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Effects of Waiting Time and Biopsy Methods on Invasive Breast Cancer Survival

Pitichote Hiranyatheb, MD
Youwanush Kongdan, MD
Panuwat Lertsithichai, MD, MSc
Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Abstract

Objective: **To examine the effects of the waiting time from biopsy to definitive surgery and the type of biopsy method on invasive breast cancer survival.**

Patients and Methods: **Three hundred and fifty-nine medical records from women who were diagnosed with unilateral, non-metastatic invasive breast cancer between January 2000 and December 2001 were reviewed. Cox regression analysis was used to determine the relationship between the waiting time, biopsy method, and overall as well as disease-free survival, adjusted for other clinical and pathological factors.**

Results: **Patients were 50 years old on the average; 80% had stage I-II disease. The median waiting time was 1.9 weeks. Fifty-five percent of patients underwent definitive surgery within two weeks of biopsy. Excisional biopsy or frozen section diagnosis was performed in 74% of patients. The 5-year overall survival was 90% and 5-year disease-free survival was 79%. There was no significant association between the waiting time and overall survival or disease-free survival after adjusting for tumor stage. Core or fine needle biopsy was significantly associated with better disease-free survival, but not with overall survival, for patients with stage I-II breast cancer.**

Conclusion: **The present study suggested that waiting time had minimal effects on breast cancer survival whereas core- or fine-needle biopsy was associated with a better disease-free survival as compared with open biopsy.**

Key words: **biopsy, breast cancer, waiting time, survival**

Introduction

Combined delays in the presentation, diagnosis and treatment of breast cancer have been shown to adversely affect survival.[1,2] Such delays are recognized measures of poor quality of care.[3,4] Delays in breast cancer management can, in the present study, be divided into two phases, namely the delay prior to diagnosis ("delayed presentation" or "delayed diagnosis") and the delay from diagnosis to treatment ("delayed treatment"). The former delay is usually patient-related and the latter provider- or system-related.[4,5] A third type of delay, the "referral delay"[5], can be included in the delay in diagnosis and is usually not a problem at the present institution. It is generally accepted that a delayed diagnosis implies a worse prognosis.[1,5,6] However, the delay from diagnosis to

Correspondence address : *Youwanush Kongdan, MD, Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand, Telephone: 066 2 2011315, Fax: 066 2 2011316; E-mail: y_kongdan@hotmail.com*

definitive treatment has not been clearly shown to pose a similar risk.[5,7,8] In particular, it is unclear whether a longer time interval from breast biopsy to definitive surgery is associated with reduced patient survival, despite the wide-spread practice of scheduling surgery within two weeks after biopsy.[1,9-11] Also of some interest is the theoretical possibility that more aggressive biopsy procedures such as excisional biopsies might be associated with poorer survival because of increased local or systemic recurrence, due to the shedding of cancer cells during operative manipulation.[12,13] The longer the delay in treatment, the more likely that an aggressive biopsy method might adversely affect survival. The objective of the present study was to determine the relationship between the time interval from breast biopsy to definitive surgery ("waiting time") and patient survival, as well as the relationship between biopsy method and the same outcome, after adjusting for the effects of confounding variables.

Methods

Medical records of women with invasive breast cancer treated between January 2000 and December 2001 were reviewed. These patients seen in the particular period between 2000 and 2001 were analyzed because a high proportion of long-term survivors with at least 5 years of follow-up could be expected. Patients presenting with carcinoma in situ, recurrent disease, bilateral breast cancer, metastatic cancer, those operated on at a different institution or given neoadjuvant chemotherapy were excluded.

The waiting time from diagnosis to treatment was defined as the time from the date of definitive biopsy to the date of definitive surgery. Biopsy method was recorded for all patients. Important clinical and pathological characteristics related to breast cancer survival were extracted (Table 1) and used in multivariable-adjusted statistical analyses.

