UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA", BUCHAREST

DOCTORAL SCHOOL

GENERAL SURGERY

SURGICAL DECISION-MAKING FACTORS REGARDING AXILLARY MANAGEMENT IN BREAST CANCER

DOCTORAL THESIS ABSTRACT

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Bucharest

2024

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1. INTRODUCTION

Breast neoplasia is the most common neoplasm in women, representing a major public health problem, with an estimated 1,384,155 new cases worldwide and nearly 459,000 associated deaths. Breast cancer remains a highly topical issue in global oncology, due to its continuously increasing frequency and the severity of its progression in advanced stages of the disease, which are extremely common in our country. From an evolutionary perspective, breast cancer is highly heterogeneous, with some tumors having a slow progression with excellent prognosis, while others are extremely aggressive locally or metastatically. According to the American Cancer Society, one in eight women in the United States will develop breast cancer in their lifetime. Predictions regarding the global incidence of breast cancer in women suggest that the incidence will reach approximately 3.2 million new cases per year by 2050. These figures reflect the magnitude of breast cancer incidence, its impact on women worldwide, and the constant and urgent need for measures in prevention and therapeutic management. Although technological advances have made it possible to detect breast neoplasia in its early stages and the development of medical services has made it possible to initiate appropriate therapy rapidly to prevent the progression of the disease to a metastatic state, all these aspects delineating an optimistic evolution of the outcomes of managing this pathology, there are still several unanswered questions regarding the molecular mechanisms underlying the aggressiveness of certain anatomopathological forms. Epidemiological studies suggest that addressing socio-economic issues is extremely important, so that any patient with breast neoplasm has equal access to medical care from screening to advanced treatment, and only such decisive action can help reduce the global burden of breast cancer. Under these circumstances, we consider that this work should outline the research, emphasizing that the study is conducted in Romania, thus permanently keeping in mind the social, economic specifics, health plans - late diagnosis, difficult access to pathology laboratories, oncology committees, and ultimately to what constitutes proper therapeutic management.

Epidemiology of Breast Neoplasia

The mammary gland, subjected to dynamic processes at different stages of a woman's life, is influenced by complex interactions among growth factors, cytokines, and hormones that regulate the cell life cycle. These factors, essential for the physiological development of mammary cells, are also present in mammary tumor cells, playing a crucial role in mammary oncogenesis. Metastatic dissemination occurs through both venous circulation and the lymphatic system, underscoring the importance of understanding the dissemination pathways and the groups of lymph nodes involved for clinical evaluation and patient prognosis.

Surgical Treatment of Breast Cancer

The therapeutic approach to breast cancer requires a multidisciplinary strategy, taking into account the evolutionary stage of the disease, age, biological status of the patient, prognosis, and histopathological type of the tumor. Radical mastectomies, though historically used for disease control, have largely been replaced by conservative treatment and sentinel lymph node biopsy, preferred for their reduced impact on patients' quality of life and effectiveness in disease control. Neoadjuvant treatment is also a key component, allowing for conservative treatment by reducing tumor volume.

Current Axillary Management in Breast Cancer

Axillary management has undergone significant transformations, evolving from complete axillary lymph node dissection to adopting sentinel lymph node biopsy as the gold standard, due to its low morbidity rate and minimal impact on quality of life. Sentinel lymph node identification is achieved through advanced techniques, including the use of vital dyes, radioactive tracers, and indocyanine fluorescence, providing high accuracy in metastasis detection. The therapeutic strategy is adapted according to the sentinel lymph node status, reducing the need for invasive surgical interventions in select cases. Additionally, axillary management in elderly patients is approached with caution, with axillary staging becoming optional when it does not influence adjuvant therapeutic decision-making, highlighting a trend towards treatment individualization and intervention minimization.

This evolution towards minimally invasive and individualized surgery, within the context of multidisciplinary collaboration, marks a paradigm shift in the approach to breast cancer, aiming to optimize therapeutic outcomes and improve patients' quality of life.

2.AIM AND OBJECTIVES

The aim of this study is to analyze the evolution of breast cancer patients from the perspective of axillary lymph node invasion.

