

Radically extended modified mastectomy of t4b-dn0-3m0 primary inflammatory breast cancer as a tool to minimize the risk of recurrence

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ABSTRACT

Introduction. Breast cancer (BC) is an important public health problem. These are BC patients in young age, hereditary (BRCA-associated) BC patients, inflammatory BC patients, synchronous cancer patients etc. In case of a large size of tumor or diffuse form of BC we often need to use extended surgery techniques in order to perform it radically and minimize a risk of recurrence.

The aim of the study to evaluate the effectiveness of surgery approaches in inflammatory BC patients.

Materials and research methods. The first stage of our research was to evaluate extended surgical treatment using techniques by Handelhail and Beck on the risk of local recurrence. The study included 39 patients with breast cancer T4b-dN0-3M0 who in the period from 2014 to 2019 received complex treatment at National Cancer Institute of Ukraine. Besides neo- and adjuvant chemotherapy, an extended radical mastectomy using a technique by Handelhail and Beck was performed in 19 patients. In 20 patients a traditional (Madden) modified radical mastectomy was done.

Results. When studying the data of a group of 20 patients we received a very high percentage of recurrence. Recurrences were classified as locoregional if they occurred in the ipsilateral breast or the axillary or supraclavicular lymph nodes, and as distant metastasis, if they occurred at any other site. Radical extended modified mastectomy consisted in the removal of the mammary gland and adjacent skin along the perimeter with subcutaneous tissue at a distance of 2-3 cm outward from the macroscopic edges of the gland, subclavian-axillary-subscapularis lymphadenectomy. The resulting defect was closed using a technique by Handelhail and Beck. The use of extended surgery made it possible to improve recurrence-free survival.

Keywords: inflammatory breast cancer, hereditary breast cancer, locally-advanced breast cancer, cervical mediastinoscopy, advanced surgical treatment, recurrence of the disease

INTRODUCTION

Breast cancer (BC) is an important public health problem. Although for most cases of BC we have well-developed guidelines to provide the most effective treatment, there are groups of patients with aggressive forms of disease who still need us to find better variants of treatment in order to improve outcomes [1]. These are not only aggressive molecular subtypes (Her2-neu-positive or triple-negative BC), locally-advanced and metastatic BC. These are BC patients in young age, hereditary (BRCA-associated) BC patients, inflammatory BC patients, synchronous cancer patients etc [2]. These groups of patients need additional diagnostic procedures (CT, MRI, bone scan, cervical mediastinoscopy, etc.) and advanced (extended) surgery after systemic treatment [3]. In case of a large size of tumor or diffuse form of BC we often need to use extended surgery techniques in order to perform it radically and minimize a risk of recurrence [4]. Hereditary BC we often extend surgery to bilateral mastectomy with the removal of maximum of glandular tissue and immediate breast reconstruction. The usage of extended surgery and reconstruction techniques should be assessed on how it improves long-term treatment results for certain groups of patients [5]. There are still debates on the best time to perform reconstruction in inflammatory BC patients [6]. Immediate reconstruction is not recommended due to a high risk of local recurrence and the loss of flap. And most authors recommend reconstruction after a year or two after primary surgery. On the other hand, in inflammatory BC patients it is very important to perform surgery with clear margins, and this usually requires the removal of extra skin tissues. And to close large skin defects we can use immediate breast reconstruction (LD, DIEP, TRAM-flaps). In this way reconstruction gives us a possibility to perform surgery wider and more radical. Besides reconstruction option, we can use Beck or Handelhail techniques to close wide wounds [7]. However, these techniques leave too big scars, and we will not be able to obtain attractive results even after delayed breast reconstruction. Nevertheless, these techniques increase radicality of the surgery, they are safe and there is no risk of flap loses [8]. In this article we would love to analyze our own experience of inflammatory BC surgical treatment. Moreover, this issue is important to discuss in terms of COVID-19 pandemics [9]. In our clinic we recommend to perform surgery (including extended and reconstruction surgeries) at least 7 weeks after the first day of COVID-19 disease, and in this case, we have no difference in complication and lethality rates comparing to patients, who had no COVID-19 disease [10].

After potentially curative treatment for breast cancer, it is common clinical practice for patients to be fol-

lowed up for many years. International figures suggest that about 30% of women will develop recurrence after treatment for primary breast cancer [11]

So, in Ukraine, the five-year disease-free survival rate with the prevalence of T4d ranges from 5 to 25%, T4b - up to 50%. Inflammatory forms of breast cancer account for about 10 % of the structure of this disease. In primary inflammatory breast cancer, the five-year survival rate is about 45%, the number of local recurrences reaches 80% [12].

