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Contemporary Approaches to The Management of Inflammatory Breast Cancer in Primary and Secondary Settings

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ABSTRACT

Breast cancer is the leading oncological disease among women in Uzbekistan, accounting for 24.9% of all cancer cases in 2022. Edematous-infiltrative (inflammatory) breast cancer (IBC) is a rare but highly aggressive subtype characterized by rapid progression, early metastasis, and poor prognosis.Objective: To develop and individualize treatment strategies for patients with primary and secondary inflammatory breast cancer.Materials and Methods: This retrospective study included 60 consecutive patients with immunohistochemically confirmed primary (n=22) and secondary (n=38) IBC treated between 2018 and 2022. Patients received either combined therapy (chemotherapy + radiotherapy) or multimodal therapy (chemotherapy + surgery + radiotherapy). Clinical, pathological, and molecular characteristics were analyzed. Survival outcomes were assessed using the Kaplan–Meier method.Results: In patients with PEV2, multimodal therapy demonstrated higher overall survival (OS: 36±8.5 months) compared to combined therapy (31±5.9 months). In contrast, in PEV3 patients, combined therapy showed superior outcomes (OS: 36±5.9 vs. 27±5.6 months). Combined therapy was more effective in primary IBC, while multimodal therapy showed better outcomes in secondary IBC.Conclusion: Treatment outcomes in IBC depend on disease form and extent of skin involvement. Personalized treatment strategies based on PEV classification and disease subtype may improve survival outcomes.

KEYWORDS

Inflammatory breast cancer, PEV classification, chemotherapy, radiotherapy, surgery, personalized treatment.

INTRODUCTION

Inflammatory breast cancer (IBC) is one of the most aggressive forms of breast cancer, accounting for approximately 1–5% of all cases but contributing disproportionately to mortality. It is characterized by rapid onset, diffuse involvement of the breast, skin edema (peau d'orange), and early metastatic spread. IBC is clinically classified into primary (without a distinct tumor mass) and secondary (with a detectable tumor or diffuse growth) forms. Accurate staging and classification are essential for selecting optimal treatment strategies [4]. The PEV (Poussée Évolutive) classification, developed at

the Gustave-Roussy Institute, provides additional prognostic value by assessing the extent of inflammatory changes and skin involvement. Modern treatment of IBC involves a multimodal approach, including systemic chemotherapy, surgery, and radiotherapy. However, the optimal combination and sequencing of these modalities remain under investigation. This study aims to evaluate treatment outcomes in primary and secondary IBC and to develop a personalized treatment algorithm based on clinical and biological characteristics [8]. Current research in inflammatory breast cancer is focused on identifying molecular targets and predictive biomarkers to enable personalized treatment strategies. Advances in genomic profiling and targeted therapies have opened new perspectives for improving outcomes in this aggressive disease. Breast cancer is a disease in which abnormal cells in the breast grow uncontrollably and form tumors. Cancer cells begin to develop within the milk ducts and/or milk lobules of the mammary gland [6]. Inflammatory breast cancer (IBC) is a rare but extremely aggressive form of cancer, accounting for 1-5% of all cases of invasive breast cancer [1,5]. This disease is characterized by a unique clinical picture, rapid progression and a high mortality rate, which makes it aggressive. The characteristics of this disease require an individualized approach to diagnosis and treatment. Combination treatment (surgery, radiation therapy, hormonal therapy and chemotherapy) is the standard of care for IBC, achieving improved survival compared to two- and three-component treatment [3].

Correct staging of primary Inflammatory breast cancer (IBC) plays a crucial role in developing appropriate treatment strategies for this patient population. In the literature and clinical practice, primary breast cancer (IBC) is currently classified as primary and secondary. The former involves the clinical presentation of breast swelling without the formation of a tumor node, while the latter involves swelling with the presence of a tumor node or diffuse tumor growth [10].

