

Surgical Treatment of Breast Cancer

Damir Grebić*

Department of Surgery, University of Rijeka, Europe

***Corresponding author:** Damir Grebić, Department of Surgery, Clinical Hospital Center Rijeka, School of Medicine, University of Rijeka, Kresimirova 42, Rijeka, Croatia, Europe. Tel: 051/658-684; Fax: 051/213-734; Email: damir.grebic@medri.uniri.hr

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ETIOLOGY, EPIDEMIOLOGY AND PATHOLOGY OF BREAST CANCER

Breast cancer is the most common malignant tumour in women worldwide. It is said that one in eight women will develop breast cancer. Morbidity and mortality increases with age, significantly after the age of 45, with peak morbidity in the 50s [1,2]. Early detection of the disease is vital. More than 90% of breast cancer patients can be cured, if the disease is detected at an early stage. Mammography is a significant screening test for early detection [3]. Although self-examination is commended, it is believed it does not have a meaningful role in early detection [4]. Risk factors include: Age, gender, positive family history, heredity, hormones, dense breasts, precancerous lesions such as atypical hyperplasia, ionising radiation, physical inactivity and obesity after menopause, and longer exposure to estrogen (hormone replacement treatment, early menarche, late menopause). Women with mammograms showing dense breasts have 4 times the risk of contracting the disease [5], as do women with atypical hyperplasia, and in the case of positive family history, the risk increases 8-12 times [6]. Women with a history of ovarian cancer have 2 times the risk (possible mutations of BRCA 1 or BRCA2 genes). Ionising radiation is unsafe during

menarche years, that is, until 18 [7]. Prognostic factors in patients include number of effected axillary lymph nodes, tumour size, hormone receptor status, and degree of tumour differentiation (grade). According to pathohistology, ductal and lobular carcinomas are differentiated, both of which may be invasive, non-invasive, or in situ. Invasive ductal carcinoma is the most common malignant breast tumour. Ductal carcinoma in situ (**DCIS**) characteristically spreads intraductally, often affecting a larger portion of breast parenchyma, because of this, it is often multicentric (present in more than one breast quadrant). Surgical treatment is necessary due to the possibility of invasive components, which are only confirmed by pathohistological analysis [8]. Lobular carcinomas are less common. Mammography often fails to detect lobular invasive cancer, therefore additional radiological techniques are required for diagnosis, such as ultrasound and magnetic resonance imaging. They are often multicentric as well. Lobular carcinoma in situ (**LCIS**) is generally not treated, but it is routinely monitored, due to the increased risk for patients to develop invasive cancer [9]. According to molecular classification, breast cancers are divided into four types based on the expression of hormone receptors, HER2 genes, and Ki67 proliferation markers: Luminal A, luminal B (HER2 positive or HER2 negative), HER2 positive and triple negative (hormone receptor and HER2 negative) [10]. This classification has its relevance in choosing treatment and in predicting response, outcome, and prognosis. Subtype luminal A has the best prognosis, while triple negative has the worst [11].

DIAGNOSING BREAST CANCER

Mammography is a test for screening and early detection of breast cancer, suitable for analysis of breast parenchyma with involutional changes. It is performed over the age of 40. In dense breasts with a lot of functional glandular tissue, mammography should be complemented by ultrasound [12]. Ultrasound is used primarily in younger patients (up to the age of 40). It differentiates solid from cystic lesions well, and for each visualised lesion, it is possible to perform ultrasound-guided fine needle aspiration (**FNA**) cytology, or a core needle biopsy (**CNB**), where a cylinder of tissue is sampled for pathohistological analysis [13] (Figure 1). Because of possible false positives with cytological analysis, the only definitive confirmation of malignant disease is pathohistological diagnosis [14].



Figure 1: Instrument for core biopsy of the breast, by which a cylinder of tumourous tissue is taken for pathohistological diagnosis.