The primary objective of the research is to evaluate the characteristics of breast cancer patients in accordance with axillary lymph node invasion. In addition to the primary objective of the study, the following specific research objectives have been formulated through the comprehensive analysis of a cohort of patients diagnosed with breast cancer:

1. Establishing the research cohort by identifying and recording the main clinical, biological, imaging, and histopathological parameters.
2. What are the predictive factors of axillary invasion in breast cancer?
3. Can factors be identified to prevent unnecessary lymphadenectomy?
4. Evaluating the implications of axillary invasion on the overall progression of mammary neoplastic disease.

3. STUDY METHODOLOGY

Based on the aim and objectives of the research, the design and methodology of the study were defined, with its main characteristics being: **Retrospective** - data were collected from November 1, 2020, to June 1, 2022, for patients hospitalized over an 8-year period - January 1, 2014, to December 31, 2021, Unicentric - including patients hospitalized and operated on in the Clinic of General and Emergency Surgery III of the Bucharest Emergency University Hospital, Descriptive and correlational Non-interventional.

Eligibility criteria for inclusion in the study cohort were: Diagnosis of breast cancer, Female sex, Stage IIA-IIIB, Single tumor, excluding multifocal, bilateral cases, Presence of all necessary data, Age > 18 years, Present axillary management, Absence of distant metastases (M0). Study Cohorts Based on the management and histopathological outcome of axillary evidence, patients included in the research were grouped into 5 study cohorts as follows:

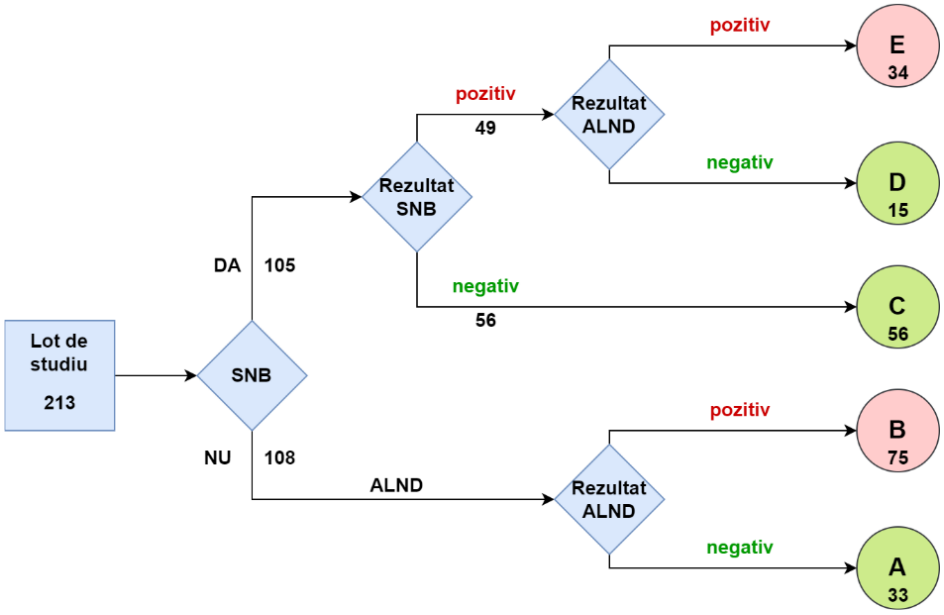

Figure no. 1 - Description of Study Cohorts

4.RESULTS

Demographic Data

The age of the patients included in the research varied between 23 and 89 years, with a mean value of 57.41 years and a standard deviation of 13.49 years. The distribution of cases highlights a maximum number of cases in the 50-60 age range - 68 cases, representing 31.92%. From the comparative evaluation of the statistical data in relation to the study cohort, we observe a mean value with the lowest value in group C - 52.37 ± 13.66 years, followed by groups B and D, with a roughly equal average around the value of 57.3 years.

Preoperative Tumor Formation Evaluation

The clinical and imaging evaluation of tumor formations involved a series of characteristics, among which we present statistically the localization of the tumor formation in relation to the quadrant and tumor size (mm).

The predominant localization of tumor formations was at the level of the supero-external quadrant - 113 cases, representing 53.05%, while the rarest localization was in the infero-internal quadrant - 19 cases, representing 8.92% (Table no. XXXVIII and Figure no. 36).

