



Surgery on primary melanoma of the breast

Qi Huang, Xiao-Hua Zhang, Ling-Ji Guo, Yu-Jun He

Department of Breast and Thyroid Surgery, Research Institute of Surgery, Daping Hospital, Army Military Medical University, Chongqing 400042, China

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Correspondence to: Yu-Jun He. Department of Breast and Thyroid Surgery, Research Institute of Surgery, Daping Hospital, Army Military Medical University, Chongqing 400042, China. Email: heyujun69@163.com.

Abstract: Malignant melanoma of the breast (MMB) is a rare disease that accounts for 3–5% of all melanomas. It can be expressed as a metastatic mammary gland or primary mammary melanin of the mammary gland. Primary MMB (PMMB) can be divided into two types: parenchymal melanoma without skin involvement and melanoma involving skin on the breast. The diagnosis of PMMB relies mainly on histopathological diagnosis. In this diagnostic approach, S100 and HMB45 have a higher specificity in the diagnosis of melanoma immunohistochemistry. At the same time, mutations in the *BRAF* (V600E) gene have further aided the diagnosis of PMMB. After the diagnosis, the main treatment is mainly based on surgery. The main surgical methods include breast-conserving surgery and mastectomy. With advances in technology and surgical skills, the combination of patient aesthetic satisfaction and tumor safety is the goal of modern breast surgeons. This article reviews the current status of PMMB surgical treatment.

Keywords: Breast; malignant melanoma; primary; surgical treatment

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Introduction

Malignant melanoma is a malignant tumor produced by skin mucosa and other organs of melanocytes, and its incidence accounts for 1% to 2% of all malignant tumors (1). Mammary melanoma is a rare disease due to its high degree of malignancy, prone to distant metastasis, poor prognosis, and high mortality. Its incidence accounts for 3–5% of all melanomas, accounting for less than 0.5% of all breast cancers (2,3). There are four manifestations in the mammary gland (2): (I) primary malignant melanoma of the breast (PMMB) skin; (II) metastasis of the malignant melanoma to the mammary gland; (III) metastasis of the malignant melanoma to the mammary gland and skin; (IV) PMMB. According to the related literature, PMMB is mainly divided into two types: parenchymal melanoma without skin involvement and melanoma involving the skin of the breast (4,5), which is extremely rare in clinical

practice.

Although significant advances have been made in the field of malignant melanoma and breast cancer research, the early diagnosis and survival of these patients remain unsatisfactory. Surgery, chemotherapy, radiotherapy, and targeted molecular therapy are the main therapies for the treatment of malignant melanoma. However, due to the high rate of incomplete resection of the tumor and the resistance of chemotherapy or radiotherapy, more effective and safe treatment options are needed (6–8). Most of the primary malignant melanomas of the breast are clinically treated with localized skin ulcers or breast lumps. The diagnosis method mainly relies on pathological immunohistochemical staining methods and tissue source methods. The treatment method mainly relies on surgical resection combined with chemotherapy, radiotherapy, and immunotherapy to form a comprehensive strategy to

prolong the survival of patients. Because of the special shape and function of the breast, the surgical treatment methods are mainly divided into two types: (I) breast-conserving treatment; and (II) mastectomy. According to the characteristics of the tumor and the principles of treatment, patients can choose a breast-conserving treatment and mastectomy. Regardless of whether the breast is removed, cancerous plastic surgery and breast reconstruction can maintain the shape and function of the patient's breast, which greatly improves the patient's quality of life and body image (9).

In this review, we will briefly review the clinical signs and diagnosis of PMMB. Second, we will focus on the current surgical treatment of PMMB. Finally, we will make a prospect for modern surgical techniques, based on the conventional surgical treatment of primary malignant melanoma, to repair breast defects and further improve the quality of life of patients.

Diagnosis of PMMB

Clinical symptoms

According to relevant literature reports, most of the primary malignant melanomas of the breast are treated with breast lumps. The early stage is a painless mass with unclear borders, fixed, hard, poor mobility, and progressive tumor enlargement (10,11). In some cases, the mammary gland and nipple areola complex can be gradually changed into a satellite focus, ulcer, repeated unhealed, and rapidly progress to form a PMMB (11,12).