BREAST CANCER SURGERY

Breast Sparing Surgery

Lumpectomy or tumourectomy

Lumpectomy is an operation in which a tumour is removed with as little surrounding normal tissue as possible in order to achieve negative margins. This is the most conservative breast surgery. It is indicated for benign tumours, for diagnostic purposes when needle biopsy fails to provide a definitive result, and for the purpose of palliative treatment in patients with advanced breast cancer, old age, comorbidities, or a great anaesthesia risk [15].

Segmentectomy

Segmentectomy is a surgery which falls between lumpectomy and quadrantectomy. It is the method of choice for tumours up to 2 cm in diameter. This surgery removes the tumour and preserves the overlying skin and underlying fascia of the large pectoral muscle. Today, the resection width is considered sufficient as long as the margins are negative, in contrast to when it was precisely specified how much the tumour must be removed from the margins in the pathohistological analysis, and if this was not achieved, re-excision was performed or even mastectomy if the breast volume was small. It is not required to obliterate the resulting cavity after surgery with sutures, however, to prevent 'dead space', and the accumulation of seroma or postoperative haematoma, it is advisable to do so [16].

Quadrantectomy

Quadrantectomy is the most comprehensive and commonly used breast sparing surgery which includes the removal of one quadrant, approximately $\frac{1}{4}$ of breast volume, along with the overlying skin and underlying fascia of the large pectoral muscle. Greater breast deformation is possible in comparison to segmentectomy and tumourectomy. It is possible to remove tumours up to 4 cm in diameter by quadrantectomy. Contraindications for quadrantectomy are the same as for other breast sparing surgery, which include: Tumours larger than 4 cm, multicentric breast cancers (present in two or more quadrants) and presence of extensive intraductal components (presence of more than 20% DCIS in pathohistological analysis) presence of diffuse malignant microcalcifications, unfavourable ratio of tumour to breast size (small breast, large tumour). Despite this, quadrantectomy is the operation of choice for multifocal breast tumours (presence of two or more tumour foci within one quadrant). The incision line for quadrantectomy must be elliptical, radially directed towards the nipple and areola. In lower quadrants, a radial incision is used, while in upper quadrants, semicircular. For a centrally located tumour, a central quadrantectomy can be performed with excision of the areola and nipple. After surgery, the resected tissue margins are marked for proper orientation by the pathologist. Rinsing before closing is favourable to remove possible residual malignant cells (Figure 2). The tumour must not be cut, as later it will be difficult to determine the resection margins. After removal, it is favourable to apply sutures to close the cavity, and for modelling the breast. Along with sutures, placing a surgical drain is recommended to prevent complications such as seroma and haematoma. Postoperatively, as with every breast sparing surgery, it is necessary to give radiotherapy by irradiating the remaining breast tissue, especially the original tumour location, which is marked during operation by placing metal clips on the large pectoral muscle (projection of the tumour on the chest wall). Radiotherapy should be carried out within 4-8 weeks after surgery (optimal time is 3 weeks after surgery) [17,18].



Figure 2: State post quadrantectomy of carcinoma in the II. quadrant.

Mastectomy

Simple or total mastectomy

A simple or total mastectomy is a surgical procedure in which the whole breast is removed with the fascia of the large pectoral muscle, along with the skin and nipple, while preserving the large and small pectoral muscles, and axillary lymph nodes. Indications include: Local recurrence after breast sparing surgery and radiotherapy, as a 'cleansing' surgery for women with ulcerated carcinoma, multicentric carcinoma, presence of diffuse malignant microcalcifications, extensive DCIS, tumours exceeding 4 cm without axillary metastases (negative sentinel lymph node), or even for large tumours in a small breast. In patients suffering from a collagenosis (systemic lupus erythematosus or scleroderma), it is advisable to do a mastectomy due to skin sensitivity, and problems in such patients during required adjuvant radiotherapy. It can be said that the indications are the same as the contraindications for breast sparing surgery. Stewart's elliptical incision is most commonly used with mandatory surgical drain placement after surgery and operative wound rinsing before closing to remove possible residual malignant cells (Figure 3). It is necessary to properly label the resection with stitches (most commonly the upper and lateral margins) to ensure correct orientation by the pathologist [19].