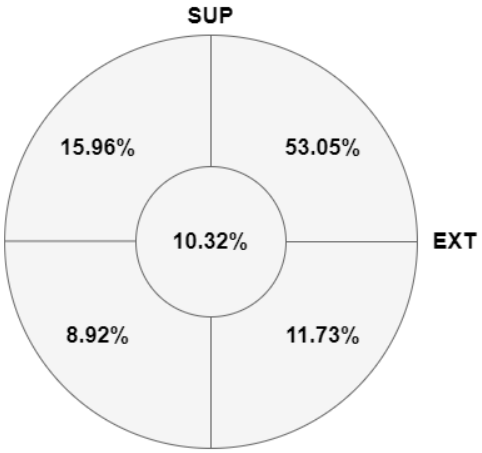

Figure no. 2 - Distribution of cases according to the localization of the tumor formation - schematic representation

Figure no. 37 and Table no. XXXIX highlight a different distribution of the localization of tumor formations in relation to the study group, with a maximum number of cases with central localization in group A - 18.82%, with localization at the SE quadrant level in group D - 80%, with localization at the SI quadrant level in group C - 35.29%, with localization at the IE quadrant level in group B - 40%, and with localization at the II quadrant level in group A - 36.84%.

The size of the tumor formation, evaluated preoperatively both clinically and imaging-wise, varied between 1 and 69 mm with a median value of 21 mm (Table no. XL). The distribution of cases presented in Figure no. 38 highlights a decrease in cases with increasing size, with most cases being diagnosed at sizes under 3 cm.

	Dimension				
	A	B	C	D	E
Valid	33	75	56	15	34
Missing	0	0	0	0	0
Mean	27.333	29.960	17.054	12.533	21.235
Median	25.000	29.000	11.000	12.000	18.000
Std. Deviation	16.224	14.833	13.548	11.154	14.078
Minimum	5.000	4.000	2.000	1.000	4.000
Maximum	61.000	69.000	65.000	47.000	58.000

Table no. I - Statistical data regarding the size of the tumor formation in the five groups (mm)

Operator Protocol

The interventions used in the local surgical management of the patients included in the research consisted of lumpectomy - 99 cases, representing 46.47%, and mastectomy - 114 cases, representing 53.52% (Table no. XLII). It should be noted that our study was retrospective, so it did not influence in any way the choice of surgical technique.

		GROUP					
Type of surgery		A	B	C	D	E	Total
Limited resection	**Count**	14.000	7.000	45.000	11.000	22.000	99.000
	% within row	14.141 %	7.071 %	45.455 %	11.111 %	22.222 %	100.000 %
	% within column	42.424 %	9.333 %	80.357 %	73.333 %	64.706 %	46.479 %

		GROUP					
Type of surgery		A	B	C	D	E	Total
Mastectomy	**Count**	19.000	68.000	11.000	4.000	12.000	114.000
	% within row	16.667 %	59.649 %	9.649 %	3.509 %	10.526 %	100.000 %
	% within column	57.576 %	90.667 %	19.643 %	26.667 %	35.294 %	53.521 %
Total	**Count**	33.000	75.000	56.000	15.000	34.000	213.000
	% within row	15.493 %	35.211 %	26.291 %	7.042 %	15.962 %	100.000 %
	% within column	100.000 %	100.000 %	100.000 %	100.000 %	100.000 %	100.000 %

Table no. II - Distribution of cases according to the surgical intervention performed in the five groups

The sentinel lymph node technique was used in 96 cases, representing 45.07%, of which 40 cases, representing 41.67%, had a positive intraoperative histopathological result, necessitating axillary lymphadenectomy (Tables no. XLIV and XLV).

SNB_rez	Frequency	Percent	Valid Percent	Cumulative Percent
0	56	58.333	58.333	58.333
1	40	41.667	41.667	100.000
Missing	0	0.000		
Total	96	100.000		

Tabelul nr. III - Distribuția cazurilor în raport cu rezultatul evaluării histopatologice a ganglionului santinelă

Axillary lymphadenectomy was performed in a total of 148 cases, representing 69.48% of the total, of which in 56 cases, representing 37.83%, it was necessitated by the positive histopathological result of the sentinel lymph node, while in the rest it was performed primarily. The result of lymphadenectomy was positive in 100 cases, representing 46.94% (Tables no. XLVI and XLVII).

Outcome From the perspective of distant survival, a total of 42 cases, representing 19.71%, had deceased at the time of data collection for the study (Table no. LXI). The highest mortality was recorded in group B - 23 cases, representing 30.66%, followed by group E - 10 cases, representing 29.41% (Table no. LXII).