The primary outcomes of the study were the survival time, defined in two ways as either the time from diagnosis or the time from definitive surgery, to the last recorded hospital visit, with the dead or alive status known; and the disease-free survival time, defined as the time from definitive surgery to the first documentation of recurrent disease or to the last recorded hospital visit with known dead or alive status. The survival time was measured from the date of

Table 1 Clinical and pathological characteristics

Characteristic (n = 359, unless stated otherwise)	Number of cases (%) (unless stated otherwise)
Age (years): Mean (SD)	49.8 (10.2)
Range	[25 to 80]
Menopausal status	
Yes	187 (52)
No	97 (27)
Unknown	75 (21)
Biopsy methods	
Fine needle aspiration biopsy	25 (7)
Core needle biopsy	56 (16)
Incisional biopsy	12 (3)
Excisional biopsy	130 (36)
Needle-localized biopsy	11 (3)
Frozen section ("double setup")	125 (35)
Tumor location	
Central	28 (8)
Upper outer quadrant	185 (52)
Upper inner quadrant	75 (21)
Lower outer quadrant	50 (14)
Lower inner quadrant	21 (6)
Nipple involvement	
Yes	8 (2)
Pathological tumor size (cm.)	
Mean (SD)	3.2 (1.6)
Median (Range)	3 (0.5 to 12)
Multifocality (in the same breast)	
Yes	7 (2)
Pathology	
Invasive ductal carcinoma	331 (92)
Others (lobular, medullary, papillary cancer, etc.)	28 (8)
Deep surgical margin >1 mm.	
Yes	344 (96)
Deep surgical margin (mm.); n = 356	
Mean (SD)	7.6 (7.6)
Median (Range)	5 (0 to 60)
Angiolymphatic invasion	
Yes	115 (32)
Tumor grade (Bloom-Richardson); n = 301	
I	39 (13)
II	171 (57)
III	91 (30)
Estrogen receptor status; n = 288[a]	
Positive	134 (47)
Number of dissected axillary lymph nodes >10	
Yes	316 (88)
TMN staging (2002)	
I	71 (20)
IIa	151 (42)
IIb	64 (18)
IIIa	39 (11)
IIIb & IIIc	34 (9)

[a]Progesterone Receptor and HER2/Neu expressions were rarely examined during the years 2000-1

diagnosis to minimize lead-time bias.[2] The TNM staging used in the present study was that of the American Joint Committee on Cancer (AJCC), 2002 edition.[14]

Continuous data were summarized as mean (SD) or median (range) as appropriate. Categorical data were summarized as counts and percentages. Estimates of patient survival were based on the Kaplan-Meier method. Estimates of the hazard of death or breast cancer recurrence in relation to the waiting time or biopsy method, and multivariable adjustment for potential confounding risk factors, were based on the Cox proportional-hazards regression model. All estimates were reported as point and interval (95% confidence interval, 95% CI) values. Tests for the significance of each risk factor were either by Wald's test or the likelihood ratio test. Statistical significance was defined as a two-sided p-value of 0.05 or less. The statistical software Stata version 9 (Stata Corp, College Station, TX, USA) was used for all statistical analyses.

Results

Of the 672 women with breast cancer operated within the period under study, 21 had ductal carcinoma in situ (DCIS), 43 had metastatic disease, 8 had bilateral breast cancer, 33 were given neoadjuvant chemotherapy, 66 underwent breast operations elsewhere and 147 had incomplete or missing medical records. Thus, medical charts of 359 (53%) breast cancer patients were reviewed.

During the period under study, most breast cancer patients were treated with total mastectomy at the present institution. Full axillary lymph node dissection was performed for all patients. Sentinel lymph node biopsy was not performed during that time. The estrogen receptor (ER) was almost the only hormonal receptor evaluated in the tumor tissues. The determination of the Human Epidermal Growth Factor Receptor-2 (HER-2/neu) expression was not available or not done.

The clinical and pathological characteristics of patients and breast tumors are presented in Table 1. Patients were 50 years old on the average and commonly presented with early breast cancer (TNM stages I and II, 80%). Breast cancer was most commonly diagnosed via open excisional biopsy (including needle-localized biopsy) or frozen section diagnosis in 39% and 35% of cases, respectively. Core needle biopsy was infrequently performed (16%), and was usually done by the surgeon in the outpatients department for palpable breast lesions only, using number 14 needle. A few patients with non-palpable lesions were biopsied by the radiologist using core needles guided by the ultrasound.