When diagnosing primary and secondary forms of breast cancer, computed tomography (CT) is of particular importance. Differences between primary and secondary infiltrative form breast cancer on computed tomography (CT) are determined by the mechanisms of their development [7].

Below are the differences between primary and secondary TNM breast cancer. We will examine the radiographic features of each form and the key differences. The ambiguity of the current TNM classification for TNM breast cancer has led to the development of an alternative staging system called " Poussee" at the Gustave-Roussy Institute (France). Evolutive (PEV), based on the assessment of signs of inflammation and tumor aggressiveness. Thus, more than a third of patients at the time of diagnosis have PEV3 with swelling and inflammation of the entire mammary gland, and the remaining patients have more localized (less than 50% of the surface) signs of inflammation (PEV2) [2].

Current research is focused on exploring new molecular targets and biomarkers to personalize treatment for ovarian cancer. Next-generation sequencing technologies allow for the identification of genetic abnormalities that can be used to develop individualized therapeutic strategies. Combinations of various treatment modalities, including chemotherapy, targeted therapy, and immunotherapy, are also being explored to achieve a synergistic effect. [9].

Inflammatory breast cancer (IBC) is an aggressive subtype of the disease characterized by rapid progression and a poor prognosis. Despite advances in oncology, treating IBC remains challenging.

Objective of the study: To develop and individualize a treatment strategy for patients with primary and secondary edematous infiltrative forms of breast cancer.

METHODS

This study is a retrospective analysis of 60 consecutive patients with immunohistochemically confirmed primary and secondary edematous-infiltrative breast cancer who received inpatient treatment at the Tashkent City Branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (Uzbekistan) between 2018 and 2022.

Inclusion criteria were: (1) confirmed diagnosis of edematous-infiltrative breast cancer based on clinical, radiological, and immunohistochemical findings; (2) availability of complete medical records; and (3) completion of the planned treatment protocol. Exclusion criteria included: (1) incomplete or missing clinical data; (2) absence of immunohistochemical verification; and (3) loss to follow-up before treatment response evaluation.

Of the 60 patients, 22 had primary inflamatory breast cancer (IBC) of breast cancer, and 38 had secondary inflamatory breast cancer (IBC). The average age was 56-65 years. Immunohistochemical status of the tumor was determined in all cases of primary and secondary infiltrative form breast cancer.

Baseline clinical and disease characteristics were collected for all patients, including primary tumor localization (unilateral/bilateral breast involvement), extent of skin involvement, and presence of regional lymph node metastases. Data on distant metastases were recorded, including the number of involved organs (bone, liver, lung, and others). Information regarding prior treatment, including adjuvant chemotherapy or hormonal

therapy, was also analyzed when available. Molecular tumor characteristics were assessed using immunohistochemistry and included estrogen receptor (ER), progesterone receptor (PR), and HER2/neu status, allowing classification into major molecular subtypes. Treatment outcomes were assessed in each group, and a comparative analysis was conducted between the groups. Statistical data processing was performed using Microsoft spreadsheet software. Excel and the SPSS v.15.0 software package were used. Long-term outcomes were assessed using the Kaplan-Meier method and the p-test. Comparisons of indicators in two parallel groups were conducted using the $\chi 2$ test (or Fisher's exact test) for qualitative and dichotomous variables and the Student's t-test for quantitative variables.

This article provides an analysis of the primary and secondary edematous-infiltrative breast cancer, including a comparative analysis between primary and secondary infiltrative form breast cancer and examines the differences in clinical presentation, diagnosis, and treatment between primary and secondary edematous-infiltrative breast cancer.

Depending on the area breast skin edema (PEV stage) and the treatment performed with both forms of edematous-infiltrative breast cancer, where the results of treatment with a combined therapy regimen including Chemotherapy + Radiation Therapy (CT+RT) and a complex therapy regimen including Chemotherapy + Surgery + Radiation Therapy (CT+Surgery+RT) were compared.