GROUP	DEATH	Frequency	Percent	Valid Percent	Cumulative Percent
A	0	29	87.879	87.879	87.879
	1	4	12.121	12.121	100.000
	Total	**33**	**100.000**		
B	0	52	69.333	69.333	69.333
	1	23	30.667	30.667	100.000
	Total	**75**	**100.000**		
C	0	53	94.643	94.643	94.643
	1	3	5.357	5.357	100.000
	Total	**56**	**100.000**		
D	0	13	86.667	86.667	86.667
	1	2	13.333	13.333	100.000
	Total	**15**	**100.000**		
E	0	24	70.588	70.588	70.588
	1	10	29.412	29.412	100.000
	Total	**34**	**100.000**		

Table no. IV - Distribution of patients according to distant survival in the five groups

CORELATIONS

The correlational statistical analysis was divided into 3 working hypotheses that targeted different comparisons among the 5 study groups, as follows (Table no. LXIII):

Hypothesis 1 - What are the risk factors for axillary lymph node dissemination in breast cancer patients? (BE vs. ACD)

Hypothesis 2 - Are there elements indicating the limitation of axillary lymphadenectomy extension in patients with positive sentinel lymph nodes? (D vs. E)

Hypothesis 3 - What are the factors that influenced mortality?

	GROUPS		TOTAL
Hypothesis 1	ACD	BE	
Number of patients	104	109	213
Hypothesis 2	D	E	
Number of patients	15	34	49
Hypothesis 3			
Number of patients	Mortality assessment		213

Table no. V - Synthesis of Evaluated Hypotheses

Hypothesis 1

The first hypothesis proposed analyzes the differences between patients in groups ACD versus patients in groups BE, the two resulting cohorts practically being patients with present axillary invasion (histopathologically proven, N1 or N2) - 109 cases, representing 51.17%, respectively patients without invasion (negative sentinel lymph node or negative lymphadenectomy, N0) - 104 cases, representing 48.82%.

The age of patients in the group with axillary lymph node invasion was higher by 3.47 years compared to the group without invasion, but this observation did not present significant statistical significance - p=0.06 (Table no. LXIV and Figure no. 53).

Among the tumor markers analyzed, carcinoembryonic antigen and CA 15-3 demonstrated a slightly higher mean value in patients with axillary invasion, with moderate statistical significance p=0.046, respectively p=0.028 (Table no. LXV and Figure no. 54).

The evaluation of cases from the perspective of the primary tumor formation's location highlights a predominance of localization in the Supero-External and Infero-External quadrants in patients with axillary lymph node invasion, the calculated risk being 4 times higher for these locations - p<0.001 (Figure no. 55 and Tables LXVI and LXVII).

Tumor size was another parameter correlated with the presence of axillary invasion in the patients included in the study; in these cases, the mean maximum tumor diameter was 3.66 mm larger compared to those with negative axillary histopathologic results (Table no. LXVIII and Figure no. 56).

From a histopathological point of view, immunohistochemical evaluation highlighted that the presence of estrogen and progesterone receptors represents positive predictive factors (OR:0.33 p<0.001, respectively OR:0.53 p=0.028), while the presence of HER2 represents a negative predictive factor (OR: 2.59 p=0.003) (Tables LXIX - LXXI).

Regarding molecular classification based on immunohistochemical data, the Luminal A subtype was correlated with the absence of axillary invasion (OR: 0.34 p<0.001), HER2 and Triple-negative subtypes with the presence of invasion (OR: 6.2 p<0.001, respectively OR: 2.69 p=0.026), while the Luminal B subtype did not demonstrate significant statistical significance (p=0.534) (Tables LXXII - LXXV).

Hypothesis 2

The second hypothesis considers patients who underwent the sentinel lymph node technique and obtained a positive result. In this situation, studies show that up to 1/3 of cases present a negative result of axillary lymphadenectomy. To evaluate the risk factors for axillary positivity, we comparatively analyzed group E - positive result of axillary lymphadenectomy (34 cases) and group D - negative result of axillary lymphadenectomy (15 cases).

The age of the patients did not statistically correlate with the presence of axillary invasion in patients with positive sentinel lymph node, even though there was a mean difference of 5.85 years - p=0.175 (Table nr. LXXVI and Figure nr. 57).

The body mass index value calculated for the two groups was higher in patients with axillary invasion, with a difference of 3.58, showing moderate statistical significance - p=0.05 (Table nr. LXXVII and Figure nr. 58).

