RESULTS OF TREATMENT FOR PAGET'S DISEASE OF THE BREAST AT THE NATIONAL CANCER HOSPITAL IN VIETNAM

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ABSTRACT

Objectives: To describe the clinical and subclinical characteristics of patients with Paget's disease of the breast at The National Cancer Hospital and to evaluate the treatment outcomes of Paget's disease of the breast.

Materials and methods: 46 patients were diagnosed and treated for Paget's disease of the breast in the Breast Surgery Department of The National Cancer Hospital from 2016 to 2020.

Results: The average age was 60.6 ± 10.8. The common symptoms were nipple pain (76.1%) and nipple ulceration (65.2%). Paget's disease with invasive ductal carcinoma accounted for 37.0%, and Paget's disease with intraductal carcinoma accounted for 28.2%. The proportions of breast cancer stages 0, 1, 2, and 3 were 63.0%, 23.9%, 8.7%, and 4.4%, respectively. The proportions of total mastectomy and breast-conserving surgery were 97.8% and 2.2%, respectively. The 5-year overall survival and disease-free survival rates were 91.3% and 84.8%, respectively.

Conclusions: A high proportion of Paget's disease of the breast cases are associated with underlying ductal carcinoma. Surgical treatment of Paget's disease has achieved positive outcomes in terms of overall survival and disease-free survival.

Keywords: *Paget's disease of the breast, National Cancer Hospital.*

1. INTRODUCTION

Paget's breast is a rare cancer, accounting for 1 - 4.3% of all breast cancer cases. According to GLOBOCAN 2020, breast cancer is the most common cancer and the leading cause of cancer death in women worldwide, with approximately 2.26 million women newly diagnosed and 684,996 cases of death each year.[1,2]

The pathogenesis of the disease is not clear, and two theories are currently proposed. The epithelial theory suggests that Paget cells arising from a breast carcinoma migrate along the milk ducts, through the basement membrane, into the nipple and areola. The transformation theory holds that nipple epidermal keratinocytes transform into malignant.

Paget cells, representing a carcinoma in situ independent of any lateral ductal carcinoma

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developing below. The epithelial theory is more widely accepted due to the ability to demonstrate involvement of the milk ducts below the nipple in many pathophysiological sections.[3]

Approximately 80 - 90% of patients with Paget's disease of the breast are associated with an underlying carcinoma. Therefore, the diagnosis and treatment of Paget's disease are closely linked to the diagnosis and treatment of associated breast cancer. The presence of Paget's disease does not alter the stage of the associated breast cancer. Clinical symptoms and histopathological images of Paget's disease can be easily confused with common dermatological diseases, making it challenging to confirm the diagnosis and leading to a prolonged course of the disease before proper treatment.[4,5]

In Vietnam, there are very few studies on Paget's disease of the breast. To contribute to improving the diagnosis and treatment of Paget's disease, we conducted a study to evaluate the treatment outcomes for Paget's disease of the breast at The National Cancer Hospital. The aim is to describe some characteristics of patients with Paget's breast disease and evaluate the treatment outcomes at The National Cancer Hospital.

2. MATERIALS AND METHODS

Study design

The research method is cross-sectional, descriptive, and involves both retrospective and prospective components.

Subjects

From January 2016 to December 2020, 46 patients diagnosed with and treated for Paget's breast at The National Cancer Hospital were included in the study. Inclusion criteria involved patients diagnosed with Paget's breast alone or in combination with other conditions. Patients with histopathology indicating Paget's mammary gland, in good overall condition (with an index from 0 - 2 according to the ECOG scale), possessing full archived records, and providing complete information about their disease status were eligible. Exclusion criteria encompassed patients with severe chronic diseases contraindicating surgery, those with other cancerous diseases, individuals who underwent tumor removal surgery at another medical department prior to The National Cancer Hospital surgery, and patients declining to continue adjuvant treatment after surgery.