Next, patients with primary and secondary IBC were divided into two groups based on the treatment strategy. The first group included patients who received combination therapy (chemotherapy + surgery + radiation therapy), including 12 patients with primary IBC and 26 patients with secondary IBC. The second group included patients who received combination therapy (chemotherapy + radiation therapy), including 10 patients with primary IBC and 12 patients with secondary IBC.

Patients received chemotherapy in the amount of 8 courses in a neoadjuvant regimen according to 4 types of regimens: AC (Doxorubicin + Cyclophosphamide) 4 courses → TR (Taxanes + Carboplatin) 4 courses, TR 6 courses or TR 12 weekly courses of chemotherapy, AC 4 → T 4 + MCA (Monoclonal antibodies - Trastuzumab), TR 6 or TR 12 eptxt + MCA.

Table 1. Distribution of patients depending on the treatment regimen

Type of treatment	primary IBC (n=22)	%	secondary IBC (n=38)	%
Combination therapy (chemotherapy + radiation therapy)	10	45.5%	12	31.6%
Complex treatment (chemotherapy + surgery + radiation therapy)	12	54.5%	26	68.4%

The area of edema was measured according to the PEV classification for both groups to be able to evaluate the effectiveness of treatment in the future (Table 2).

Table 2. Chemotherapy regimens depending on the degree of PEV.

Treatment regimen	primary IBC (n=22)	%	PEV 2	PEV 3	secondary IBC (n=38)	%	PEV 2	PEV 3
AC 4 → TR 4	4	18.2%	2	2	13	34.2%	8	5
TR 6 / TR 12 weekly	9	40.9%	3	6	10	26.3%	7	3
AC 4 → T 4 + MKA	4	18.2%	2	2	8	21.1%	5	3
TR 6 / TR 12 + MKA	5	22.7%	2	3	7	18.4%	3	

The surgical management of the studied cohort included radical mastectomy and radical breast resection, selected according to the clinical form of the disease and extent of local involvement. In patients with primary inflammatory breast cancer (IBC), surgical treatment was limited exclusively to radical mastectomy. A total of 12 patients in this group underwent this procedure, which was

performed with the intent of achieving maximal local disease control through en bloc removal of the breast, including the affected skin areas, a margin of clinically uninvolved tissue, and regional lymphatic structures. Given the diffuse nature of skin and lymphatic involvement characteristic of primary IBC, breast-conserving or limited resections were considered oncologically inadequate and therefore not performed in this subgroup.

In contrast, a more individualized surgical approach was applied in patients with secondary IBC, reflecting differences in tumor biology and patterns of progression. Among these patients, radical mastectomy was performed in 22 cases, while radical breast resection was carried out in 4 patients. The choice of surgical procedure in the secondary IBC group was determined by factors such as tumor localization, extent of skin involvement, response to neoadjuvant therapy, and overall resectability (Table 3).

Table 3. Characteristics of Surgical Intervention

Type of operation	primary IBC (n=22)	secondary IBC (n=38)
Radical mastectomy	12	22
Radical resection	0	4

All patients subsequently underwent radiation therapy to the mammary gland and areas of regional metastasis, as well as to the postoperative bed with a single focal dose of 2 Gy and a total focal dose of 40-70 Gy.

RESULTS

Treatment response was assessed according to standard clinical criteria and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The overall response rate (ORR) was defined as the sum of CR and PR. Complete response was observed in a subset of patients, as presented in Tables 4 and 5, and was included in the calculation of ORR.

In patients with PEV 2 and PEV 3 skin lesion volume who received complex treatment, the treatment effect, according to standard examination data 6 months IBC ter the course of treatment, was assessed as “complete remission” in 10 patients (50%) and 5 (27.8%) patients, respectively.