Evaluation of routine biological analysis values collected at admission comparatively showed relatively small differences between the groups discussed in this hypothesis. The only parameter that demonstrated moderate statistical significance was the number of leukocytes, with a mean difference of 1.44, p=0.065 (Table nr. LXXVIII and Figure nr. 59). Tumor markers did not show statistically significant differences.

The location of the tumor formation did not correlate with the degree or extent of axillary invasion, even though there were differences in the distribution of cases based on this parameter; the statistical significance was not relevant (Tables nr. LXXIX and LXXX).

Regarding the assessment of hormonal receptor presence in the immunohistochemical evaluation of breast resection specimens, only estrogen receptors represented a risk factor for axillary invasion beyond the sentinel lymph node, with a calculated risk of 7.33 times and a statistical significance of p=0.005 (Tables nr. LXXXII-LXXXIV).

From the perspective of molecular subtypes, classification into Luminal A, Luminal B, and Triple-negative did not show a statistical correlation with the presence of axillary lymph node invasion in patients with positive sentinel lymph node. In the case of the HER2 subtype, the risk of axillary invasion was nearly 10 times higher - p=0.084 (Tables nr. LXXXV – LXXXVIII).

Hypothesis 3

The third hypothesis aimed to identify negative prognostic elements associated with increased mortality. We present only succinctly the parameters that demonstrated moderate or high statistical significance.

Among the preoperative laboratory analyses collected, elevated levels of tumor markers ACE and CA 15-3 were correlated with increased mortality. The mean difference for the group of deceased patients compared to those alive was 1.25 ng/dl ($p=0.003$) for ACE and 9.54 ($p=0.012$) for CA 15-3 (Table nr. LXXXIX and Figure nr. 62).

Tumor size presented higher values in cases of deceased patients at the time of data collection - 22.63 ± 15.20 mm compared to 27.23 ± 16.35 mm, $p=0.085$ (Table nr. XC and Figure nr. 63).

Lymph node invasion significantly influenced mortality, with a percentage of 7.86% in stage N0, increasing to 59.25% in stage N3 - $p<0.001$ (Table nr. XCI).

Among the immunohistochemical evaluation elements considered in our study, the presence of ER and PR were predictive factors (OR: 0.12, $p<0.001$, and OR: 0.27, $p<0.001$, respectively), while the presence of HER2 negatively influenced prognosis (OR: 2.37, $p=0.02$) (Tables nr. XCII -XCIV).

Among the four molecular subtypes in which cases were categorized according to histopathological results, Luminal A represented a protective factor (OR: 0.06, $p<0.01$), while HER2 and Triple-negative represented risk factors (OR: 3.20, $p=0.007$, and OR: 12.07, $p<0.001$, respectively), with Luminal B not showing statistical significance ($p=0.557$).

5.Discussion

The study cohort consisting of 213 patients was divided into five subgroups based on the results of sentinel lymph node biopsy (SNB) and axillary lymph node dissection (ALND). Out of the 213 patients, 105 underwent SNB, and among them, 49 had positive results requiring subsequent ALND. These represent Group E (34 cases with positive ALND results) and Group D (15 cases with negative ALND results).

Positive SNB results indicated an increased necessity for ALND. Interestingly, even within the negative SNB group (Group C, 56 cases), the subsequent disease progression and treatment were not negatively influenced, suggesting that SNB could be a reliable indicator for avoiding unnecessary ALND. In contrast, 108 patients did not benefit from initial SNB and underwent ALND directly, of which 75 (Group B) had positive ALND results and 33 (Group A) had negative results.

An important point of discussion is the potential to avoid unnecessary lymphadenectomy. We observe that a significant number of patients from the negative SNB group (Group C) and negative ALND group (Group A) could benefit from less invasive therapeutic approaches.

These findings necessitate a detailed analysis of management strategies for different age groups. In particular, the possibility that younger patients, such as those in Group C, may benefit from a different protocol regarding investigations for axillary metastases compared to older ones, from Group E, should be considered.

There is evidence in the literature suggesting that early menarche may increase the risk of breast cancer. Early onset of menstruation may indicate prolonged exposure to female sex hormones, which is a known risk factor for breast cancer. In our study, the average age for menarche was 12.95 years, which falls within the normal range but is close to its lower limit, indicating the need for careful monitoring of this cohort regarding the risk of breast cancer.