Figure 3: State post simple mastectomy by Stewart incision with a surgical drain of the operative wound.

Modified radical mastectomy

A modified radical mastectomy is a surgical procedure in which the entire breast is removed along with the fascia of the large pectoral muscle, the skin, the nipple, and the lower two levels of lymph nodes in the armpit, usually as one piece. Indications for this surgery are: Breast tumours

larger than 4 cm with a clinically positive axilla, tumours which infiltrate the skin and nipple with a clinically positive axilla, as a 'cleansing' mastectomy in women with ulcerated carcinoma in which it is possible to remove axillary lymph nodes, breast cancer during pregnancy, multicentric carcinoma with involved axillas, recurrence of carcinoma with involved axillas, positive resection margin after re-excision. Contraindications are inflammatory breast cancer for which it is first necessary to carry out neoadjuvant chemotherapy, and primary inoperable carcinomas where radical removal and achievement of negative margins is impossible. The most common incision used is Stewart's elliptical incision with mandatory surgical drain placement in the axilla after surgery and operative wound rinsing before closing. This procedure is still more conservative in comparison to Halsted's radical mastectomy, as it preserves the pectoral musculature (better cosmetic outcome) and the third level of axillary lymph nodes, which significantly reduces postoperative arm lymphoedema. Survival rates are the same in comparison to Halsted's procedure [20]. Complications of this operation are possible injury to major blood vessels or neural structures of the upper extremities [21]. Other common complications are lymphoedema, seroma, haematoma, and infection.

Halsted's radical mastectomy

This procedure is of historical significance only. This is an extremely complex and mutilating surgery where the whole breast, both pectoral muscles, and all three levels of axillary lymph nodes are removed. Arm lymphoedema, large seroma, and poor cosmetic outcomes are common complications. Since the survival rate is comparable to less radical operations, this operation has become a part of history, and has been replaced by the less aggressive form of surgical treatment as the modified radical mastectomy [21,22].

Skin and nipple sparing mastectomy

This is a newer procedure in which breast tissue is removed, but the skin envelope of the breast is preserved, if the nipple and areola are also saved in the process, then it is called nipple sparing mastectomy. The main indication for this type of mastectomy is an interest in primary breast reconstruction. The technique is suitable for prophylactic mastectomy since it is followed by immediate breast reconstruction, usually with a prosthesis, or autologous tissue (muscle). Additionally, it is indicated for extensive DCIS and for early invasive carcinoma which does not involve the skin, and is removed from the nipple a minimum of 2 cm (a requirement for nipple sparing). Small or medium sized breasts can be operated using this method. For sagging or ptotic breasts, additional mastopexy is recommended. The skin incision is often periareolar or combination radial and periareolar (omega incision), or less commonly in the inframammary furrow. The goal of each successful mastectomy by this technique is to achieve a uniform thickness of the skin-subcutaneous layer; otherwise the surface of the reconstructed breast is uneven. The operator must also take into account that the necessary thickness of the skin layer is between 0.5 to 1 cm. If too thin, a possible complication is necrosis of the skin flap [23]. The disadvantage

of this technique is a radical issue. Namely, with this surgery, glandular breast tissue can never be completely removed due to the unclear boundary between subcutaneous fat and breast tissue. As a result, a question of oncological assurance arises, or rather a greater chance for local recurrence (this very reason makes it most suitable for operating extensive DCIS and prophylactic mastectomy). On the other hand, some authors have concluded that the development of local recurrence is the result of increased biological aggressiveness of the tumour, rather than the result of preserving the skin envelope, since T1 and T2 stage tumours rarely infiltrate the skin [24]. Still, it must be stressed that standard mastectomy does not guarantee the complete removal of all glandular tissue either.