Procedures

The research procedure involved the review of medical records and conducting clinical examinations through direct patient interviews or phone conversations with the patient and their family. The research variables and indices included clinical features such as age, medical history, reasons for admission, progression timeline, lesion location, and the presence of functional or organic symptoms. Paraclinical features were assessed through breast ultrasound, mammography, cytology, histopathology, and immunohistochemistry. Additionally, the study examined treatment methods, complications, recurrence and metastasis rates, and survival time.

Statistical analysis

The data were encrypted and analyzed using the statistical algorithm with SPSS 20.0. The T-test and the Chi-square test were employed to compare the difference between means and prevalence. The difference was considered statistically significant at $p < 0.05$.

Ethical approval

The study was approved by the Ethical Review Board of the The National Cancer Hospital, Vietnam, and written informed consent was obtained from all subjects before their enrollment in the study.

3. RESULTS

3.1. Clinicopathological characteristics

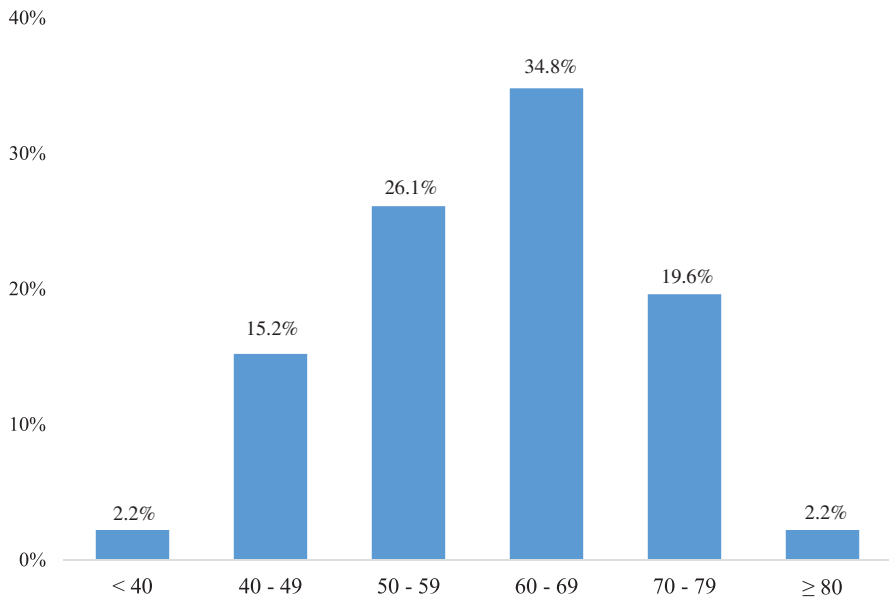

Figure 1. Age distribution of patients

The patients had an average age of 60.6 ± 10.8 years, ranging from 35 to 84 years. The majority of patients, accounting for 54.5%, were 60 years or older (as shown in Figure 1).

Table 1. Characteristics of Paget's lesions

Characteristics		n	%
Physical symptoms	Ulcer of niple/ areola/ skin	45	97.8
	Rash of niple/ areola/ skin	16	34.8
	Thick skin, scrabs of niple/areola	13	28.3
	Flat/dropping nipple	4	8.7
	Nipple discharge	3	6.5
	Palpable mass of breast	18	39.1
	Enlarged axillary lymph nodes	9	19.6

Characteristics		n	%
Position	Right breast	22	47.8
	Left breast	24	52.2
Part of breast	Nipple	46	100
	Areola	12	26.1
	Skin	1	2.2
Measurements	< 1cm	20	43.4
	1 - 3cm	21	45.7
	> 3cm	5	10.9

Among the patients, 97.8% exhibited ulcers in the nipple/areola/breast skin. Breast cancer examinations and subsequent detection were observed in 39.1% of cases. Approximately 19.6% of patients presented with accompanying axillary lymph nodes. The incidence of lesions was similar in both the left and right breasts, with none of the patients showing lesions in both breasts. Nipple lesions were observed in 100% of patients, while only 2.2% had lesions appearing in the breast skin. The majority of lesions were 3cm or less in size (as shown in Table 1).