Table 4. Clinical Effectiveness of Treatment in Primary versus Secondary Inflammatory Breast Cancer

Complex treatment (chemotherapy + surgery + radiation therapy)					
Form	**n**	**Full effect**	**Partial effect**	**Progression**	**Stabilization**
PIBC	12	3 (25%)	2 (16.7%)	5 (41.6%)	2 (16.7%)
SIBC	26	13 (50%)	10 (38.5%)	1 (3.8%)	2 (7.7%)
Combination therapy (chemotherapy + radiation therapy)					
Form	**n**	**Full effect**	**Partial effect**	**Progression**	**Stabilization**
PIBC	10	6 (60%)	3 (30%)	0 (0%)	1 (10%)
SIBC	12	2 (16.7%)	3 (25%)	4 (33.3%)	3 (25%)

A partial response was achieved in 7 patients (35%) with PEV stage 2 skin involvement and in 6 patients (33.3%) with PEV stage 3. Disease stabilization was observed in 1 patient (5%) with PEV 2 and in 4 patients (22.2%) with PEV 3, whereas disease progression occurred in 2 (10%) and 3 (16.7%) patients, respectively (Table 5). Overall, no marked differences in the initial distribution of treatment response categories were observed between PEV stage 2 and stage 3 groups, suggesting comparable baseline treatment sensitivity.

In patients receiving combination (multimodal) therapy, treatment efficacy was reassessed 6 months after completion of therapy using standard clinical and radiological criteria. Complete remission was achieved in 3 patients (25%) with PEV stage 2 and in 7 patients (70%) with PEV stage 3, indicating a numerically higher complete response rate in the latter group. Partial response was observed in 4 patients (33.3%) with PEV 2 and in 2 patients (20%) with PEV 3, while disease stabilization was documented in 4 (33.3%) and 1 (10%) patient, respectively.

Importantly, disease progression was rare after combination therapy, occurring in only 1 patient (8.4%) with PEV stage 2, whereas no progression events were recorded in patients with PEV stage 3. These findings suggest a favorable disease control profile in both groups, with particularly strong response durability in the PEV 3 cohort.

Although a trend toward higher complete remission rates in PEV stage 3 patients was observed, these differences should be interpreted cautiously due to the limited sample size and lack of formal statistical testing in the present analysis. Further studies with larger cohorts are required to confirm the potential predictive value of PEV stage on treatment response and long-term outcomes.

Table 5. Treatment Efficacy According to PEV Status

Complex Therapy					
PEV	**n**	**Full effect**	**Partial effect**	**Progression**	**Stabilization**
PEV 2	20	10 (50%)	7 (35%)	2 (10%)	1 (5%)
PEV 3	18	5 (27.8%)	6 (33.3%)	3 (16.7%)	4 (22.2%)
Combination Therapy					
PEV	**n**	**Full effect**	**Partial effect**	**Progression**	**Stabilization**
PEV 2	12	3 (25%)	4 (33.3%)	1 (8.4%)	4 (33.3%)
PEV 3	10	7 (70%)	2 (20%)	0 (0%)	1 (10%)

When analyzing survival rates in patients with primary and secondary IBC who received complex and combined treatment, combined treatment was more effective in primary IBC both in terms of relapse-free survival (33 months versus 26 months) and overall survival (36 months versus 29 months). In contrast to complex treatment, which was more effective in secondary IBC with overall survival rates of 36 months versus 31 months. However, it should be noted that relapse-free survival was higher with combined treatment (28 months versus 31 months). All differences have a significance criterion of p=0.05, which indicates a statistically significant difference between the treatment groups (Table 6).

Table 6. Survival Outcomes in Patients with Primary and Secondary Inflammatory Breast Cancer

Form	Type of treatment	n	Relapse-free survival (months)	Overall survival (months)	p
PIBC	Complex	12	26 ± 6.5	29 ± 4.5	0.05
PIBC	Combined	10	33 ± 3.5	36 ± 5.9	0.05
SIBC	Complex	26	31 ± 4.7	36 ± 5.6	0.05
SIBC	Combined	12	28 ± 2.9	31 ± 4.9	0.05

Comparison of the main clinical, morphological and biological characteristics of primary breast cancer (mean age, menstrual status, stage distribution, lesion localization, histological structure of the tumor, degree of tumor differentiation, receptor and HER2/ neu status) did not reveal statistically significant differences between the primary and secondary forms of the disease.