AXILLARY SURGERY

Sentinel Lymph Node Biopsy

The sentinel lymph node is the first node to which cancer metastases spread. A biopsy is indicated for every invasive and microinvasive breast carcinoma, and for DCIS, but only when a mastectomy is done, as it can then be included in the pathohistological analysis of invasive components, where if a mastectomy is done in a second act, radiopharmaceutical cannot be applied to mark the sentinel node. Definite indications for sentinel lymph node biopsy (**SLNB**) are predominantly early stage T1 and T2 carcinomas, while contraindications are inflammatory, ulcerated, and skin-infiltrating carcinomas (**T4**), and clinically positive axilla (or confirmed metastases in the axilla by lymph node aspiration). Sentinel biopsy is not indicated in malignant stromal breast tumours, as they spread hematogenously [25]. It should be noted that multicentricity is not a contraindication for SLNB. SLNB has led to the decrease in the number of unnecessary axillary dissections and unwanted complications (irreversible arm lymphoedema, neurological disorders, or chronic postoperative seroma). This means that axillary dissection is not primarily indicated in the case of a negative sentinel. However, new guidelines report that even in the case of a positive sentinel (up to 2 positive sentinels), axillary dissection is not indicated, although axillary radiotherapy would be required instead of dissection, new evidence supports that axillary radiotherapy is equivalent to axillary dissection, and dissection has no advantage in terms of reducing mortality and prolonging life [26]. Numerous techniques exist to preoperatively mark the sentinel lymph node. Some of these techniques use dye (methylene blue), while others are methods of nuclear medicine (lymphoscintigraphy), which involves the injection of radioactive technetium, then scanning the patient with a gamma camera, and labelling the sentinel. Then (no longer than 24 hours, otherwise the radioactivity is excreted) the surgical procedure is performed during which the sentinel lymph node is identified using a gamma probe to detect radioactivity. The lymph node with the highest level of radioactivity (at least 10 times higher than its surroundings) is the sentinel lymph node to be surgically extirpated and sent for imprint cytology evaluation, and in the case of a positive result or suspected presence of malignant cells in the intraoperative biopsy (frozen section), then a definitive conclusion can be made of the existence of malignant

infiltrate in the sentinel. Only then is the scope of the operation extended, that is, an axillary dissection is performed. It is possible to label sentinel lymph nodes in up to 99% of cases with lymphoscintigraphy. By combining the two techniques, it is possible to identify the sentinel in almost all patients with breast cancer [27]. Application of only methylene blue leads to a high incidence of false positives in breast cancer, as the technique is not 100% accurate. In the case of unsuccessful sentinel lymph node identification, it is necessary to perform an axillary dissection. It is not contraindicated to repeat SLNB in the case of recurrence, but sentinel identification is less successful since the lymphatic pathways were resected during the first operation and in the majority of these patients, an axillary dissection is required.

Axillary Lymphadenectomy (Axillary Dissection)

Axillary lymphadenectomy is a procedure to remove the lower two levels of axillary lymph nodes located in the triangular area bounded cranially by the axillary vein, medially by the serratus anterior muscle, and from the rear and laterally by the latissimus dorsi muscle. In addition to its role in treatment, it also has a role in staging, that is, in determining the degree to which disease has spread. Indications for this procedure include positive sentinel lymph node, preoperative clinically positive axilla, or confirmation of malignant cells in a cytological aspirate of a suspicious axillary lymph node [28]. Stewart's incision is used if mastectomy is also being performed, or if breast sparing surgery is also being performed, then a separate incision is used in the shape of the letter S beginning on the front armpit crease (large pectoral muscle), and ending on the rear armpit crease (latissimus dorsi muscle). When the tumour is located in the upper outer quadrant of the breast, the axilla is simply an extension of the radial incision made for a quadrantectomy of the upper outer quadrant. During surgery, an incision is made in the clavipectoral fascia covering axillary neurovascular structures. Then, the thoracoepigastric vein is isolated and tied. The axillary vein is prepared as the cranial border for cleaning, then the medial borders for cleaning, the serratus anterior muscle and the long thoracic nerve which follows the medial section along the thoracic wall. The thoracodorsal bundle (thoracodorsalis artery, vein, and nerve) is then prepared and the nodes along this bundle are removed laterally and back all the way to the latissimus dorsi muscle. The depth of the axilla and rear are cleaned to the subscapularis muscle. Although classic lymphadenectomy does not involve the preservation of the intercostobrachial nerve, if possible, it is advised to preserve it to prevent paresthesia and sensory loss of the medial and rear surface of the proximal third of the upper arm. A minimum of 10 lymph nodes are required to determine the stage of the disease [28]. Upon completion, it is necessary to rinse the surgical wound and place a Redon drain. Postoperatively, arm exercises are important. The drain is retained as needed. The most serious complications include injury to major vascular structures and risk of bleeding, followed by injury to neural structures (long thoracic nerve and thoracodorsalis nerve which results in the paralysis of the serratus anterior and latissimus dorsi muscles). This complication manifests during the late postoperative period (even a month after surgery) either as a "winged scapula" (lifted scapula as the serratus anterior