The inflammatory form of breast cancer is characterized by several distinctive biological features [13]. These tumors are more often poorly differentiated; aneuploidy and receptor-negative. It is well known that there is a direct correlation between the inflammatory form of breast cancer with overexpression of HER-2/neu. [14]

Several researchers attribute the total inflammatory lesion of the mammary gland, in addition to stage IV of the disease, to one of the important factors of an unfavorable prognosis of an inflammatory form of breast cancer. [15]

There are known attempts to avoid the operation, but they were extremely unsuccessful. A retrospective analysis of the results of treatment of 91 patients with locally advanced breast cancer was carried out, of which 75% had T4b-d and/or lymph node involvement. Preoperative chemotherapy (according to various schemes) was effective in 61% of cases, additional radiation therapy increased the efficiency to 93% (including 56% of cases of full effect). But, at the same time, the 3- and 5-year disease-free survival rate was only 18% and 8%; and 3- and 5-year overall survival - 28% and 11%, respectively. The return of the disease in 31% of cases was manifested by the development of local relapse and in 15% - by the simultaneous development of local relapse and distant metastases [16].

According to some authors, primary breast reconstruction does not interfere with pre-and postoperative radiation therapy, neoadjuvant and adjuvant chemotherapy [17].

The study aims to evaluate the effectiveness of using the methods of extended surgical interventions in patients with primary inflammatory breast cancer T4b-dN0-3M0.

Materials and methods of the study. This study was approved by the institutional Ethics Committee of the National Cancer Institute of Ukraine (Minutes No. 163 of June 23, 2020). Authors declare no conflicts of interest and no funding. The study is conducted according to the ethics principles of Helsinki Declaration, GCP (Good Clinical Practice), and Law of Ukraine "On medications". All patients were informed about the research and signed the agreement.

Since immediate breast reconstruction in inflammatory BC patients is currently contraindicated according to local recommendations of National Cancer Institute of Ukraine, the first stage of our research was to evalu-

ate extended surgical treatment using techniques by Handel hail and Beck on the risk of local recurrence.

The study included 39 patients with breast cancer T4b-dN0-3M0 who in the period from 2014 to 2019 received complex treatment at National Cancer Institute of Ukraine. Besides neo- and adjuvant chemotherapy, an extended radical mastectomy using a technique by Handel hail and Beck was performed in 19 patients. In 20 patients a traditional (Madden) modified radical mastectomy was done. Radical extended mastectomy allows to reduce the incidence of locoregional metastasis to 36% within 5 years compared to 84% when using traditional radical mastectomies.

Chemotherapy in neoadjuvant mode (6-8 courses) was carried out according to the CAF/FAC regimen in 13 (69%) patients. In 6 (31%) cases, other chemotherapy regimens were used: Adriamycin 50 mg/m² + Taxotere 75 mg/m², Adriamycin 50 mg/m² + Paclitaxel 175 mg/m², cisplatin mg/m² + Navelbine 20-25 mg/m² in 1 th, 8th days; Cisplatin mg/m² + Gemzar 1000 mg/m² on the 1st, 8th days.

Antiestrogenic therapy was carried out using tamoxifen or aromatase inhibitors, analogs of the hypothalamic releasing factor when indicated.

However, we paid close attention to the dynamics of clinical manifestations during neoadjuvant therapy of inflammatory forms of breast cancer, until certain signs disappeared, surgical treatment was strictly prohibited due to the high percentage of local recurrences (Table 1).

The presence of any of the absolute signs of inoperability was combined with a 5-year recovery rate of 0%.

RESULTS

When studying the data of a group of 20 patients who, for one reason or another, did not achieve the ef-

fect of complete disappearance of the above symptoms, we received a very high percentage of recurrence (Table 1).

TABLE 1. Signs of categorical inoperability

Signs of categorical inoperability	n	Frequency of local recurrence + metastasis over 5 years, %
Widespread (> 30%) breast edema	15	80
Satellites on the skin of the breast	11	87
Parasternal or supraclavicular lymph node metastases	6	26,2
All	20	84

P < 0.05

Radical extended modified mastectomy consisted in the removal of the mammary gland and adjacent skin along the perimeter with subcutaneous tissue at a distance of 2-3 cm outward from the macroscopic edges of the gland, subclavian-axillary-subscapularis lymphadenectomy. The resulting defect was closed using a technique by Handel hail and Beck.

The use of extended surgery made it possible to improve recurrence-free survival, first of all, by reducing the incidence of continued growth in comparison with a similar group of patients who underwent a radical mastectomy in a standard volume (Table 2).

Recurrences were classified as locoregional if they occurred in the ipsilateral breast or the axillary or supraclavicular lymph nodes, and as distant metastasis, if they occurred at any other site.



