

Role of Time Interval and Lymph Nodes Status at Excisional Biopsy of Breast Cancer

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Abstract: Introduction. Opinions of influence of the Excisional Biopsy (EB) and delayed mastectomy on survival at Breast Cancer (BC) remain inconsistent. Studying of influence of a time interval between EB and a mastectomy on ten-year the general (OS) and disease free (DFS) survival of patients with BC became the purpose of this research. The analysis of patients with BC (n = 698) at stages T2 N0-3 M0 is carried out. Group A - the patients who had a mastectomy on day of EB (n = 556). Group B - the patients who had the delayed mastectomy (n = 142). Ten-year OS and DFS survival is investigated (Kaplan-Meier, log-rank test). The status of regional lymph nodes (LNs) (N0 or N1-3) and the BC laterality were considered. At N0 the survival of Group A was significantly below, than survival of Group B (OS: p = 0.0081; DFS: p = 0.009). At N1-3 of difference of survival of the compared groups were not significant (OS: p = 0.69; DFS: p = 0.39). At the right-sided BC at N0 of distinction of survival of groups were not significant (OS: p = 0.17; DFS: p = 0.25). At the left-sided BC at N0 the survival of Group A was significantly below, than survival of Group B (OS: p = 0.024; DFS: p = 0.012). Influence of delayed mastectomy on survival can depend on LNs status and BC laterality.

Key words: Breast cancer, biopsy, lumpectomy, excisional biopsy, breast resection, open biopsy

INTRODUCTION

The diagnosing technology of breast tumors actively develops but the biopsy remains the gold standard of modern diagnostic algorithms. There are many methods of a biopsy and devices for its execution. Core needle biopsy is popular. However recent researches allow to doubt safety of core needle biopsy (Mathenge EG *et al.*, 2014; Shyamala K *et al.*, 2014)

The most reliable method and often final step in the course of verification of a tumor is the Excisional Biopsy (EB) (Stolnicu S *et al.*, 2006; Zhang Y-J *et al.*, 2013). Having a set of advantages, according to some researchers, EB is not deprived of shortcomings. Scientific dispute is conducted on two questions. First, about safety of the EB procedure as there is a hypothesis of possible risk of a dissemination of cancer as a result of this manipulation (Petris GD *et al.*, 1999; Hansen NM *et al.*, 2004; Peters-Engl C *et al.*, 2004). Secondly, researchers discuss an admissible time interval between EB and a mastectomy.

According to basic clinical recommendations, radical surgical treatment has to be as close as possible to EB. In favor of this theory there are clinical trials stating decrease in survival and increase of frequency of locoregional recurrence if radical operation is delayed (Toi

M *et al.*, 1989). However other researches did not reveal negative influence of the delayed mastectomy on survival (Jackson PP *et al.*, 1959; Hattori T *et al.*, 1980; Fujiwara A *et al.*, 1984; Bertario D *et al.*, 1985; Fujimori M *et al.*, 1987; Hansen NM *et al.*, 2004) and some researchers reported even about improvement of survival in such cases (Abramson DJ *et al.*, 1976; Samur M *et al.*, 2002).

Thus, the analysis of the world literature showed that the biological value of EB and the delayed mastectomy is not clear and judgments of their influence on survival of patients with BC remain inconsistent. Studying of influence of a time interval between EB and a mastectomy on ten-year the general (OS) and Disease Free (DFS) Survival of patients with BC became the purpose of this research.

MATERIALS AND METHODS

The retrospective analysis of sampling of patients with BC (n = 698) who were treated and observed in State Budgetary Institution of the Rostov region “Oncologic dispensary” (Russia) 1990-2004 is carried out. Sampling consisted of patients with stages of T2 N0-3 M0.

