



## Evolution of the Surgical Treatment of Mammary Paget's Disease in Men: Updated Review of Case Reports from 2017 to 2021

Alberto Bouzón-Alejandro<sup>1\*</sup>, Benigno Acea-Nebril<sup>1</sup>, Ángela Iglesias-López<sup>2</sup>, Alejandra García-Novoa<sup>1</sup>, Carlota López-Domínguez<sup>1</sup>, Carlota Czesstokowa Díaz-Carballada<sup>3</sup> and Carmen Conde Iglesias<sup>3</sup>

<sup>1</sup>Department of Surgery, University Hospital of A Coruña (CHUAC), Spain

<sup>2</sup>Department of Radiology, University Hospital of A Coruña (CHUAC), Spain

<sup>3</sup>Department of Gynecology, University Hospital of A Coruña (CHUAC), Spain

### Abstract

**Background:** Mammary Paget's Disease (MPD) in men is extremely rare, with only 57 patients reported in the literature up to 2016, accounting for about 2% of all patients with MPD. Histopathological and immunohistochemical analyses are essential for diagnosis. Surgery is usually the first treatment that male patients with MPD receive.

**Purpose:** This review updates case reports published since 2017 and describes the evolution of the surgical treatment.

**Methods:** A systematic search for case reports of MPD in men published from 2017 to 2021 was performed.

**Results:** Twelve articles containing data of 14 male patients with MPD were included. The mean age was 63.6 years. Nine patients (64.3%) underwent mastectomy with Sentinel Lymph Node Biopsy (SLNB). The pathological examination of surgical specimens found an underlying Invasive Breast Carcinoma (IBC) in 7 cases (50%). Radical mastectomy and modified radical mastectomy were the predominant surgical procedures up to 2016.

**Conclusion:** The standard surgical treatment of MPD in male patients has changed from radical mastectomy to mastectomy with SLNB.

**Keywords:** Mammary Paget's disease; Breast carcinoma; Sentinel lymph node biopsy

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#### \*Correspondence:

Alberto Bouzón-Alejandro, Department of Surgery, Breast Unit, University Hospital of A Coruña (CHUAC), Paseo Sir John Moore (Abente y Lago Hospital), 15001, A Coruña, Spain, E-mail: dr.alberto@aecirujanos.es

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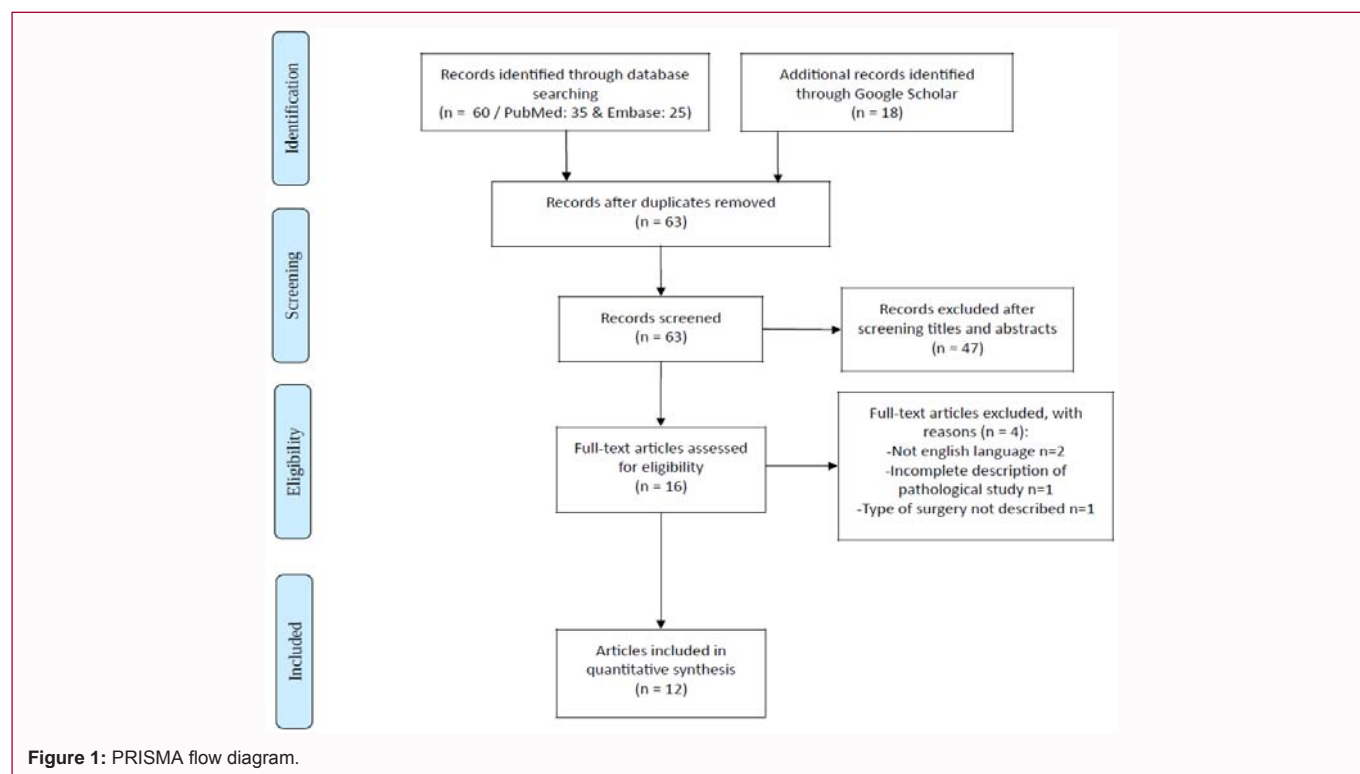
### Introduction

