors predicting involvement of nonsentinel axillary lymphnodes in breast cancer patients: Is axillary dissection always indicated?* Ann Ital Chir, 2010; 81:335-41.
3. Scomersi S, Torelli L, Zanconati F, Tonutti M, Dore F, Bortul M: *Evaluation of a breast cancer nomogram for predicting the likelihood of additional nodal metastases in patients with a positive sentinel node biopsy*. Ann Ital Chir, 2012; 83:461-68.
4. Straver ME, Meijnen P, van Tienhoven G, van de Velde CJ, Mansel RE, Bogaerts J, Duez N, Cataliotti L, Klinkenbijl JH, Westenberg HA, van der Mijle H, Snoij M, Hurkmans C, Rutgers EJ: *Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial*. Ann Surg Oncol, 2010; 17: 1854-861.

5. Cipolla C, Fricano S, Vieni S, Amato C, Napoli L, Graceffa G, Latteri S, Latteri MA: *Validity of needle core biopsy in the histological characterisation of mammary lesions*. Breast 2006; 15:76-80.
6. Caruso G, Cipolla C, Costa R, Morabito A, Latteri S, Fricano S, Salerno S, Latteri MA: *Lymphoscintigraphy with peritumoral injection versus lymphoscintigraphy with subdermal periareolar injection of technetium-labeled human albumin to identify sentinel lymph nodes in breast cancer patients*. Acta Radiol, 2014; 55:39-44.
7. Cipolla C, Cabibi D, Fricano S, Vieni S, Gentile I, Latteri MA: *The value of intraoperative frozen section examination of sentinel lymph nodes in surgical management of breast carcinoma*. Langenbecks Arch Surg, 2010; 395:685-91.
8. Lumachi F, Norberto L, Zanella S, Marino F, Basso SMM, Basso U, Brunello A, Fassina A: *Axillary node sampling in conjunction with sentinel node biopsy in patients with breast cancer. A prospective preliminary study*. Anticancer Res, 2011; 31:693-97.
9. Petronella P, Scorzelli M, Benevento R, Corbisiero MC, Freda F, Canonico S: *The sentinel lymph node: A suitable technique in breast cancer treatment?* Ann Ital Chir, 2012; 83:119-23.
10. Reed J, Rosman M, Verbanac KM, Mannie A, Cheng Z, Taffa L: *Prognostic implications of isolated tumor cells and micrometastases in sentinel nodes of patients with invasive breast cancer: 10-year analysis of patients enrolled in the prospective East Carolina University/Anne Arundel Medical Center Sentinel Node Multicenter Study*. J Am Coll Surg, 2009; 208:333-40.
11. Solà M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, Moral A, Ballester B, Vidal S: *Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: Final results from the multicenter clinical trial AATRM 048/13/2000*. Ann Surg Oncol, 2013; 20:120-27.
12. Galimberti V, Cole BF, Zurrada 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 (International Breast Cancer Study Group Trial 23-01 investigators): *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.
13. Galimberti V, Botteri E, Chifu C, Gentilini O, Luini A, Intra M, Baratella P, Sargenti M, Zurrada 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; 131:819-25.
14. Pepels MJ, de Boer M, Bult P, van Dijck JA, van Deurzen CH, Menke-Pluymers M.B, 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: 116-21.
15. Duraker N, Caynak ZC: *Axillary lymph node status and prognosis in multifocal and multicentric breast carcinoma*. Breast J, 2014; 20:61-8.
16. García Fernández A, Chabrera C, García Font M, Fraile M, González S, Barco I, González C, Cirera L, Veloso E, Lain JM, Pessarrodona A, Giménez N: *Differential survival and recurrence patterns of patients operated for breast cancer according to the new immunohistochemical classification: Analytical survey from 1997 to 2012*. Tumor Biol, 2013; 34:2349-355.
17. Li C.Y, Zhang S, Zhang XB, Wang P, Hou GF, Zhang J: *Clinicopathological and prognostic characteristics of triple-negative breast cancer (TNBC) in Chinese patients: A retrospective study*. Asian Pac J Cancer Prev, 2013; 14:3779-784.
18. Howland NK, Driver TD, Sedrak MP, Wen X, Dong W, Hatch S, Eltorkey MA, Chao C: *Lymph node involvement in immunohistochemistry-based molecular classifications of breast cancer*. J Surg Res, 2013; 185:697-703.
19. Jatoi I, Tsimelzon A, Weiss H, Clark GM, Hilsenbeck SG: *Hazard rates of recurrence following diagnosis of primary breast cancer*. Breast Cancer Res Treat, 2005; 89:173-78.
20. van der Heiden-van der Loo M, Schaapveld M, Ho VK, Siesling S, Rutgers EJ, Peeters PH: *Outcomes of a population-based series of early breast cancer patients with micrometastases and isolated tumour cells in axillary lymph nodes*. Ann Oncol, 2013; 24:2794-801.