

Review Article

Surgical management of Paget's disease of the breast: an update on treatment strategies

Hisham Abdullah Almottowa^{1*}, Adian Abdulrahman Wahhas², Hasan Mohamed Marhoon³,
Ahmad Abdrabalamier Alfajri⁴, Afnan Mousa Maashi⁵, Ragheed Ahmad Justanieah⁶,
Ahmed Hasan Alkooheji⁷, Aseel Saba Alkhambashi⁸, Razan Rafat Babour⁶,
Abdulaziz Mustafa Alsharif⁹

¹Department of General Surgery, King Fahad Hospital, Jeddah, Saudi Arabia

²Department of General Surgery, Ministry of Health, Jeddah, Saudi Arabia

³College of Medicine, Cairo University, Cairo, Egypt

⁴Emergency Medical Services, Prince Saud bin Jalawi Hospital, Al Ahsa, Saudi Arabia

⁵Department of General Surgery, King Fahad Central Hospital, Jazan, Saudi Arabia

⁶College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

⁷College of Medicine, Ain Shams University, Cairo, Egypt

⁸College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

⁹Department of Urology, Prince Saud bin Jalawi Hospital, Al Ahsa, Saudi Arabia

Received: 05 December 2024

Accepted: 18 December 2024

*Correspondence:

Dr. Hisham Abdullah Almottowa,

E-mail: hishamalmottowa@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Paget's disease of the breast, or mammary Paget's disease (MPD), is a rare and often misdiagnosed form of breast cancer, typically presenting as eczematous or ulcerative lesions on the nipple-areola complex. Occurring in about 1-3% of all breast malignancies, MPD is frequently associated with underlying ductal carcinoma *in situ* (DCIS) or invasive carcinoma, necessitating a high degree of clinical vigilance for early diagnosis and treatment. Traditionally, surgical excision has been the cornerstone of treatment, with mastectomy serving as the standard approach. However, advances in imaging and surgical techniques have introduced breast-conserving surgery (BCS) and oncoplastic methods as viable alternatives, particularly for cases with localized disease. This review explores current surgical strategies for MPD, discussing indications, outcomes, and aesthetic considerations for mastectomy and BCS, as well as the role of sentinel lymph node biopsy (SLNB) in cases involving invasive carcinoma. In addition to surgical management, adjuvant therapies, including radiation and systemic treatments, are reviewed to highlight their role in reducing recurrence and enhancing patient survival. Emerging treatments such as cryoablation, photodynamic therapy (PDT), and immunotherapy are discussed for their potential as adjuncts or alternatives to traditional surgery. Future research in the genetic and molecular profiling of MPD may provide new pathways for targeted therapies, ultimately advancing patient care and outcomes.

Keywords: Paget's disease of the breast, Surgical management, Mastectomy, BCS, Oncoplastic surgery, Adjuvant treatment

INTRODUCTION

Paget's disease of the breast, also known as MPD, is a rare form of breast cancer, first described by Sir James

Paget in 1874. It is characterized by malignant epithelial cells known as Paget cells that infiltrate the epidermis of the nipple-areola complex, often leading to visible changes such as erythema, scaling, ulceration, and

sometimes discharge. Due to the similarity of these symptoms to benign dermatologic conditions like eczema, MPD is frequently misdiagnosed, leading to delays in appropriate management.¹ This delay can be consequential, as MPD is associated with an underlying malignancy, most commonly DCIS or invasive carcinoma in over 90% of cases.²

MPD is most often seen in postmenopausal women, with an average onset age of around 57 to 64 years, although cases have been documented in younger women and even in men, albeit rarely.³ There are two main theories regarding the pathogenesis of Paget cells in MPD. The epidermotropic theory suggests that these cells originate from an underlying carcinoma and migrate to the nipple epithelium. This theory is widely supported by the frequent detection of HER2 overexpression in Paget cells, which mirrors the HER2 positivity often observed in underlying ductal carcinoma.⁴ In contrast, the intraepidermal origin theory posits that Paget cells arise independently within the epidermis of the nipple, explaining cases where MPD occurs without an associated carcinoma. This theory is backed by the morphological resemblance between Paget cells and Tokier cells, which are benign epithelial cells found in the nipple.⁵

Historically, mastectomy, including removal of the nipple-areola complex, has been the standard treatment for MPD, particularly in cases with extensive disease or when DCIS or invasive carcinoma is present. However, recent advances in imaging and surgical techniques have broadened the range of treatment options. BCS is now considered a feasible alternative for selected patients with localized disease confined to the nipple-areola complex. Oncoplastic techniques, which integrate oncologic and reconstructive approaches, have further expanded the surgical landscape, offering improved aesthetic outcomes without compromising oncologic control.⁶