Mammary Paget's Disease (MPD) in men, which accounts for about 2% of all cases with MPD, is an extremely rare form of breast malignancy [1]. Fifty-seven male patients with MPD have been reported up to 2016 and included in 2 systematic reviews [2,3].

Clinically, MPD usually presents as an eczematous or ulcerated unilateral lesion affecting the Nipple-Areolar Complex (NAC), while a breast lump is found in about 40% of patients [4]. A skin biopsy should be performed when MPD is suspected to not delay diagnosis and treatment. Histopathological and immunohistochemical analyses are essential for the differential diagnosis with other entities such as Bowen's disease, Tokel cell hyperplasia or melanoma.

Imaging evaluation is recommended in patients with suspected or diagnosed MPD due to its association with a breast carcinoma in more than 90% of cases [5]. Mammography and ultrasonography should be performed in all male patients to detect an underlying breast carcinoma. Magnetic resonance imaging is less useful in men than in women, due to the lower rate of conservative surgery.

Surgery is considered the primary therapeutic approach for male patients with MPD. Traditionally, radical mastectomy has been the surgical treatment of choice. The presence of an underlying Invasive Breast Carcinoma (IBC), as well as the tumor subtype, and the axillary nodal status determine adjuvant treatment and prognosis.



This review aims to update the list of case reports of MPD in men published since 2017 and describe the evolution of the surgical treatment.

## Materials and Methods

### Data sources and searches

Comprehensive searches of PubMed, Embase and Google Scholar databases were performed to identify and extract case reports or case series published from January 2017 to December 2021. The search strategy followed the PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analyses) guidelines and included the following terms: «Paget's disease», «Paget disease», «male», «men», «breast», «nipple», «nipple-areolar complex» and «mammary».

### Inclusion and exclusion criteria

The following criteria were required to be included: 1) Male patients with diagnosis of MPD, 2) patients treated with surgery, and 3) pathological description of the surgical specimen.

### Study selection and data management

Two reviewers independently evaluated potentially eligible articles. We examine the methodological quality of case reports based on the method proposed by Murad et al. [6]. Data extracted from eligible articles included the first author, year of publication, patient's age at diagnosis, laterality, form of clinical presentation of the disease, type of surgical treatment, status of axillary lymph nodes, presence of an associated invasive or in situ breast carcinoma, description of immunohistochemical markers and follow-up time without recurrence.

### Statistical analysis

The statistical analyses were performed using SPSS version 23.0. Continuous variables were reported as "mean ± Standard Deviation (SD)" and categorical variables were reported as frequencies and percentages.

## Results

### Search results

The initial search using PubMed, Embase and Google Scholar identified 78 references since 2017, of which 15 were duplicates and were removed. After the first screening, 16 articles were assessed for eligibility. Finally, 12 publications available in English, describing 14 male patients with MPD treated with surgery, were considered eligible (Figure 1).

### Characteristics of case reports published since 2017

Table 1, 2 summarize the main features of the 14 male patients with MPD included in our review [7-18]. Mean age was 63.6 years (range, 41 to 87 years). The most frequent clinical presentation was an erosive or scaly lesion affecting the NAC. A palpable mass was described in 5 patients (35.7%). Nine patients underwent mastectomy with SLNB (64.3%). Local excision was performed only in 1 patient. All cases included in the study presented an underlying breast carcinoma (50% of them with an IBC). Pathological examination demonstrated the presence of an IBC in 4 of the 5 patients with palpable mass (80%) and in 3 of the 9 patients without a palpable mass (33.3%). Overall, 3 patients had axillary nodal involvement (21.4%). However, axillary nodal involvement was found in 2 of the 5 patients with palpable mass (40%). SLNB was performed in 9 patients, with a negative result in 8 cases (88.9%); one case presented one lymph node with micro-metastases without extra-nodal extension. Seven patients received a follow-up of more than 18 months, with no recurrence observed.