In our study, the first hypothesis investigated the risk factors for axillary lymph node dissemination in breast cancer patients, comparing Groups ACD (104 patients) and BE (109 patients), totaling 213 patients. The discussion focuses on identifying variables such as tumor size, histological grade, hormonal receptor status, and HER2 status in cancer spread to lymph nodes. The results could reflect the literature's findings and provide valuable insights into optimizing treatment

strategies for breast cancer patients. current suggesting that tumor size and degree of invasion are among the most important predictors for lymph node metastases, which can contribute to defining a risk profile for these patients.

The second hypothesis explored the possibility of limiting the extent of axillary lymphadenectomy in patients with positive sentinel lymph nodes, by analyzing 49 patients from Groups D (15 patients) and E (34 patients). This analysis is particularly relevant in the context of debates in the literature about the role of axillary lymphadenectomy and the potential morbidity associated with extensive procedures. The discussion revolves around the possibility of adapting the surgical approach based on tumor characteristics, such as response to neoadjuvant chemotherapy.

To evaluate the elements influencing mortality, the third hypothesis included the entire study sample of 213 patients. Here, the analysis included a wide range of potential factors that can influence survival, from patient age, disease stage, type of treatment, and comorbidities, to socioeconomic factors and social support. This part of the discussion underscores the need to understand how the interaction between clinical and social factors contributes to health outcomes and survival.

Therefore, our study aims to contribute to the existing body of knowledge by contextualizing the risk factors for lymph node metastases, the necessity and extension of surgical procedures in breast cancer management, and the complexity of influences on mortality. Despite its contributions, the study acknowledges its limitations, including sample size and demographic peculiarities, which may affect the generalizability of the results. These findings highlight the importance of future research to refine the understanding and approach to breast cancer.

Our initial hypothesis suggested that the presence of estrogen receptor (ER) and progesterone receptor (PR) hormone receptors is a positive predictor of treatment response and survival in breast cancer, while HER2 overexpression portends an unfavorable prognosis. The data obtained from our study provide substantial support for this hypothesis, demonstrating a significant correlation between the presence of hormone receptors and an increased likelihood of favorable clinical outcomes.

The findings showed that patients with positive ER expression have an adjusted Odds Ratio (OR) of 0.33 ($p < 0.001$), indicating a reduction of over three times in the risk of disease progression or death compared to ER-negative patients. This observation corroborates with previous studies that have recognized ER receptors

as significant indicators of better clinical outcomes and have supported the effectiveness of endocrine therapy in this patient population.

6. CONCLUSIONS

1. The local management of breast neoplasms focuses on two essential components: the mammary tumor formation and axillary control. While tumor management is relatively well-defined, the approach to axillary adenopathy continues to generate controversy regarding indications and intervention extent, with significant implications for patient survival and quality of life.
2. Axillary management approach requires a comprehensive integration of data from preoperative investigations, including clinical, imaging, histopathological evaluations, as well as relevant epidemiological information for breast cancer.
3. The main dilemma in axillary management lies in avoiding both overtreatment and undertreatment. Unjustified axillary lymphadenectomy, based even on sentinel lymph node biopsy (SLNB) results, persists as an issue, suggesting the need for additional criteria, such as evaluating the degree of lymph node invasion. Avoiding axillary lymphadenectomy can result from a negative SLNB, either real or due to an incorrectly performed procedure, emphasizing the importance of mastering and correctly applying this technique.
4. Risk factors associated with lymph node dissemination in the study included: tumor localization in the outer quadrants of the breast, increased tumor size, presence of estrogen receptors, and HER2 positive molecular subtype.
5. Prognostic elements indicative of extensive lymph node dissemination in patients with positive sentinel lymph nodes were identified as leukocyte count, tumor size, and negative estrogen receptor status.
6. Negative prognostic factors associated with mortality in the study were local tumor extension, number of affected lymph nodes, and lack of estrogen and progesterone receptors.
7. The implementation of the sentinel lymph node technique was once considered the final frontier in axillary management; however, like in other cases, this method has revealed its limitations and disadvantages over time, requiring reassessment. This study aims to modestly contribute to this discussion. Although SLNB remains a fundamental tool, it is not exclusive or absolute in therapeutic decisions.