Imaging diagnosis

The clinical symptoms and imaging findings of primary breast malignant melanoma are similar to those of breast cancer. The mammography showed more calcified lesions and clearer borders. The whole mass showed small lobular shape, and ultrasonography (US) showed irregular shape, clear boundary, multi-phase hypoechoic, no calcification, and abnormal blood flow signal characteristics around the mass (4,12). In magnetic resonance imaging (MRI), primary breast malignant melanoma is characterized by high signal intensity on T1- and T2-weighted images (12). In positron emission tomography (PET), PET-CT is a very effective method for staging tumors and evaluating lymph node metastasis and distant organ metastasis.

Pathological diagnosis

The diagnosis of this disease mainly depends on biopsy pathology. The main pathological features of microscopic examination are tumor cells with relatively uniform size and morphological changes. Moreover, the volume of the nucleus in the tumor cells increases and the mitotic figures increase (13). The scattered pigment particles are also visible in some tumor tissues, and immunohistochemistry shows HMB45(+), S100(+), ER(-), PR(-). S100 and HMB45 have high specificity in the most commonly used immunohistochemical markers for the diagnosis of primary mammary malignant melanoma (14-16). According to related literature reports, BRAF (V600E) mutations have further helped the diagnosis of malignant melanoma (17). At the same time, Koh *et al.* (11) reported that the mutation of BRAF (V600E) further supports the diagnosis of PMMB.

Surgery on primary melanoma of the breast

There are two main types of surgical treatment for primary breast malignant melanoma (preservation treatment and mastectomy). Breast-conserving treatment can be subdivided into local enlarged tumor resection, partial mastectomy (PM) and oncoplastic surgery (OS). Mastectomy includes mastectomy (M) and mastectomy with reconstruction (MR). Through PubMed article reference to search for primary breast malignant melanoma in the past 5 years, the surgical treatment methods and basic data of patients were summarized (*Table 1*). At the same time, we will review the various surgical treatments for PMMB.

Local expanded resection of the tumor

For melanoma involving the surface of the breast, the treatment should be performed as soon as possible after the biopsy diagnosis, and the surgical approach is similar to malignant melanoma. The cutting edge is determined according to the depth of tumor invasion (Breslow thickness) in the pathological report: (I) when the thickness of the lesion is ≤ 1.0 mm, the safety margin is 1 cm; (II) when the thickness is 1.01–2 mm, the safety margin is 1–2 cm; (III) when the thickness is > 2 mm, the safety cutting edge is 2 cm; (IV) when the thickness is > 4 mm, the safety cutting edge is 2 cm. A European multicenter, randomized study included 936 melanoma patients with tumor thickness > 2.0 mm, in whom extended resection with a cutting edge

Table 1 Patients with primary melanoma of the breast reported in the literature

| Reference | Age (years) | Size (cm) | Location (quadrant) | LN/metastases | BRAF mutations | Treatment | Outcome |
|-----------|-------------|-----------|------------------------|---------------|----------------|--|----------------------------------|
| (10) | 26 | 3.0 | L upper inner | Yes | NA | None | Died in 2 months |
| (4) | 50 | 1.2 | R | No | V600E | Breast-conserving surgery + SLNB + adjuvant IFN-a for 9 months | NED at 12 months |
| (3) | 54 | 10.0 | L upper outer | No | NA | Right mastectomy + AIND + one-stage reconstruction | NED at 6 months |
| (12) | 59 | 4.0 | L nipples | Yes | NA | Right mastectomy + AIND + chemotherapy | NED at 7 years |
| (11) | 70 | 2.1 | R upper inner quadrant | No | V600E | Breast-conserving surgery + SLNB | survival at 26 months |
| (11) | 30 | 3.0 | L | Axillary node | V600E | Breast-conserving surgery + AIND | After 8 months lost to follow-up |

L, left; R, right; NA, not available; IFN-a, interferon a; NED, no evidence of disease; OS, overall survival; AIND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

of 2 or 4 cm was performed; the results showed the overall 5-year survival rates were similar in both groups (18). These findings were similar to previous studies (19-21). Systematic review and meta-analysis also showed that a cutting edge of 2 cm is sufficient. From a surgical point of view, primary breast malignant melanoma surgery should not only consider tumor removal but also fully consider retaining function, especially appearance. Therefore, simple resection and axillary dissection are a last resort. We do not advocate the use of simple resection and axillary dissection.