### Surgical treatment evolution

Figure 2 summarizes the surgical treatment evolution since the publication of the first case of MPD in a male patient, considering the periods covered by the 3 reviews. Radical mastectomy and modified radical mastectomy were the standard surgical procedures up to 1996 (85.3%), and the predominant surgical procedures from 1997 to 2016 (46.2%). However, mastectomy with SLNB was the most practiced

**Table 1:** Cases of Paget’s disease of the male breast since 2017.

Reference	Age (years)	Laterality	Initial lesion in NAC	Surgical treatment	Axillary involvement	Associated carcinoma	IHC	Follow-up without recurrence
Bouzón et al. [7]	70	Left	Erosive lesion	Mastectomy + SLNB	No	DCIS	CK 7-, HER2-GATA3+, AR+ CAM5.2+, ER+	30 months
Salih et al. [8]	54	Left	Ulceration	Mastectomy + SLNB	Yes	DCIS + IDC	Unknown	Unknown
Rodríguez et al. [9]	41	Left	Erosion	Mastectomy + SLNB	No	DCIS	Unknown	8 years
Roy et al. [10]	87	Left	Scaly rash	Segmental mastectomy		DCIS	CK 7+, ER+, CAM5.2+	23 months
Roy et al. [10]	62	Right	Erythematous nodule and scaly rash	Mastectomy + SLNB	No	IDC	CK 7+, ER+, CK 20-	9 months
Moore et al. [11]	76	Right	Scaly lesion	Local excision		DCIS	CK 7+, AR+, ER- GATA3+, MUC1+	Unknown
Nyland et al. [12]	62	Left	Erosion	Mastectomy + SLNB	No	DCIS + IDC	Unknown	1 year
Vergine et al. [13]	77	Right	Ulcerated mass	Mastectomy + SLNB	No	DCIS + IDC	CK 7+, ER+, HER2+	Unknown
Wang et al. [14]	64	Left	Breast mass and nipple inversion	Modified radical mastectomy	Yes	IDC	ER+, HER2-	Unknown
Wang et al. [14]	55	Left	Breast mass and nipple inversion	Modified radical mastectomy	Yes	IDC	ER+, HER2+	Unknown
Sato et al. [15]	56	Right	Eczema and lump	Mastectomy + SLNB	No	DCIS	ER+, CK 7+, CAM5.2+, HER2-	38 months
Lopes et al. [16]	61	Right	Erosive lesion	Mastectomy + SLNB	No	DCIS	CK 7+	18 months
Borghi et al. [17]	66	Right	Pigmented lesion	Modified radical mastectomy	No	IDC	CK 7+, ER+	2 years
Zhang et al. [18]	60	Left	Erythema and erosion	Mastectomy + SLNB	No	DCIS	ER-, CK 5/6+, CK 8/18+, HER2+	18 months

NAC: Nipple Areola-Complex; IHC: Immunohistochemistry; SLNB: Sentinel Lymph Node Biopsy; DCIS: Ductal Carcinoma *in situ*; IDC: Invasive Ductal Carcinoma

**Table 2:** Patients and disease characteristics.

Variables	Mean ± SD	
	Mean ± SD	Range
Age (years)	63.6 ± 11.4	41-87
	Frequency	Percentage
<b>Surgical treatment</b>		
-Mastectomy + SLNB	9	64.3
-MRM	3	21.4
-Segmental mastectomy	1	7.1
-Local excision	1	7.1
<b>Axillary node involvement</b>		
-No	9	64.3
-Yes	3	21.4
-Unknown	2	14.3
<b>Associated breast carcinoma</b>		
DCIS	7	50
IDC	4	28.6
DCIS + IDC	3	21.4

SLNB: Sentinel Lymph Node Biopsy, MRM: Modified Radical Mastectomy, DCIS: Ductal Carcinoma *in situ*, IDC: Invasive Ductal Carcinoma

surgery (64.3%) during the last period (2017-2021).