7. RESEARCH CONTRIBUTIONS

The study brings several significant contributions to the field of breast cancer management, focusing on detailed aspects of tumor localization, lymph node involvement, and implications of different diagnostic and therapeutic approaches. Clarifications Regarding Axillary Management: The research provides insights into breast neoplasm management, emphasizing the dual components of management: concerning the tumor formation and axillary control. Comprehensive Approach in Management: It underscores the need for comprehensive integration of data from preoperative investigations, including clinical, imaging, histopathological evaluations, and relevant epidemiological information, to refine management strategies for breast cancer. Balancing Overtreatment and Undertreatment: The study contributes to the debate on avoiding overtreatment and undertreatment in axillary management. It suggests the need for additional criteria, such as evaluating the degree of lymph node invasion, to effectively guide the decision-making process. Identification of Risk Factors: The research identifies risk and protective factors associated with lymph node dissemination. Negative Prognostic Factors Associated with Mortality: It highlights local tumor extension, number of affected lymph nodes, and lack of estrogen and progesterone receptors as negative prognostic factors associated with mortality in the study. Reassessment of Sentinel Lymph Node Technique: The study contributes to the ongoing discussion regarding the role of the sentinel lymph node technique in axillary management. It acknowledges the limitations and disadvantages revealed over time, advocating for a reassessment and balanced view of its application in therapeutic decisions. By addressing these aspects, the study aims to refine the understanding and approach to breast cancer management, emphasizing the importance of personalized strategies based on individual risk profiles and diagnostic results. It acknowledges the complexity of breast cancer as a multifaceted disease, requiring ongoing research and adaptation of management practices.

8. STUDY LIMITATIONS

While our research provides current contributions to the field of breast cancer management, it is important to acknowledge certain limitations that may influence the interpretation and scalability of the results:

Small Number of Patients: One significant limitation of the study is the relatively small number of included patients. This restriction limits the statistical power of the analysis and may affect the ability to extrapolate the results to the general population.

Evaluation of Long-Term Mortality: Another important limitation is the inability to evaluate 5-year mortality for all cases due to the inclusion of patients up to one year prior to statistical analysis. This restriction affects the ability to assess long-term survival and the effectiveness of different therapeutic approaches.

Demographic Diversity and Socioeconomic Factors: The study did not deeply address the impact of demographic diversity and socioeconomic factors on breast cancer management and outcomes. These factors may play a significant role in access to care, treatment adherence, and ultimately, patient prognosis.

Need for Further Research: The study underscores the need for further research in this field to confirm and extend current findings. Additional research with larger samples and varied methodologies is essential to strengthen understanding of risk factors, pathophysiological mechanisms, and optimization of therapeutic strategies.

By acknowledging these limitations, we aim to encourage the development of future studies that address these challenges, thereby contributing to the continuous improvement of care for patients with breast cancer.

9. FUTURE RESEARCH DIRECTIONS

Acknowledging the limitations of the present study paves the way for numerous promising directions for future research, which could significantly contribute to optimizing the management of breast cancer. Below are some of these directions proposed:

Studies with Larger Samples: To strengthen current findings and improve the scalability of results, further studies with larger patient samples are needed. This would allow for a more detailed analysis of patient subgroups and the effects of specific treatments.

Longitudinal Research: Implementing longitudinal studies that follow patients over the long term would provide valuable data on survival, recurrence, and long-term effects of different therapeutic approaches.

Analysis of Socioeconomic Factors: It is essential to conduct studies that explore the impact of socioeconomic and demographic factors on access to care, treatment adherence, and clinical outcomes, in order to identify and address disparities in breast cancer care.

Evaluation of Biological Diversity Impact: In-depth exploration of how the biological and molecular diversity of breast tumors influences treatment response and prognosis, to further personalize therapeutic approaches.

Innovative Techniques in Diagnosis and Treatment: Research should continue to explore and evaluate innovative techniques in the diagnosis and treatment of breast cancer, including targeted therapies, immunotherapy, and the use of emerging technologies such as artificial intelligence in predicting disease progression and treatment response.

Impact of Lifestyle Factors: Studies investigating in detail the impact of lifestyle factors such as diet, physical activity, and environmental exposures on the risk of developing and progressing breast cancer.

Optimization of Screening Strategies: Developing and evaluating more efficient and personalized screening strategies based on individual risk and biological characteristics of the tumor, to improve early detection and reduce the incidence of advanced disease stages.

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