The treatment and outcomes data are presented in Table 2. The median waiting time from diagnosis to

Table 2 Treatment and outcomes

Treatment and Outcomes (n = 359, unless stated otherwise)	Summary: number (%) (unless stated otherwise)
Surgery of the breast	
Total mastectomy	355 (99)
Partial mastectomy	4 (1)
Surgery of the axilla	
Complete axillary dissection	359 (100)
Postoperative adjuvant chemotherapy	
Yes	262 (73)
Hormonal therapy	
Yes	188 (52)
Radiotherapy	
Yes	104 (30)
Duration of hormonal treatment (months); n = 188	
Mean (SD)	52 (16.8)
Median (range)	60 (5 to 75)
Duration of FU after surgery (months)	
Mean (SD)	58.8 (21.6)
Median (Range)	66 (1 to 88)
Disease recurrence at last follow-up	
Overall	73 (20)
Local	31 (9)
Distant	60 (17)
Disease-related death at last follow-up	
Yes	33 (9)
Waiting time between biopsy & definitive surgery (weeks)	
Mean (SD)	2.2 (2.8)
Median (Range)	1.9 (1 day to 32 wks)
Waiting time for the core/fine needle biopsy group (n = 81)	
Mean (SD); weeks	3.6 (3.7)
Median (Range); weeks	2.9 (1 to 32)
Waiting time for the open biopsy group (n = 153)	
Mean (SD); weeks	3.1 (2.3)
Median (Range); weeks	2.6 (4 days to 22 wks)

definitive surgery was 1.9 weeks, ranging from within one day (for frozen section diagnosis) to 32 weeks. Only 55% of patients had a waiting time shorter than two weeks. Most patients had invasive ductal carcinoma (92%). Postoperative adjuvant chemotherapy was given in 73% of cases, hormonal treatment in 52% (corresponding to a positive ER rate of 47%) and radiotherapy in 30%. The median follow-up time was 66 months. The 5-year overall survival was 90% (95% CI, 86% to 93%) and the 5-year disease-free survival was 79% (95% CI, 74% to 83%), as measured from the date of definitive surgery.

Shorter waiting time was significantly associated with decreased overall survival on univariable Cox regression analysis (Table 3). Biopsy method was categorized into three groups: the frozen section group, the open biopsy group (in which patients undergoing incisional and needle localized biopsy were also included) and the core and fine needle biopsy (CNB and FNB) group. Compared with the frozen section group, the open biopsy and CNB and FNB groups had significantly better overall survival. Other significant univariable risk factors for breast cancer death included large tumor size, presence of angiolymphatic invasion, high tumor grade, high TNM stage and radiotherapy. On multivariable Cox regression analysis, after including all significant risk factors in Table 3, waiting time and biopsy group were not significantly associated with overall survival. The only remaining significant risk factor was the TNM stage (Tables 4 and 5). These analyses were also done for the survival time measured from the date of diagnosis, with minor differences in the results.

The results of the univariable analysis of the association between the risk factors and disease-free survival were similar to those of the overall survival

Table 3 Significant risk factors: univariable analysis

Risk Factor	Overall mortality		Breast cancer-related recurrence or mortality	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Tumor size (per cm. increase)	1.36 (1.17 to 1.57)	<0.001	1.27 (1.14 to 1.42)	<0.001
Angiolymphatic invasion (yes)	3.11 (1.57 to 6.18)	0.001	2.76 (1.75 to 4.36)	<0.001
Tumor grade (per higher grade; n = 301)	2.87 (1.50 to 5.49)	0.001	1.96 (1.31 to 2.94)	0.001
TMN stage (per higher stage)	2.10 (1.61 to 2.73)	<0.001	1.77 (1.49 to 2.10)	<0.001
Hormonal treatment (yes)	0.389 (0.189 to 0.803)	0.011	0.469 (0.293 to 0.751)	0.002
Radiotherapy (yes)	1.96 (0.981 to 3.91)	0.056	1.87 (1.17 to 2.97)	0.008
Waiting time (per week increase)	0.765 (0.608 to 0.962)	0.022	0.821 (0.713 to 0.946)	0.006
Biopsy method				
Frozen section diagnosis	1 (reference)		1 (reference)	
Open biopsy[a]	0.511 (0.244 to 1.07)	0.075	0.513 (0.267 to 0.987)	0.046
Core or fine needle biopsy	0.325 (0.109 to 0.965)	0.043	0.343 (0.143 to 0.825)	0.017
Local recurrence (yes)	9.46 (4.61 to 19.4)	<0.001	NA	
Distant recurrence (yes)	235 (32.0 to 1723)	<0.001	NA	

[a]Opened biopsy is defined as excisional, needle-localized or incisional biopsy; NA: not applicable

Table 4 Effect of "waiting time" after adjusting for TMN staging: multivariable analysis