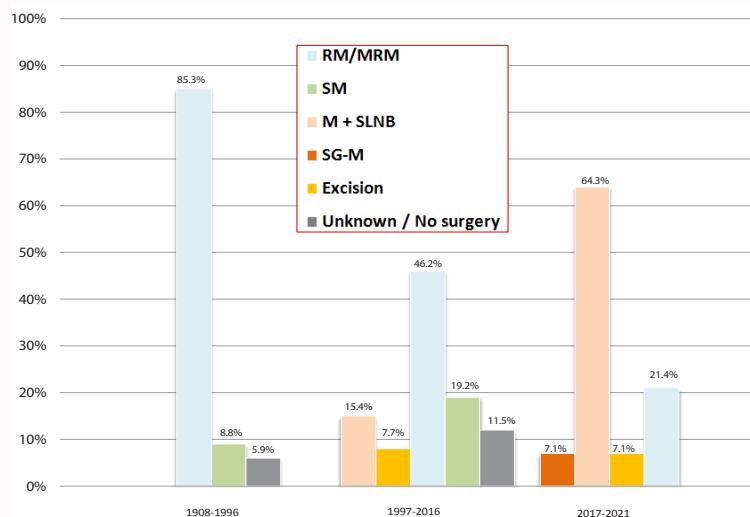
## Discussion

MPD represents less than 2% of all male breast cancers. Fifty-seven male patients with MPD reported up to 2016 were included in 2 systematic reviews [2,3]. Our update of the last 5 years adds 14 more patients to this list.

MPD is usually a unilateral disease, which generally appears in the sixth decade of life. Bilateral disease in men has been reported [19,20]. The average age of diagnosis of MPD in men is approximately 68 years. In this review, 10 patients (71.4%) were diagnosed with ≥ 60 years (mean age was 63.6 years). Most men with MPD present with an eczematous or erosive lesion involving the NAC, with or without a breast mass. A palpable breast lump was found in 9 of the 26 cases (34.6%) listed in Adam’s review [3], similar to the result of our update (35.7%).

In case of clinical suspicion of MPD, a biopsy of the lesion must be performed to confirm the diagnosis. The morphological characteristics of the lesion on hematoxylin and eosin analysis (invasion of the epidermis by atypical epithelial cells with pale cytoplasm and large hyperchromatic nuclei, often with prominent nucleoli) coupled with the immunohistochemical study are essential for the differential diagnosis of MPD. Staining of Paget’s cells with Cytokeratin 7 (CK7) is positive in at least 98% of cases [21]. Several cases of MPD with CK7-negative variant in women have been reported [22-24]. More recently, this variant has been described in a male patient [7]. In the setting of this rare variant, the use of GATA3 immunostain should be performed, since Paget’s cells are usually immunoreactive for this marker [22]. The positivity of Paget’s cells for other markers, such as CAM5.2, MUC1, androgen or estrogen receptors may also be helpful for the diagnosis.

The first surgical treatment performed in a male patient with MPD was a radical mastectomy [25]. Radical mastectomy and modified radical mastectomy were considered the predominant techniques during the 20<sup>th</sup> century. However, this changed when SLNB became the standard of care for axillary nodal staging. The first male patient with MPD treated with SLNB was reported in 2003 [26]. In the last



**Figure 2:** Surgical treatment evolution in male MPD.

RM: Radical Mastectomy; MRM: Modified Radical Mastectomy; SM: Simple Mastectomy; SG-M: Segmental Mastectomy; M+SLNB: Mastectomy + Sentinel Lymph Node Biopsy

ten years, 12 of the 21 patients reported (57.1%) underwent SLNB. Unlike female patients, in which breast conserving surgery followed by radiation therapy is increasingly used, mastectomy continues to be the treatment of choice in male patients with MPD. The frequent central location of the disease and the small size of the male breast offer few possibilities for breast conservation. In addition, concern about body image after mastectomy is lower in male patients. Of all cases of male MPD published up to 2016, only 2 patients were treated with local excision [27,28]. In this review, one case underwent local excision due to the initial suspicion of Bowen's disease [11]. Although surgery is the first therapeutic approach for men with MPD, neoadjuvant chemotherapy has been described [14].

In addition, the presence of a palpable lump increases the risk of finding an associated IBC and axillary nodal involvement. In our update, IBC was found in 80% of cases with a breast palpable mass, compared with 66.7% in Adam's review [3]. The incidence of axillary nodal involvement in patients with a palpable mass was similar in both reviews (40% vs. 44.4%, respectively).

In conclusion, MPD is extremely rare in male patients, with less than 80 cases reported in the literature. Accurate and early diagnosis minimizes the presence of an underlying IBC and axillary nodal involvement, improving the prognosis. The current standard surgical management in clinically node-negative patients is mastectomy, including the NAC, with SLNB.

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