A study of relapse-free survival in patients with edematous-infiltrative forms of breast cancer revealed a significant impact of skin edema volume (PEV) on the effectiveness of various therapeutic strategies. In patients with PEV 2 skin lesion volume, a comprehensive treatment regimen was more effective (OS = 36±8.5 months) than a combination treatment regimen (OS = 31±5.9 months).

In patients with skin lesions grade PEV 3, combination therapy showed better results (OS=36±5.9 months) than combination therapy including surgical treatment (OS=27±5.6 months). (tab 7).

Table 7. Survival Outcomes in Patients with Stage II and III PEV

PEV	Type of treatment	n	Relapse-free survival (months)	Overall survival (months)	p
PEV 2	Complex	9	31 ± 5.9	36 ± 8.5	0.05
PEV 2	Combined	12	28 ± 5.9	31 ± 5.9	0.05
PEV 3	Complex	18	21 ± 1.7	27 ± 5.6	0.05
PEV 3	Combined	10	32 ± 5.9	36 ± 5.9	0.05

Based on the above research results, an algorithm was created for individualizing approaches to the diagnosis and treatment of breast cancer, which will increase the effectiveness of overall and relapse-free survival.

DISCUSSION

A comparative analysis of the principal clinical, morphological, and biological characteristics of primary and secondary inflammatory breast cancer (IBC), along with treatment strategies and survival outcomes, demonstrated statistically significant differences between these groups. These findings underscore the necessity for individualized therapeutic approaches tailored to disease presentation. Management of patients with edematous-infiltrative breast cancer should be guided by disease stage, extent of skin involvement, histopathological features, and immunohistochemical (IHC) profile.

In this context, a comprehensive, multimodal treatment strategy is recommended, incorporating the full spectrum of contemporary breast cancer therapies. In particular, patients with secondary IBC appear to benefit more from combined modality treatment including chemotherapy, surgery, and radiotherapy, whereas in primary IBC, combination therapy consisting of chemotherapy and radiotherapy may be more appropriate.

Safety and tolerability were evaluated based on available clinical documentation. Toxicity was assessed at the patient level, whereby each patient was counted once regardless of the number of adverse events experienced. Owing to the retrospective nature of the study, detailed grading of adverse events and differentiation between individual toxicity episodes were limited, and this should be taken into account when interpreting the safety data.

CONCLUSIONS

The observed treatment outcomes should be interpreted as descriptive findings, as the study design did not include a control group for direct comparison. While the results appear consistent with previously published data on multimodal treatment approaches in inflammatory breast cancer, no definitive conclusions regarding superiority over standard treatment regimens can be made. Further prospective, controlled studies are required to validate these findings. The study allowed us to thoroughly evaluate the significance of complex and combined treatment strategies IBC fecting relapse-free and overall survival in patients with primary and secondary IBC ib breast cancer, which will allow us to refine treatment regimens for both forms of edematous infiltrating breast cancer. IBC ter the complex therapy and complete pathological regression (cPR) was 50% in patients with secondary BC than in patients with primary BC, cPR was 25%. While the combination therapy regimen was statistically more effective with pPR - 60% in patients with primary IBC BC, than in patients with secondary IBC pPR - 16%. Relapse-free survival of patients with edematous-infiltrative forms of breast cancer is determined by the skin surface area volume (PSV). Analysis of survival rates demonstrated that with PEV 2, combination therapy provides a higher median overall survival rate (OS = 36±8.5 months) compared to a combination treatment regimen (OS = 31±5.9 months). At the same time, in patients with PEV 3, the greatest effectiveness was observed with combination therapy (OS = 36±5.9 months), while combination treatment, including surgery, is characterized by lower effectiveness (OS = 27±5.6 months).

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