Risk Factor	Overall mortality		Breast cancer-related recurrence or mortality	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
TMN stage (per higher stage)	2.01 (1.54 to 2.63)	<0.001	1.61 (1.34 to 1.95)	<0.001
Waiting time (per week increase)	0.866 (0.703 to 1.07)	0.178	0.887 (0.778 to 1.01)	0.072
Angiolymphatic invasion (yes)	NS		1.70 (1.04 to 2.78)	0.034

NS: not significant and not included in model

Table 5 Effect of biopsy method after adjusting for TMN staging: multivariable analysis

Risk Factor	Overall mortality		Breast cancer-related recurrence or mortality	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
TMN stage (per higher stage)	2.03 (1.54 to 2.66)	<0.001	1.57 (1.30 to 1.90)	<0.001
Biopsy method				
Frozen section diagnosis	1 (reference)		1 (reference)	
Open biopsy	0.799 (0.373 to 1.72)	0.566	0.648 (0.388 to 1.08)	0.097
Core- or fine-needle biopsy	0.553 (0.183 to 1.67)	0.294	0.420 (0.201 to 0.877)	0.021
Angiolymphatic invasion (yes)	NS		1.77 (1.08 to 2.90)	0.021

NS: not significant and not included in model

Table 6 Biopsy method and the risk of breast cancer recurrence or death for patients with various stages of disease

Risk Factor	Stage I-II disease (n = 286)		Stage III disease (n = 73)	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Angiolymphatic invasion (yes)	2.27 (1.24 to 4.22)	0.008	1.16 (0.541 to 2.48)	0.707
Biopsy method				
Frozen section diagnosis	1 (reference)		1 (reference)	
Open biopsy	0.670 (0.360 to 1.25)	0.207	0.477 (0.189 to 1.20)	0.116
Core- or fine-needle biopsy	0.204 (0.060 to 0.695)	0.011	1.01 (0.394 to 2.58)	0.986
TNM stage (per higher stage)	1.97 (1.25 to 3.12)	0.004	NS	

NS: not significant and not included in model

(Tables 3-5). On multivariable Cox regression, three factors remained significant: TNM stage, presence of angiolymphatic invasion, and biopsy method. However, the effect of biopsy method was not consistent for all disease stages. In Table 6, in patients with TNM stage I-II disease, after adjusting for angiolymphatic invasion and TNM stage, CNB and FNB were associated with significantly better disease-free survival than that of frozen section diagnosis, while open biopsy was not significantly different from the frozen section diagnosis in terms of the same outcome. For patients with stage IIIa-c disease, however, none of the two biopsy methods was clearly better than the frozen section diagnosis. In particular, CNB and FNB had a very similar disease-free survival as that of the frozen section diagnosis (Table 6).

Subgroup analyses (not presented) for patients who underwent open biopsy exclusive of frozen section diagnosis, and for those who underwent either open biopsy, CNB or FNAB also revealed that waiting time was not significantly associated with either overall or disease-free breast cancer survival.

A Cox regression analysis of the outcome time-to-local recurrence, revealed that neither the waiting time nor biopsy method was significantly associated with the risk of local recurrence, although there was a tendency for patients in the CNB and FNB group to have less risk of local recurrence. Only higher TNM stage was associated with a significantly increased risk of local recurrence. A similar Cox regression analysis for the time-to-distant recurrence (metastatic disease) revealed similar results, but now the CNB and FNB group had a significantly less risk of distant recurrence as compared with the frozen section diagnosis group (analyses not presented).

Discussion

There is no clear evidence in the present study that the waiting time from biopsy to surgical treatment influenced the treatment outcome both in terms of overall survival or disease-free survival. It appeared that waiting time was associated with better survival on univariable analysis only because patients with better prognosis (lower TNM stage) had to wait longer. In particular, patients with more advanced stage cancer often underwent frozen section diagnosis in the setting of a "double setup" strategy, i.e., upon a positive frozen section biopsy result, a modified radical mastectomy was immediately performed. Thus, these patients had

the shortest possible waiting time (within half an hour). Similarly, waiting time was not significantly associated with survival in the subgroup of patients who did not undergo double setup, as well as in those who underwent open biopsy only.