In addition to surgical intervention, adjuvant therapies such as radiation therapy, endocrine therapy, and chemotherapy are essential components of comprehensive care for MPD, particularly in cases with invasive carcinoma or when BCS is employed. Emerging therapies, including cryoablation, PDT, and immunotherapy, are currently under investigation as non-surgical alternatives or adjuncts, with promising early results in selected cases.^{7,8} This review provides a comprehensive analysis of the current surgical and adjuvant management strategies for MPD, discussing treatment outcomes, considerations for patient quality of life, and the potential of emerging therapies to reshape the clinical approach to this complex disease.

LITERATURE SEARCH

This review is based on a comprehensive literature search conducted on 5 November 2024 in the PubMed, Medline, and Cochrane databases. Utilizing medical subject

headings (MeSH) and relevant keywords, the search aimed to identify pertinent studies on the surgical management of Paget's disease of the breast. To ensure thoroughness, a manual search was also performed through Google Scholar, examining the reference lists of identified papers to locate additional relevant studies. We focused on articles discussing the epidemiology, clinical presentation, surgical options, outcomes, and adjuvant therapies associated with Paget's disease of the breast. No restrictions were applied regarding publication date, language, or type of publication, allowing for a comprehensive exploration of the existing literature.

DISCUSSION

Epidemiology and pathophysiology

MPD is a relatively rare condition, constituting only 1-3% of all breast cancers, with a strong correlation to DCIS or invasive ductal carcinoma (IDC) in over 90% of cases.⁵ This association has important implications for both diagnosis and treatment, as the presence of an underlying malignancy often necessitates a more aggressive therapeutic approach. The pathogenesis of MPD remains a subject of debate, with two prevailing theories: the epidermotropic theory and the intraepidermal origin theory. The high rate of HER2 positivity among Paget cells lends support to the epidermotropic theory, suggesting that Paget cells migrate from an underlying malignancy. Conversely, the intraepidermal origin theory posits that Paget cells arise from the malignant transformation of nipple epithelial cells, explaining cases where no associated carcinoma is detected.⁹ These theories underscore the heterogeneous nature of MPD and the need for tailored treatment approaches based on individual disease characteristics.¹⁰

Clinical presentation and diagnosis

Patients with MPD typically present with nipple-areola complex symptoms, including erythema, scaling, and sometimes ulceration or discharge. Due to its clinical similarity to benign dermatologic conditions, MPD is often misdiagnosed as eczema or contact dermatitis, leading to delayed diagnosis and treatment.¹¹ Diagnostic workup for MPD includes imaging studies—mammography, ultrasound, and magnetic resonance imaging (MRI)—to identify any underlying carcinoma. While mammography detects associated carcinoma in about 50% of cases, MRI is particularly effective in revealing DCIS or invasive carcinoma in patients with MPD.¹²

A definitive diagnosis is established through histopathological examination, with a skin punch or full-thickness nipple biopsy often used to identify Paget cells.¹³ Immunohistochemical markers, including HER2, are frequently positive in Paget cells, aiding in the diagnosis and potentially guiding treatment.¹⁴

Surgical management options

Surgical management is the primary treatment modality for MPD, with mastectomy as the traditional standard. Advances in imaging and a better understanding of disease pathology have made BCS a viable option in selected cases, broadening the spectrum of surgical approaches.¹⁵

Mastectomy

Mastectomy remains the most definitive surgical treatment for MPD, especially for cases involving extensive disease or associated invasive carcinoma.¹⁶ Mastectomy procedures vary depending on the extent of tissue removal required. A total mastectomy involves the removal of the entire breast, including the nipple-areolar complex, to ensure all cancerous tissue is excised.¹⁷ Skin-sparing mastectomy preserves the skin envelope while removing breast tissue and the nipple-areolar complex, enhancing reconstructive outcomes, and is suitable for patients without significant skin involvement. Nipple-sparing mastectomy retains both the skin and nipple-areolar complex, offering better aesthetic results; however, it is generally reserved for cases where the nipple-areola is not affected by the cancer. This approach has been found to be oncologically safe in selected patients, though it carries a risk of nipple necrosis.¹⁸

SLNB

SLNB is often performed with mastectomy in cases with invasive carcinoma to assess for regional lymph node involvement, which can impact staging and treatment decisions. Patients with negative SLNB findings typically have lower recurrence risks and may avoid additional systemic treatments.¹⁹