All patients underwent of EB with the subsequent mastectomy. By EB of a tumor was carried out for the purpose of verification in the form of lumpectomy. Material

was directed to histologic research. Further, morphological verification or was received at once and the mastectomy was carried out immediately, i.e. on day of EB, or material was exposed to paraffin and the mastectomy was delayed. The delay of mastectomy was connected also with other reasons: refusal of patients of immediate performance of radical operation; By EB it was carried out in out-patient situations. When the mastectomy was carried out is delayed, a median (Me [25%; 75%]) of time interval between EB and a mastectomy was 8 [4; 14] days. I.e. actually 95% of patients had a mastectomy within 24 days after EB.

Thus, two groups are created: Group A - the patients who had a mastectomy on day of EB (n = 556) and Group B - the patients who had the delayed mastectomy (n = 142).

The comparative analysis of survival was carried out differentially depending on the status of regional Lymph Nodes (LNs): N0 and N1-3. The part of the analysis is devoted to a survival assessment in groups of the right-sided and left-sided BC. All compared groups on structure of age, histologic types and the size of primary tumor were comparable. Strategy of adjuvant treatment in groups did not differ.

10-year OS and DFS are shown as a percentage with a standard error (\pm). Value $P < 0.05$ was considered as the statistically significant. Processing of statistical data, including an assessment of the OS and DFS, was carried out with use of the Statistica 10 program (Kaplan-Meier, log-rank test).

RESULTS

In the absence of metastasis in regional LNs (T2 N0 M0) the survival of the patients who had a mastectomy on day of EB (Group A, n = 402) was significantly below, than survival of the patients who had the delayed mastectomy (Group B, n = 113) (Fig.1). This result was observed as in the analysis of the OS ($p = 0.0081$) and in the analysis of the DFS ($p = 0.009$). In the presence of metastasis in LNs (T2 N1-3 M0) of difference of survival of Group A (n = 154) and Group B (n = 28) were not significant (OS: $p = 0.69$; DFS: $p = 0.39$) (Fig.2). Indicators 10-year OS and the DFS are presented in Table 1.

The analysis of survival is continued taking into account a BC laterality. At patients with the right-sided pBC in the absence of metastasis in regional LNs (T2 N0 M0) of distinction of survival of Group A (n = 199) and Group B (n = 56) were not significant as on the OS indicators ($p = 0.17$) and on the DFS indicators ($p = 0.25$). In the presence of metastasis in regional LNs the number of patients in groups was insignificant therefore the comparative analysis of survival was not carried out.

Table 1: Survival of patients who had mastectomy in various time after EB

Survival	Group A Mastectomy on day of EB	Group B Delayed mastectomy
In the absence of metastasis in lymph nodes (T2 N0 M0)		
10 year OS	77.9 \pm 2.4%	92.1 \pm 3.2%
10 year DFS	77.0 \pm 2.5%	89.8 \pm 3.6%
In the presence of metastasis in lymph nodes (T2 N1-3 M0)		
10-year OS	63.2 \pm 4.6%	65.3 \pm 6.2%
10-year DFS	58.5 \pm 4.9%	60.1 \pm 5.7%

DFS: Disease-free survival, EB:Excisional biopsy, OS: Overall survival

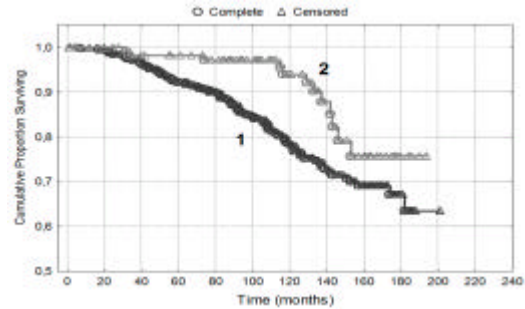


Fig. 1: Overall survival of patients with BC at stage T2 N0 M0 who had mastectomy in various time after EB: mastectomy on day of EB (Group A); delayed mastectomy (Group B) (log-rank test: $p = 0.0081$).