muscle plays a role in holding the scapula to the thoracic wall), or as difficult retroflexion of the arm in the shoulder joint (role of latissimus dorsi muscle). Another undesirable complication is arm lymphoedema which occurs as a late complication (sometimes many years after surgery), treated with physical therapy or elastic compression bandage of the upper extremity, which yields modest results [29] (Figure 4). Surgical treatment is possible using microsurgical techniques to create anastomoses between lymph vessels and vascular structures, but success is also limited [30]. Other complications include seroma, haematoma, and wound infection, as with any surgical procedure [31].



Figure 4: Extensive lymphoedema of the left arm after axillary dissection (ten years after surgery).

SURGICAL TREATMENT OF LOCALLY ADVANCED BREAST CANCER

Locally advanced breast cancer is defined by skin infiltration and regional axillary lymph node involvement. According to TNM classification, this would be classified as T4 (skin infiltration). Inflammatory breast cancer is considered to be the worst type of breast cancer, which diffusely infiltrates the skin making it red, swollen, and thick, giving it an appearance akin to an orange peel, with abundant lymphoedema [32]. The diagnosis of locally advanced breast cancer is achieved by clinical examination and core biopsy for pathohistological confirmation. As the most malignant form of breast cancer in general, it is necessary to determine the immunoprofile of the tumour, then carry out neoadjuvant chemotherapy, and when partial remission is achieved, perform a modified radical mastectomy. The same procedure should be done for every advanced cancer with confirmed distant metastases and extensive axillary lymph node involvement. An exception

can be made for ulcerated carcinomas which are actively bleeding and lead to anaemia, when it is desirable to perform surgery before chemotherapy with the goal of improving the quality of life of the patient [33] (Figure 5). For locally advanced cancer, radiotherapy of the thoracic wall is also required. Despite all of this, prognosis is poor, although it depends on the carcinoma subtype (hormonal dependent tumours have a better prognosis than HER2-positive and triple negative).



Figure 5: Bleeding ulcerated breast cancer.

SURGICAL TREATMENT OF RECURRENT BREAST CANCER

The frequency of local recurrence (on the thoracic wall) or regional recurrence (in the axilla) depends on the aggressiveness and biological behaviour of the tumour (HER2-positive and triple negative are more malignant), as well as the staging of the disease, that is, the number of effected lymph nodes at the time of diagnosis. Local recurrence after breast sparing surgery with radiotherapy is an indication for a simple mastectomy (often with lymphadenectomy), while recurrence on the thoracic wall after mastectomy requires radical removal (if necessary resection of the pectoral muscle or even the entire thickness of the thoracic wall with reconstruction of the same using a myocutaneous flap and mesh) [34,35]. Many patients at the time of locoregional recurrence have or soon develop distant metastases. Therefore, it is necessary to do a thorough diagnostic evaluation to confirm metastases (**PET-CT**). Metastatic tumours have a locational predilection for the lungs, bones, liver, and brain. The difference between recurrence and new primary carcinoma is also worth noting. A carcinoma which appears a long time after surgery (over 5 years) and is not near the scar is considered to be new. Recurrence commonly develops within the first 5 years and near (2-3 cm) the scar. It is important to keep in mind the heterogeneity of tumours and new mutations which explains why recurrent and previous carcinomas may

not be the same immunohistochemical profile in terms of hormonal receptor and HER-2 gene expression, making it necessary to determine the exact immunoprofile for each recurrence or new tumour for the application of adequate oncological therapy. Survival and prognosis are bad, few patients survive for more than three years [36]. In patients with locoregional recurrence, postoperative radiotherapy and chemotherapy is absolutely necessary, as long as the patient can handle this, taking into consideration comorbidity and general condition.