BCS

BCS has gained acceptance as an alternative to mastectomy for patients with limited disease confined to the nipple-areola complex. This approach removes only the affected tissue, preserving most of the breast. Studies indicate that with postoperative radiation, BCS offers comparable local control rates to mastectomy. However, achieving clear surgical margins is crucial to minimize recurrence, which may require re-excision in cases where initial margins are inadequate. For patients with extensive disease, BCS is associated with a higher likelihood of recurrence and may require re-excision to achieve oncologic control.⁶

Oncoplastic surgery

Oncoplastic surgery combines oncologic and plastic surgery techniques to enhance aesthetic outcomes after partial or total mastectomy. Techniques like the Grisotti mastopexy and Wise-Pattern mammoplasty enable better cosmetic results while ensuring oncologic control. For

patients undergoing nipple or areola resection, nipple-areolar reconstruction (e.g., C-V flap or tattooing) can restore symmetry and appearance. Oncoplastic techniques are particularly beneficial for MPD patients as they address both cancer removal and breast contour preservation, improving quality of life post-surgery.²⁰

Adjuvant therapies

Adjuvant therapies are essential in the treatment of malignant phyllodes tumors (MPD), targeting residual microscopic disease after surgery. Radiation therapy is commonly used following BCS to minimize the risk of local recurrence, with whole-breast radiation and tumor bed boost being standard practices, particularly for patients with close or positive margins. Studies indicate that radiation therapy following BCS in MPD patients provides local control rates comparable to those of mastectomy, making it a crucial component of treatment.²¹ Systemic therapies, including chemotherapy, endocrine therapy, and HER2-targeted treatments such as trastuzumab, are recommended for patients with invasive carcinoma or hormone receptor-positive disease. These therapies help prevent metastasis, especially in HER2-positive cases, where trastuzumab has been shown to improve survival rates, making systemic treatments particularly beneficial for high-risk patients with aggressive disease phenotypes.²²

Outcomes of surgical treatments

Among MPD patients without a palpable mass or detectable mammographic anomaly, DCIS is the most common underlying malignancy, and these cases generally show no axillary lymph node involvement, making breast-limited treatment adequate. A meta-analysis of patients who underwent mastectomy for MPD reported a specific breast carcinoma mortality rate of 1.7% over 8.6 years, indicating high survival and local control, though rare invasive recurrences post-mastectomy suggest that this approach may not completely eliminate recurrence risk.

In BCS cases, the addition of whole-breast radiation therapy has demonstrated significant success in lowering recurrence rates. However, studies have shown that achieving clear margins can be challenging. Cone excision of the nipple often results in incomplete excision due to the proximity of the malignancy to the nipple-areolar complex, with local recurrence rates as high as 40% in cases with an in-situ component near the nipple. Complete resection of the nipple-areolar complex, followed by radiotherapy, is recommended in cases with DCIS or invasive carcinoma extending beyond this region. SLNB or axillary node dissection may be indicated if lymph node involvement is suspected.²³

Research comparing BCS to mastectomy suggests that survival and recurrence rates can be similar, provided that BCS is followed by adjuvant radiation. A long-term

retrospective study found that the type of surgery, whether BCS or mastectomy, had no significant impact on disease-free survival, with the main factors influencing outcomes being the presence of invasive carcinoma and a palpable mass. Among patients undergoing BCS, recurrence rates vary but tend to be low with adequate radiation. For instance, in a study of 61 patients without invasive carcinoma, only 7% experienced recurrence following nipple-areolar complex excision and radiation therapy over a median follow-up of 75 months.

Further studies have shown that local recurrence following partial or complete nipple-areola resection combined with radiotherapy can range from 5-11% over extended follow-up periods. In cases of recurrence, salvage mastectomy has proven effective in achieving disease control. Comparatively, long-term studies from the American Cancer Society and the European Organization for Research and Treatment of Cancer reported 5-year local recurrence rates of 9% and 5.2%, respectively, for MPD patients treated with BCS and radiotherapy, underscoring the efficacy of BCS combined with radiation in managing localized MPD.²⁴

Emerging treatments and future directions

New therapies and approaches are emerging as adjuncts or alternatives to surgery including followings.