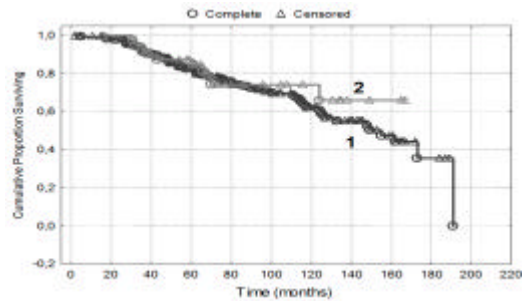


Fig. 2: Overall survival of patients with BC at stage T2 N1-3 M0 who had mastectomy in various time after EB: mastectomy on day of EB (Group A); delayed mastectomy (Group B) (log-rank test: $p = 0.69$).

At the left-sided BC in the absence of metastasis in regional LNs (T2 N0 M0) the survival of the patients who had a mastectomy on day of EB (Group A, n = 203) was authentically below, than survival of the patients who had the delayed mastectomy (Group B, n = 57). Distinctions of survival were statistically significant as on the OS indicators ($p = 0.024$) and on the DFS indicators ($p = 0.012$). In the presence of metastasis in regional LNs the number of patients in groups was insignificant therefore the comparative analysis of survival was not carried out. So, it is possible to focus attention on the main results of this research:

- The EB with the mastectomy delayed to 24 days does not worsen survival of patients with BC at stages T2 N0-3 M0
- Influence of delayed mastectomy on patients survival can depend on LNs status and BC laterality
- The EB with the mastectomy delayed to 24 days can increase of patients survival with BC at stage T2 N0 M0

DISCUSSION

Research showed that the time interval between EB and a mastectomy in certain conditions is capable to affect significantly of patients survival at the size of primary tumor T2. The status of regional LNs is applicant for a role of a factor capable to modify influence of this time interval. The analysis showed that significantly higher survival was observed at patients who had a EB with the delayed mastectomy and who had not at the same time metastasis in regional LNs. I.e., the combination, first, of intact LNs and, secondly, a time interval between EB and a mastectomy, positively influenced survival of patients. It should be noted that existence of metastasis in regional LNs eliminated effect of a time interval.

What mechanism can underlie of this phenomenon? So, at EB there is a considerable emission of tissue fragments and separate cells in the lymphatic channel. Biological effect of this movement is still authentically not established (Kinoshita S *et al.*, 2007; Loughran CF *et al.*, 2011). It can be the movement of biologically inert material (Carter BA *et al.*, 2000) but maybe the event capable to activate immunoregulatory processes. The main place where debut immunoregulatory processes are formed, of course, are regional LNs. Realization of these effects requires time (Steele RJ *et al.*, 1983). Thus, delay of a lymphodissection (in cases with the delayed mastectomy) can promote fuller realization of immune processes. Indirect confirmation of this hypothesis: in this sampling in the presence of metastasis in a LNs the influence of EB on survival of patients was minimum. It can be explained with the concept of regional immunosuppression. The essence of the concept is that metastasis in regional LNs block immunoregulatory processes and, above all, maturing of dendritic cells and process of the presentation (Mansfield *et al.*, 2011).

Laterality the second key factor which defined influence of a biopsy on a survival of patients of the BC. Only at left-sided cancer significantly higher survival of patients who received EB with the delayed mastectomy was observed. This circumstance the following confirmation of existence of lateral distinctions of

antitumoral resistance at the BC. In literature was already reported about epidemiological, morphological, immunological and predictive differences of the right-sided and left-sided BC (Hartveit *et al.*, 1984; Aareleid *et al.*, 1987; Tulinius *et al.*, 1990; Ereendeva LE *et al.*, 2002; Weiss *et al.*, 1996; Perkins *et al.*, 2004; Poroshenko *et al.*, 2004; Dmitrenko, 2016). Also was reported about anatomic features of right-sided and left-sided axillary LNs (Sapin, 1980; Cappello *et al.*, 2001; Dane *et al.*, 2008; Pan *et al.*, 2009). Nouh *et al.* (2004), showed features of emergence of metastasis in axillary LNs at the right-sided and left-sided BC (Nouh *et al.*, 2004). I.e. the laterality of the BC can influence a course of a disease.