Substantial melanoma without skin involvement should be performed as soon as possible after the biopsy is diagnosed. In Koh *et al.*'s study (11), both patients underwent a PM plus sentinel lymph node biopsy (one of them underwent axillary lymph node dissection). In a randomized controlled trial analysis, there was no statistically significant difference in the 5-year overall survival and disease-free survival between the multiple methods [appropriate range of resection, wide resection group (edge 3–5 cm) resection and Narrow resection group (edge 1–2 cm) resection]. Surgical resection with a border of less than 2 cm has the same prognosis as a wider resection (22,23). Therefore, the surgical treatment of PMMB can be used to complete the local enlargement of the tumor under the premise of ensuring a negative margin. Mastectomy does not have any advantage over extensive local excision (i.e., local excision) (3). Sentinel lymph nodes are often the first stop for lymph node metastasis of breast malignancies,

so sentinel lymph node biopsy is generally recommended for patients with a thickness greater than 0.8 mm or a primary tumor with a solid mass. Sentinel lymph node biopsy is the criteria for determining whether axillary lymphadenectomy is needed, and such treatment can help reduce adverse complications (24-26).

Mastectomy

PMMB has a high degree of malignancy and poor prognosis. The literature reported 187 cases of PMMB (2,5,13,25,27-32). Mastectomy combined with axillary lymph node resection or axillary sentinel lymph node resection is the preferred treatment. This type of surgery was further confirmed in reports by Drueppel *et al.*, Bernardo *et al.*, Roy *et al.* (3,33,34). In the recent case reported by Nagata *et al.* (12), mastectomy and axillary lymph node dissection were performed in the nipple areola in the patient's lesion.

OS or MR after tumor resection

With the advancement of breast surgery and the improvement of patients' quality of life, the need for breast reconstruction after a mastectomy has become an indispensable part of a complete treatment plan. Breast reconstruction improves the patient's quality of life and psychological satisfaction. The awareness of breast reconstruction is recognized and accepted by more and more

cancer surgeons. In the case reported by Nagata *et al.* (12), after performing mastectomy combined with axillary lymph node dissection, implanted dilator or implant for one-stage reconstruction, the tumor safety of patients with lesions at the nipple areola is guaranteed. At the same time, the quality of life of patients has also improved. Studies have shown that breast shape can be better preserved when the amount of gland removed by breast surgery is <20%; when the amount of gland removed is $\geq 20\%$, the shape of the breast will be significantly deformed (35-37). Among them, the preservation of the breast in the upper quadrant of the breast or the lower extremity of the breast is more obvious (38). Therefore, for patients with a resection volume less than 20% of the breast, the preservation of the breast surgery has little effect on the shape of the breast, and generally, no significant breast deformation occurs. The surgical method only needs to select the incision with cosmetic effect, and the tissue surrounding the lesion is moderately free, and the residual cavity can be closed. For patients with relatively large primary mammary malignant melanoma, a personalized cancerous orthopedic surgery should be selected based on the size of the patient's breast. Commonly used cancerous plastic surgery has volume replacement and volume shift (39), and this surgical approach has rarely been reported in primary mammary breast tumors.

Systemic adjuvant therapy for PMMB

Adjuvant therapy refers to various treatments other than surgery, the main purpose of which is to reduce the risk of recurrence and metastasis. The most current evidence is the combination of high-dose interferon alpha (40,41) with traditional cytotoxic drugs, including dacarbazine, temozolomide, fluoxetine, paclitaxel, albumin paclitaxel, cisplatin and carboplatin (40-42) Treatment with cytotoxic drugs. In patients with primary breast malignant melanoma for *BRAF* (V600E) gene mutations, new compounds have been approved by the FDA and EMA or entered phase II/III clinical trials as single or combination therapies, such as PD-1 inhibitors (nivolumab, pembrolizumab) (40,41). These new targeted drugs may significantly improve the survival of patients with primary breast malignant melanoma.

In conclusion, PMMB is a very rare tumor with a poor prognosis. Diagnosis depends on histopathological examination and immunohistology. Early diagnosis, correct

surgical resection, and comprehensive adjuvant therapy are important factors influencing the efficacy of surgery. With the development of breast surgery and the strengthening of multidisciplinary collaboration to ensure the survival of patients with primary breast malignant melanoma, the treatment should further improve the quality of life of patients. Therefore, local tumor enlargement and sentinel lymph node biopsy is the first choice for early PMMB. At the same time, it is not a bad choice for patients with cancerous plastic surgery due to severe breast deformation after breast-conserving surgery.

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