Cryoablation

Cryoablation is a minimally invasive technique that destroys cancer cells by freezing them. It has shown promise as an alternative to surgical excision in select cases of MPD with limited skin involvement, though more studies are needed to establish its long-term efficacy.²⁵ There are several advantages to be gained from ablation performed at very low temperatures and these include the method's simplicity, lack of pain, low morbidity, cost-effectiveness, and potential for positive cryo-immunologic effects.²⁶

PDT

PDT, which uses a topical or intravenous photosensitizing agent that is activated by a light source to ablate abnormal tissue, offers a minimally invasive alternative. This approach offers a non-surgical option for superficial MPD lesions, particularly in patients unfit for surgery. Evidence of the effectiveness of PDT for Paget's disease is promising but limited. Early studies indicate PDT's potential, but further research is required to validate its effectiveness in MPD.²⁷

Immunotherapy

Immune checkpoint inhibitors targeting PD-L1 are being investigated for their potential to improve immune response against MPD cells. Given MPD's frequent HER2 positivity, PD-L1 inhibitors could enhance

outcomes for patients with HER2-positive, aggressive MPD phenotypes.^{28,29}

Genomic and biomarker research

Ongoing research into the genetic profile of MPD aims to identify biomarkers that could guide personalized therapies.³⁰ Molecular profiling could enable targeted treatments for patients with specific genetic mutations, improving survival outcomes and reducing treatment-related morbidity.^{31,32}

CONCLUSION

Paget's disease of the breast presents unique diagnostic and treatment challenges due to its rarity and association with underlying carcinoma. Surgical intervention, primarily through mastectomy or BCS, remains the standard of care, with adjuvant therapies playing a critical role in achieving optimal outcomes. Emerging treatments, such as cryoablation, PDT, and immunotherapy, offer promising alternatives, especially for patients with limited disease or contraindications to surgery. As research advances, personalized treatment approaches guided by genetic and molecular profiling may become feasible, providing more targeted and less invasive options for MPD management. Future studies should continue exploring these novel therapies and refining surgical techniques to improve quality of life and survival for patients with MPD.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Kawase K, Dimaio DJ, Tucker SL, Thomas AB, Merrick IR, Barry WF, et al. Paget's disease of the breast: there is a role for breast-conserving therapy. *Ann Surg Oncol*. 2005;12(5):391-7.
2. Kanitakis J. Mammary and extramammary Paget's disease. *J Eur Acad Dermatol Venereol*. 2007;21(5):581-90.
3. Caliskan M, Gatti G, Sosnovskikh I, Nicole R, Edoardo B, Simona M, et al. Paget's disease of the breast: the experience of the European Institute of Oncology and review of the literature. *Breast Cancer Res Treat*. 2008;112(3):513-21.
4. Sakorafas GH, Blanchard K, Sarr MG, Farley DR. Paget disease of the breast. *Cancer Treatment Reviews*. 2001;27(1):9-18.
5. Markarian S, Holmes DR. Mammary Paget's Disease: An Update. *Cancers*. 2022;14(10):2422.
6. Onoe S, Kinoshita T, Tamura N, Tomoya N, Hirofumi K, Takashi H, et al. Feasibility of breast conserving surgery for Paget's disease. *The Breast*. 2011;20(6):515-8.
7. Nardelli AA, Stafinski T, Menon D. Effectiveness of photodynamic therapy for mammary and extra-