Table 2. Characteristics of associated breast tumors on ultrasound and mammography

Images of ultrasound and mammography		n	%
Features of breast tumors on ultrasound			
Accompanying breast tumor	Yes	23	50.0
	No	23	50.0
Number of breast tumors (n = 23)	1	16	69.6
	≥ 2	7	30.4
Breast tumor size on ultrasound (n = 23)	< 1cm	6	26.1
	1 - 3cm	14	60.9
	> 3cm	3	13.0
Features of breast tumors on mamography			
Yes		24	52.2
No		22	47.8

Half of the patients diagnosed with Paget's breast cancer had breast tumors detected on ultrasound images. The majority, comprising 69.6%, exhibited one associated breast tumor. Additionally, 52.2% of patients displayed abnormal lesions on mammography (as shown in Table 2).

Table 3. Histopathological results and disease stage

Classification		n	%
Pathology	Paget alone	16	34.8
	Paget and intraductal carcinoma	13	28.2
	Paget and invasive carcinoma	17	37.0
Staging	0	29	63.0
	1	11	23.9
	2	4	8.7
	3	2	4.4
	4	0	0

The highest rate, at 37.0%, was observed in cases of Paget with invasive breast cancer. The majority of patients were in stage 0 and stage 1 of breast cancer, with rates of 63.0% and 23.9%, respectively (as shown in Table 3).

3.2. Treatment outcome

Table 4. Treatment methods

Treatment methods	n	%
Surgery alone	30	65.2
Surgery followed by chemotherapy	11	23.9
Surgery followed by endocrine therapy	2	4.4
Surgery followed by radiotherapy and endocrine therapy	1	2.2
Surgery followed by chemotherapy and radiotherapy	2	4.4

The majority of patients, totaling 65.2%, required only surgery (as shown in Table 4).

Table 5. Surgical methods

Surgical methods	n	%
Simple mastectomy	15	32.6
Mastectomy and axillary lymph node dissection	30	65.2
Conservative surgery	1	2.2

The majority, comprising 65.2%, underwent mastectomy alone, while one case, accounting for 2.2%, opted for breast-conserving surgery (as shown in Table 5).

Table 6. Metastatic or recurrence event

Metastatic or recurrence event	n	%
Local recurence	1	2.2
Lung metastasis	3	6.5
Lung and brain metastases	1	2.2
Bone and lung metastases	1	2.2
Distal metastases	5	10.9
Local and distal metastases	6	13.1

The majority of patients, at 89.1%, showed no signs of distant metastases. Among those with recurrent metastases, the lungs were the most common site (as shown in Table 6).

Table 7. Total survival time at time points

Time points	One year	Two years	Three years	Four years	Five years
n	45	44	43	43	42
%	97,8	95,7	93,5	93,5	91.3

The study subjects demonstrated a 5-year survival rate of 91.3% after treatment (as shown in Table 7).

4. DISCUSSION

The results of our study on 46 patients with Paget's breast disease revealed an average age of 60.6 ± 10.8 years, ranging from 35 to 84 years, with the majority (82.7%) aged 50 years or older. This aligns with findings from various global studies, indicating that Paget's disease commonly occurs in individuals aged 50 or older.

All patients in our study presented clinical symptoms when seeking medical attention, with 97.8% showing ulcerative lesions in the breast, 34.8% exhibiting red skin lesions, and 28.3% presenting with thickened, scaly skin. However, these results differ from studies by Naser Tayyebi Meibodi[4] possibly due to variations in the characteristics of the study populations and locations. In developed countries, proactive screening for breast cancer risk factors often leads to the earlier detection of Paget's disease.

Regarding lesion distribution, in our study, 52.2% of patients had Paget lesions on the left breast, 47.8% on the right breast, and none on both breasts. This contrasts with studies suggesting that Paget's disease typically involves a solitary lesion in one breast, with no significant difference in incidence between the left and right sides.[5]

Notably, all patients in our study presented with nipple lesions, while 26.1% had areola lesions, and only 2.2% exhibited lesions in the breast skin. These findings align with other literature indicating that Paget's lesions primarily manifest in the nipple and areola, rather than the breast skin.[6]

In our study, most of the lesions were 3 cm or less in size, in which the proportion of lesions < 1cm in size accounted for 43.4% and only 10.9% of patients had lesion size > 3 cm, the smallest is 0.3 cm and the largest is 5 cm. The size of the lesions in our study was much smaller, possibly reflecting improved screening and early disease detection.