Thus, it is possible to assume that the modern surgical treatment of the BC providing of preservation of regional LNs in the absence of metastasis in them is perspective. Now such opportunities are given by sentinel LN biopsy. And the significance of this technique, in our opinion, not only in decrease in frequency of postoperative complications. First of all, keeping "the receptor field" of immune system, we promote mobilization of own resources of the patient. The remote results of such approach to surgical treatment of the BC already begin to be published. Researchers note that with other things being equal the survival of patients who had only a sentinel LN biopsy significantly above, than survival of the patients who had an axillary lymphodissection (Langer *et al.*, 2009).

The achieved results are new information on influence of the EB and delayed mastectomy on survival of patients with BC. These data supplement our opinion on a role of the status of regional LNs in aspect of time intervals. It can have serious practical significance. Retrospective nature of research imposes known restrictions on the received results and, of course, performance of prospective research is expedient.

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REFERENCES

- Aareleid, T.P. and E.K. Khint, 1987. About prevalence of tumors in the left breast. *Questions Oncol.*, 33: 37-42.
- Abramson, D.J., 1976. Delayed mastectomy after outpatient breast biopsy: Long-term survival study. *Am. J. Surg.*, 132: 596-598.
- Bertario, L.U.C.I.O., D. Reduzzi, D.O.M.E.N.I.C.O. Piromalli, L.U.I.G.I. Piva and D.S.E.R.G.I.O. Pietro, 1985. Outpatient biopsy of breast cancer, influence on survival. *Ann. Surg.*, 201: 64-67.