FIGURE 1. a. newly identified inflammatory-infiltrative form of breast cancer; b. view after performing mastectomy using Beck's technique; c. view after performing mastectomy with primary reconstructive plastic surgery of the breast with its tissues (microsurgical interventions)

TABLE 2. The frequency of recurrences depends on the operation variant

Operation variant	n, number of operations	Recurrences ± metastases, %	Disease-free period, months	Overall survival, months
Traditional radical mastectomy	20	84	19,3±3,3	42,0±4,0
Radical extended modified mastectomy using a technique by Handelhail or Beck	19	36,0±3,9	30,9±3,3	64,3±5,2

P <0.001 <0.008 <0.014 <0.001

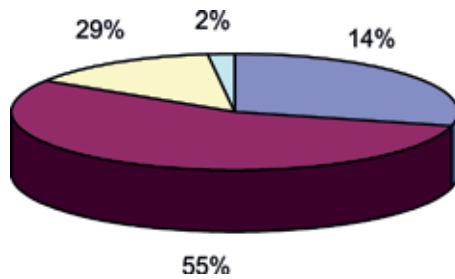


FIGURE 2. Radical extended modified mastectomy using a technique by Handelhail or Beck, patients' distribution (n = 19)

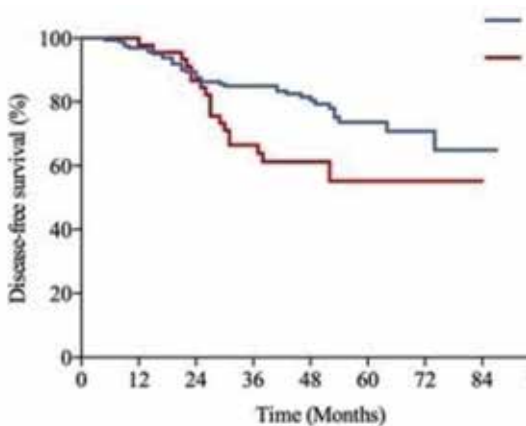


FIGURE 3. Disease-free survival depends on the operation variant (Log-rank test, P = 0.015)

DISCUSSION

To determine the option of plastic closure of the chest wall defect it is necessary to take into account the length of the defect in the area of maximum tension of the cutaneous edges of the wound, the extensibility of the skin and subcutaneous tissues, and the patient's anthropometric characteristics. That is why we chose one of the options (a technique by Handelhail or Beck).

In the group of radical extended surgery using a technique by Handelhail or Beck the recurrence was recorded in 7 (36%) patients (a complete dataset was available for 19 of these patients), with a disease-free interval ranging from 10 months to 5 years. Overall, 7 patients developed recurrence and metastatic disease, and 4 patients developed only metastatic disease. Most recurrences occurred in the second or third year after diagnosis. This rate is significantly lower comparing to

the traditional surgery rates. On the other hand, the techniques by Handelhail or Beck leave big scars, and we will not be able to obtain attractive results even after delayed breast reconstruction. The esthetic results are worse compared to traditional radical mastectomy or reconstructive surgeries.

This finding gives us an idea for further research to categorized patients and finds those who could be potential candidate for immediate reconstruction. In this case we will have not only better cosmetic results, but also lower recurrence rates. The data obtained suggest that immediate breast reconstruction should not be considered as an absolute contraindication for inflammatory BC patients. Patients with a good response to systemic treatment, patients with clear resection margins or other categories should be considered for immediate reconstructive surgery, and this is the topic of our further research.

Reconstructive surgery gives us not only cosmetic results, but also positive psychological effect on patients, which also leads to better oncological outcomes. Moreover, immediate breast reconstruction has also financial advantages for medical systems. Summing up all the advantages, we should provide more research on immediate breast reconstruction for certain groups of inflammatory BC patients.

Conclusions and prospects:

1. Based on current evidence, long-term routine follow-up after treatment for inflammatory breast cancer appears to the risk of recurrence is highest in the first 2-3 years and then decreases continuously, although it never reaches zero. 40% of all recurrences are isolated locoregional recurrences.
2. Performance of surgery in the volume of radical extended modified mastectomy using a technique by Handelhail and Beck in the treatment of inflammatory breast cancer allows to reduce the cases of locoregional metastasis to 36% within 5 years compared to 84% when using traditional radical mastectomies (p <0.001).
3. Until certain signs disappear, surgical treatment is strictly prohibited due to the high percentage

of local recurrences (widespread (> 30 %) edema of the breast skin; satellites on the skin of the mammary gland; metastases in the parasternal or supraclavicular lymph nodes). The presence of any of the absolute signs of inoperability was combined with a 5-year recovery rate of 0%.

4. To close the defect of the chest wall a technique by Handelhaul and Beck can be used. The choice of the flap depends on the shape and length of the defect in the area of maximum tension of

the joined edges of the wound, which are determined by the volume of removed tissues and the anthropometric characteristics of the patient.

5. The wider introduction into a daily practice of using a technique by Handelhaul and Beck will reliably lead to a decrease in the recurrence of breast cancer in the inflammatory form of the disease.

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