Breast ultrasound in our study detected associated breast tumors in 50% of patients, with 30.4% having 2 or more breast tumors. While nonspecific, ultrasound and mammography proved important in detecting associated lesions.

In terms of disease characterization, 34.8% of patients in our study had Paget alone, while 65.2% had carcinoma, with 37% being invasive and 28.2% intraductal. These rates differ from some international studies, possibly due to sample size variations.[7]

In the study, 63.0% of patients were evaluated for breast cancer at stage 0. The rate of patients in stage 1 was 23.9%. There are 13.1% of patients are at stage 2 or 3 cancer and none at stage 4. The study of Sonia Ortiz-Pagan et al (2011) in 32 patients with Paget's breast disease has the rate patients have cancer stage classification stage 0 is 38.0%, stage 1 is 25.0%, stage 2 is 13.0%, stage 4 is 6%.[8] The accurate assessment of the cancer stage will be very helpful for the doctor to prescribe the right treatment regimen for the patient.

The choice of treatment depends on the clinical and laboratory features, the histopathology of the breast cancer, and the involvement of the metastatic lymph nodes. Mastectomy with or without axillary lymph node dissection, even in the absence of associated malignancies, is considered the most radical therapy for Paget's disease of the breast. Recently, with the increase in early diagnosis of breast cancer, many trials have been performed showing that conservative treatments can be alternatives with equivalent efficacy, if the disease is limited to the center of the breast. Patients will be surgically removed areola nipple with a part of breast parenchyma, accompanied by adjuvant radiation therapy after surgery. In our study, 97.8% of the patients underwent mastectomy, of which 65.2% were treated with mastectomy combined with lymph node dissection and 32.6% of the patients with mastectomy alone and only 1 patient underwent conservative surgery. About one third of patients received adjuvant treatment (chemotherapy, radiation therapy) after surgery with a rate of 32.7%.

The recurrence rate in our study was 13.1%, including 1 patient with local recurrence and 5 patients with distant metastasis (all with lung metastases). In other studies around the world, the recurrence rate is quite different because the surgical method is selected and the follow-up time is not uniform. Research results of Dixon AR et al (1991) on 37 Paget's breast patients treated with mastectomy alone, the recurrence rate was only 5%, with an average follow-up time of 40 months.[9] Marshall et al. 4 published 15-year follow-up data in 2003 for 36 patients treated with partial or total mastectomy, nipple and areola complex followed by radiation therapy. Results showed a local recurrence rate of 17%.[10]

At the end of the study, 4 patients died from all causes, accounting for 8.7%. Overall survival (OS) was 91.3%, of which disease-free survival (DFS) accounted for 84.8%. According to the American Cancer Society (NCI) SEER program, the 5-year survival rate for all women in the United States diagnosed with Paget's disease of the breast between 1988 and 2001 is 82.6%.[11] The

overall survival rate after 5 years in our study was higher than the above statistics, possibly because the sample with Paget alone and Paget combined with intraductal carcinoma were higher than in other studies around the world.

5. CONCLUSION

Paget's disease is a rare malignancy of the breast. Due to its uncommon nature and clinical symptoms that easily mimic other common dermatological diseases, it often presents challenges in both diagnosis and treatment. Histopathological examination serves as the gold standard for accurate diagnosis. Paget's disease is frequently associated with concurrent breast cancer lesions, as observed in 65.2% of cases in our research and reported at 80 - 90% in other studies worldwide. Consequently, the treatment of Paget's disease must be closely linked with the treatment of the accompanying breast cancer to prevent any oversight. The staging and treatment of cancer depend on the underlying breast cancer, if present. Given its metastatic and relapsing nature, Paget's disease can lead to mortality, as evidenced by our study with rates of 13.1% and 8.7%, respectively. Therefore, a systematic approach following oncological protocols and regular follow-up post-treatment is essential for effective management.

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