A few studies also found that longer waiting time from diagnosis to treatment was associated with better survival, and was partly explained away as a confounding effect of tumor extent (i.e. TNM stage).[5] After adjusting for the extent of the tumor, no significant relationship was found between waiting time and survival.[5,15]

Many surgeons have urged that delayed operations for breast cancer be minimized, based on the hypothesis that delayed treatment following breast biopsies is associated with worse patient survival. Some authors advocate the "two week waiting rule".[9,10] More recent observational studies failed to support this hypothesis.[5,6,8,15] Although in most studies patients were treated within a few weeks after biopsy, some were treated after a delay of 3 months or more without apparent adverse outcome.

The apparent lack of association between waiting time and survival in early breast cancer patients should not be interpreted to mean that long delays in treatment can be tolerated. Indeed, it defies common sense not to advocate early definitive surgery. In most studies, the overwhelming majority of patients were treated in a timely manner.[5,8,15] It is therefore possible that patients who were left waiting for a relatively longer time, for whatever reason, were too few to have a significant influence on the trend in the data.

An implication of these observations could be that the two-week waiting rule should not be a fixed law binding all patients and physicians to an unshakable agreement. Instead, the patient should be given enough time to decide on the most appropriate treatment based on due consideration of all information provided by the physician and other breast cancer specialists. The patient should be encouraged to seek the opinion of other professionals, if such is her wish, and to spend time discussing the issues with her family as well as other breast cancer patients. If the time needed must exceed two weeks, then the physician can reassure the patient that the extra time delay, if not too excessive, will not likely affect the outcome of treatment.

Another interesting finding in the present study was that the biopsy method was related to disease-free survival, but not to overall survival. Further analyses showed that this relationship was most likely confined to early breast cancer patients (TNM stage I-II). The relationship was a reduced risk of both local and distant recurrence in the CNB and FNB group, as compared with the frozen section and open biopsy groups, although only the risk of distant recurrence was significantly reduced. This risk reduction remained significant even after adjusting for TNM staging and presence of angiolymphatic invasion.

Clinical studies have examined the influence of various biopsy methods on local recurrence in breast cancer patients undergoing breast conserving surgery (BCS), who were given postoperative breast irradiation. No clear evidence exists for a significant increase in local recurrence whether open biopsy or CNB was the biopsy technique, or when preoperative CNB was compared with no CNB.[16-18] In the present study, almost all patients had total mastectomy, and local recurrence (mainly at the surgical site and ipsilateral chest wall or axilla) was not clearly associated with biopsy method, as may be expected. However, a significant relation between open biopsy (excisional or frozen section) and increased risk of distant recurrence was found in the present study, which was not explained by the effect of possible confounders such as extent of disease or presence of angiolymphatic invasion.

Experimental and animal studies have demonstrated that malignant cells can be shed into the blood stream during surgical manipulation of the primary tumor, leading to apparent metastatic lesions.[19,20] Studies in the human are also suggestive of systemic cancer cell dissemination during breast cancer surgery,[12,13] but whether this procedure-related spread is clinically meaningful remains to be proven,[21] despite some evidence that patients with higher number of circulating tumor cells (CTC) have a worse prognosis.[22] The present study seemed to support the hypothesis that cancer cell shedding during aggressive surgical manipulation might indeed be associated with significantly increased risk of disease recurrence, if only for early-stage breast cancer patients.

Another plausible explanation for the above findings is that patients with stage I-II disease constituted a heterogeneous group, with more significant variations in prognosis than can be captured by the TNM staging system.[23] Therefore the relationship between the biopsy method and disease-free survival might be

explained by other cancer-related risk factors which were not taken into account in the present study. What these other risk factors might be need to be investigated further in future studies. Some support for this explanation can be seen in the following. During the period under study, CNB and FNB were usually performed for two distinct groups of patients: those with small lesions difficult to palpate, and those with locally advanced lesions. Hence, as can be seen in Table 6, patients with stage I-II disease who underwent CNB and FNB seemed to have had excellent prognosis, and those with stage III disease who underwent the same biopsy procedure did rather poorly, even when compared with patients who had frozen section diagnosis.

A possible implication of the findings concerning biopsy methods is that the method of choice should be the least invasive, at least for early breast cancer patients. Core needle and fine needle biopsy should be considered primary biopsy methods in breast cancer. Core needle tracts must subsequently be excised or irradiated to prevent needle tract seeding and local disease recurrence.[18,24] The finding that CNB and FNB were associated with higher disease-free survival should be considered provisional. However, and should await further confirmatory studies before the above recommendations concerning CNB and FNB can be made with confidence.