- Cappello, F., M. Bellafiore, A. Palma, V. Marciano, G. Zummo, F. Farina and F. Bucchieri, 2001. Study of axillary lymph node asymmetry in a female population. *J. Anat.*, 199: 617-620.
- Carter, B.A., R.A. Jensen, J.F. Simpson and D.L. Page, 2000. Benign transport of breast epithelium into axillary lymph nodes after biopsy. *Am. J. Clin. Pathol.*, 113: 259-265.
- D.G. Petris, D.R. Gnepp and J.D. Henley, 1999. Does open biopsy before mastectomy affect the prevalence of so-called axillary lymph node micrometastases detected immunohistochemically?. *Arch. Pathol. Lab. Med.*, 123: 140-142.
- Dane, S., S. Yildirim, M. Koc, M. Aktan and C. Gundogdu, 2008. Asymmetries in breast cancer lateralization and both axillary lymph node number and metastatic involvement. *Lymphol.*, 41: 75-79.
- Dmitrenko, A.P., 2016. Lateral differences in Ki-67 in breast cancer. *Mol. Clin. Oncol.*, 4: 1041-1044.
- Fujimori, M., O. Senga, N. Terai, M. Miyagawa and F. Iida *et al.*, 1987. Relationship between biopsy and prognosis of breast cancer. *Jpn. Surg. J.*, 88: 1619-1623.
- Fujiwara, A., S. Watanabe, M. Hori, F. Kasumi and A. Fukami *et al.*, 1984. Effect of pre-operative biopsy for breast cancer on survival rate. *Jpn. J. Cancer Clin.*, 30: 1351-1356.
- Hansen, N.M., X. Ye, B.J. Grube and A.E. Giuliano, 2004. Manipulation of the primary breast tumor and the incidence of sentinel node metastases from invasive breast cancer. *Arch. Surg.*, 139: 634-640.
- Hartveit, F., M. Tangen and E. Hartveit, 1984. Side and survival in breast cancer. *Oncol.*, 41: 149-154.
- Jackson, P.P. and H.H. Pitts, 1959. Biopsy with delayed radical mastectomy for carcinoma of the breast. *Am. J. Surg.*, 98: 184-189.
- Kinoshita, S., K. Uchida, S. Kyoda, H. Shioya and H. Takeyama *et al.*, 2007. Impact of fine-needle aspiration on long-term survival rate and axillary lymph node micrometastasis in patients with early breast cancer. *Breast J.*, 13: 216-217.
- Langer, I., U. Guller, H.S.F. Schmitz, A. Ladewig and C.T. Viehl *et al.*, 2009. Sentinel lymph node biopsy is associated with improved survival compared to level I and II axillary lymph node dissection in node negative breast cancer patients. *Eur. J. Surg. Oncol.*, 35: 805-813.
- Loughran, C.F. and C.R. Keeling, 2014. Seeding of tumour cells following breast biopsy: A literature review. *Br. J. Radiol.*, 84: 869-874.
- Mansfield, A.S., P. Heikkila, V.K. Smitten, J. Vakkila and M. Leidenius, 2011. Metastasis to sentinel lymph nodes in breast cancer is associated with maturation arrest of dendritic cells and poor co-localization of dendritic cells and CD8+ T cells. *Virchows Arch.*, 459: 391-398.
- Mathenge, E.G., C.A. Dean, D. Clements, V.A. Kashani and S. Photopoulos *et al.*, 2014. Core needle biopsy of breast cancer tumors increases distant metastases in a mouse model. *Neoplasia*, 16: 950-960.
- Nouh, M.A., H. Ismail, E.D.N.H. Ali and E.M.N. Bolkainy, 2004. Lymph node metastasis in breast carcinoma: Clinicopathologic correlations in 3747 patients. *J. Egypt Natl. Canc. Inst.*, 16: 50-56.
- Perkins, C.I., J. Hotes, B.A. Kohler and H.L. Howe, 2004. Association between breast cancer laterality and tumor location, United States, 1994-1998. *Cancer Causes Control*, 15: 637-645.
- Peters, E.C., P. Konstantiniuk, C. Tausch, A. Haid and B. Hoffmann *et al.*, 2004. The impact of preoperative breast biopsy on the risk of sentinel lymph node metastases: Analysis of 2502 cases from the Austrian sentinel node biopsy study group. *Br. J. Cancer*, 91: 1782-1786.
- Samur, M.U.S.T.A.F.A., H.S. Bozcuk, G.A.M.Z.E. Dalmaz, S. Karaveli and F.G. Koseoglu *et al.*, 2002. Treatment delay in breast cancer: Does it really have an impact on prognosis. *Turk. J. Canc.*, 32: 138-147.
- Sapin, M.R., 1980. Human asymmetry of lymph nodes and its applied value. *Arch. Anat. Gistology Jembriology*, 79: 58-63.
- Shyamala, K., H.C. Girish and S. Murgod, 2014. Risk of tumor cell seeding through biopsy and aspiration cytology. *J. Intl. Soc. Preventive Community Dent.*, 4: 5-11.
- Steele, R.J.C., R.A.S. Blackie, J.D. McGregor and A.P.M. Forrest, 1983. The effect of breast biopsy on reactive changes in the axillary lymph nodes. *Br. J. Surg.*, 70: 317-318.
- Stolnicu, S.I.M.O.N.A., D.O.I.N.I.T.A. Radulescu, I.E. Plesea, D.A.N.A. Dobru and C. Podoleanu *et al.*, 2006. The value of intraoperative diagnosis in breast lesions. *Rom. J. Morphol. Embryol.*, 47: 119-123.
- Toi, M., T. Nakamura, T. Wada, A. Yamamoto and T. Toge *et al.*, 1989. The acceptable delay between biopsy and radical mastectomy in breast cancer patients. *Jpn. J. Surg.*, 19: 679-683.
- Tulinius, H., H. Sigvaldason and G. Olafsdottir, 1990. Left and right sided breast cancer. *Pathol. Res. Pract.*, 186: 92-94.

- Weiss, H.A., S.S. Devesa and L.A. Brinton, 1996. Laterality of breast cancer in the United States. *Cancer Causes Control*, 7: 539-543.
- Zhang, Y.J., L. Wei, J. Li, Y.Q. Zheng and X.R. Li, 2013. Status quo and development trend of breast biopsy technology. *Gland Surg.*, 2: 15-24.