- mammary Paget's disease: a state of the science review. *BMC Dermatol*. 2011;11(1):13.
8. Pérez JC, Salgado AC, Pérez-Mies B, Jose ADR, Ajuria-Illarramendi O, Eva MGA, et al. Extramammary Paget Disease: a Therapeutic Challenge, for a Rare Entity. *Curr Oncol Rep*. 2023;25(10):1081-94.
9. Gaurav A, Gupta V, Koul R, Dabas S, Sareen R, Geeta K, et al. Practical consensus recommendations for Paget's disease in breast cancer. *South Asian J Cancer*. 2018;7(2):83-6.
10. Karakas C. Paget's disease of the breast. *J Carcinogenesis*. 2011;10:31.
11. Sakorafas GH, Blanchard K, Sarr MG, Farley DR. Paget's disease of the breast. *Cancer Treatment Reviews*. 2001;27(1):9-18.
12. Glechner A, Wagner G, Mitus JW, Birgit T, Irma K, Nina B, et al. Mammography in combination with breast ultrasonography versus mammography for breast cancer screening in women at average risk. *Cochrane Database Syst Rev*. 2023;3(3):CD009632.
13. Lopes Filho LL, Lopes IM, Lopes LR, Enokihara MM, Michalany AO, Matsunaga N. Mammary and extramammary Paget's disease. *An Bras Dermatol*. 2015;90(2):225-31.
14. Cai Y, Cheng Z, Nangong J, Zheng X, Yuan Z. Using immunohistochemistry to classify the molecular subtypes of Paget's disease of the breast. *Cancer Med*. 2023;12(13):14104-111.
15. Chen CY, Sun LM, Anderson BO. Paget disease of the breast: changing patterns of incidence, clinical presentation, and treatment in the U.S. *Cancer*. 2006;107(7):1448-58.
16. Mota BS, Riera R, Ricci MD, Jessica B, De Castria TB, Atallah AN, et al. Nipple- and areola-sparing mastectomy for the treatment of breast cancer. *Cochrane Database Syst Rev*. 2016;11(11):CD008932.
17. Horton CE, Dascombe WH. Total mastectomy: indications and techniques. *Clin Plastic Surg*. 1988;15(4):677-87.
18. Galimberti V, Vicini E, Corso G, Consuelo M, Sabrina F, Virgilio S, et al. Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. *The Breast*. 2017;34:S82-4.
19. Yi M, Giordano SH, Meric-Bernstam F, Elizabeth AM, Henry MK, Rosa FH, et al. Trends in and outcomes from sentinel lymph node biopsy (SLNB) alone vs. SLNB with axillary lymph node dissection for node-positive breast cancer patients: experience from the SEER database. *Ann Surg Oncol*. 2010;3(3):343-51.
20. Kijima Y, Yoshinaka H, Hirata M, Akihiro N, Hideo A, Hiroshi O, et al. Oncoplastic breast surgery combining partial mastectomy with immediate breast reshaping using a keyhole-shaped skin glandular flap for Paget's disease. *Surg Today*. 2014;44(9):1783-8.
21. Hata M, Koike I, Wada H, Miyagi E, Kasuya T, Kaizu H, et al. Radiation therapy for extramammary Paget's disease: treatment outcomes and prognostic factors. *Ann Oncol*. 2014;25(1):291-7.
22. Takahagi S, Noda H, Kamegashira A, et al. Metastatic extramammary Paget's disease treated with paclitaxel and trastuzumab combination chemotherapy. *J Dermatol*. 2009;36(8):457-61.
23. Bulens P, Vanuytsel L, Rijnders A, van der Schueren E. Breast conserving treatment of Paget's disease. *Radiotherapy Oncol*. 1990;17(4):305-9.
24. Goh SSN, Syn NLX, Lim CJE, Lee RE, Samuel M, Ng CWQ. Oncologic outcomes after breast-conserving surgery with radiotherapy versus mastectomy in patients with Paget's disease of the breast: systematic review and meta-analysis. *Brit J Surg*. 2023;110(11):1451-7.
25. Rzaca M, Tarkowski R. Paget's disease of the nipple treated successfully with cryosurgery: A series of cases report. *Cryobiology*. 2013;67(1):30-3.
26. Tarkowski R, Rzaca M. Cryosurgery in the treatment of women with breast cancer-a review. *Gland surgery*. 2014;3(2):88-93.
27. Yanovsky RL, Bartenstein DW, Rogers GS, Isakoff SJ, Chen ST. Photodynamic therapy for solid tumors: A review of the literature. *Photodermatol Photoimmunol Photomed*. 2019;35(5):295-303.
28. Yang J, Chen Y, Zhang X, Ziyang T, Shanshan W, Ning Z et al. Immunotherapy may be more appropriate for ERBB2 low-expressing extramammary paget's disease patients: a prognosis analysis and exploration of targeted therapy and immunotherapy of extramammary paget's disease patients. *Cancer Immunol Immunother*. 2024;73(12):252.
29. Bartoletti M, Mazzeo R, De Scordilli M, Anna Del F, Maria GV, Lucia B, et al. Human epidermal growth factor receptor-2 (HER2) is a potential therapeutic target in extramammary Paget's disease of the vulva. *Int J Gynecol Cancer*. 2020;30(11):1672-7.
30. Neves Rebello Alves L, Dummer Meira D, Poppe Merigueti L, Matheus CC, Do Prado Ventorim D, Almeida JF, et al. Biomarkers in Breast Cancer: An Old Story with a New End. *Genes*. 2023;14(7):1364.
31. Gatalica Z, Vranic S, Krušlin B, Kelsey P, Phillip S, Denisa K, et al. Comparison of the biomarkers for targeted therapies in primary extra-mammary and mammary Paget's disease. *Cancer Med*. 2020;9(4):1441-50.
32. Jing W, Li L, Zhang X, Shouxin W, Jiangman Z, Qunxing H, et al. Genetic Profiling of Breast Cancer with and Without Preexisting Metabolic Disease. *Translational Oncol*. 2020;13(2):245-53.

Cite this article as: Almottowa HA, Wahhas AA, Marhoon HM, Alfajri AA, Masshi AM, Justanieah RA, et al. Surgical management of Paget's disease of the breast: an update on treatment strategies. *Int J Community Med Public Health* 2025;12:514-8.