Conclusion

There was no evidence that the delay in the waiting time from breast biopsy to definitive surgery in early breast cancer patients adversely affected survival or disease-free survival in the present study. Patients who had delayed treatment were usually those with less extensive disease. The method of breast tumor biopsy might have an effect on the disease-free survival in early breast cancer patients, however. CNB and FNB were significantly associated with higher disease-free survival when compared with frozen section diagnosis or open biopsy in the present study.

REFERENCES

1. Coates AS. Breast cancer: delays, dilemmas, and delusions (commentary). Lancet 1999;353:1112-3.
2. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet 1999;353:1119-26.
3. Chung KP, Lai KS, Cheng SH, et al. Organization-based performance measures of cancer care quality: core measure development for breast cancer in Taiwan. Eur J Cancer Care 2008;17:5-18.
4. Saint-Jacques N, Younis T, Dewar R, Rayson D. Wait times for breast cancer care. Br J Cancer 2007;96:162-8.
5. Sainsbury R, Johnston C, Haward B. Effect on survival of delays in referral of patients with breast cancer symptoms: a retrospective analysis. Lancet 1999;353:1132-5.
6. Raabe NK, Fossaa SD. Primary invasive breast carcinoma in Oslo 1980-1989. Incidence and delay. Acta Oncol 1996;35:9-15.
7. Fisher ER, Sass R, Fisher B. Biologic considerations regarding the one and two step procedures in the management of patients with invasive carcinoma of the breast. Surg Gynecol Obstet 1985;161:245-9.
8. Bertario L, Reduzzi D, Piromalli D, Piva L, Di Pietro S. Outpatient biopsy of breast cancer. Influence on survival. Ann Surg 1985;201:64-7.
9. Urban JA. The case against delayed operation for breast cancer. CA Cancer J Clin 1971;21:132-3.
10. Hattori T, Niimoto M, Nakano A, Itagaki E, Inoue K, Morimoto T. Biopsy of the breast. Jpn J Surg 1980;10:270-6.
11. Toi M, Nakamura T, Wada T, et al. The acceptable delay between biopsy and radical mastectomy in breast cancer patients. Jpn J Surg 1989;19:679-83.
12. Brown DC, Purushotham AD, Birnie GD, George WD. Detection of intraoperative tumor cell dissemination in patients with breast cancer by use of reverse transcriptase polymerase reaction. Surgery 1995;117:96-101.
13. Choy A, McCulloch P. Induction of tumor cell shedding into effluent venous blood breast cancer surgery. Br J Cancer 1996;73:79-82.
14. Greene FL, Page DL, Fleming ID, Fritz A, Balch CM, Haller DG, Morrow M, eds. AJCC cancer staging manual. 6th ed. New York: Springer-Verlag, 2002.
15. Richards MA, Smith P, Ramirez AJ, Fentiman IS, Rubens RD. The influence on survival of delay in the presentation and treatment of symptomatic breast cancer. Br J Cancer 1999; 79:858-64.
16. King TA, Hayes DH, Cederbom GJ, et al. Biopsy technique has no impact on local recurrence after breast-conserving therapy. Breast J 2001;7:19-24.
17. Chen AM, Haffty BG, Lee CH. Local recurrence of breast cancer after breast conservation therapy in patients examined by means of stereotactic core-needle biopsy. Radiology 2002;225:707-12.
18. Fitzal F, Sporn EP, Draxler W, et al. Preoperative core needle biopsy does not increase local recurrence rate in breast cancer patients. Breast Cancer Res Treat 2006;97:9-15.
19. Liotta L, Kleineman J, Saidel GM. The significance of hematogenous tumor cell clumps in the metastatic process. Cancer Res 1976;36:889-94.

20. Nishizaki T, Matsumata T, Kanematsu T, Yasunaga C, Sugimachi K. Surgical manipulation of VX2 carcinoma in the rabbit liver evokes enhance ment of metastasis. J Surg Res 1990;49:92-7.
21. Hu XC, Loo WTY, Chow WCL. Surgery-related shedding of breast cancer cells as determined by RT-PCR assay. J Surg Oncol 2003;82:228-32.
22. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 2004;351:781-91.
23. Lyman GH, Burstein HJ. Breast cancer: translational therapeutic strategies. New York: Informa Healthcare; 2007. p. 103-45.
24. Uriburu JL, Vuoto HD, Cogorno L, et al. Local recurrence of breast cancer after skin sparing mastectomy following core needle biopsy: case reports and review of the literature. Breast J 2006;12:194-8.