SURGICAL TREATMENT OF BREAST CANCER IN SPECIAL CIRCUMSTANCES

Breast Cancer during Pregnancy

The basic principle that applies here is to treat the cancer and secure the pregnancy. The ideal procedure is a modified radical mastectomy. Breast sparing surgery is contraindicated as it is accompanied by radiotherapy in the postoperative period, which due to pregnancy is absolutely contraindicated. Similarly, lymphoscintigraphy with a radiopharmaceutical to mark the sentinel lymph node is contraindicated; therefore an axillary dissection must be done. This explains why the method of choice is a modified radical mastectomy. It is possible to perform conservative surgery at a later stage of pregnancy (III. trimester) with mandatory radiotherapy after delivery (no later than 8 weeks postoperatively) [37].

Paget's Breast Cancer

This is a rare form of cancer that first affects the nipple. Therefore, every eczematous change of the nipple should be biopsied. Pathohistological analysis can confirm, besides ductal and lobular, medullary and papillary breast carcinomas as well. When invasive components are present, but axillas are clinically negative, it is indicated to do a SLNB. Mastectomy is usually indicated, although it is possible to do a central quadrantectomy with radiotherapy, especially in large breasts [38]. Breast reconstruction is possible (since skin and nipple sparing mastectomy is contraindicated) during the later course of treatment, first with tissue expander, then with a permanent prosthesis [39]. In cases of central quadrantectomy, it is possible to reconstruct the nipple with a skin flap, and the areola with a tattoo.

Breast Cancer in Men

Breast cancer is rare in men. In the aetiology, risk factors include obesity and gynaecomastia, although this connection is not proven. It is usually detected at an advanced stage, and considering the small breast size, modified radical mastectomy is the surgical method of choice. Pathohistologically speaking, most tumours are hormonally dependent, while few are HER-2 positive or triple negative [40].

Occult Breast Cancer

Occult breast carcinoma is not visible by mammography, but the axilla is clinically positive.

Therefore, any palpable formation of the axilla should be considered to be a metastasis and requires a biopsy. Differential diagnosis includes lymphomas, but a large percentage of axillary lymphadenopathy are also benign (reactive lymphadenitis, cat scratch disease, etc.). If malignancy is confirmed, a modified radical mastectomy is indicated [41].

OTHER RARE STROMAL BREAST TUMOURS

Malignant Phyllodes Breast Tumours

This is a biphasic tumour with an epithelial and stromal component of which the stromal component is malignant, and behaves like a sarcoma (older name cystosarcoma phyllodes). Diagnosis is made by core biopsy. A simple mastectomy is indicated for malignant types (without axillary dissection since the tumour spreads hematogenously) [42].

Breast Sarcoma

In addition to the malignant phyllodes tumour, which is a type of sarcoma, malignant fibrous histiocytoma and many other malignant stromal tumours may develop in the breast. What must be kept in mind as a late complication of radiotherapy after breast sparing surgery is angiosarcoma or lymphangiosarcoma development. These tumours often manifest as a purple macula with irregular margins which is well-defined from its surroundings (Figure 6). Any such suspicious changes should be biopsied to exclude angiosarcoma and should not be attributed as side effects of radiotherapy, or identified as a haematoma. In the case of pathohistologically proven angiosarcoma, a simple mastectomy is indicated [43]. Axillary lymphadenectomy is not indicated since this tumour spreads hematogenously. Prognosis depends on the stage of the disease, but in most patients it is poor with a small percentage of five-year survival.



Figure 6: Breast angiosarcoma which developed as a late complication of radiotherapy after breast sparing surgery of invasive cancer (six years after radiotherapy). Purple macula with irregular margins is shown.

PROPHYLACTIC OR PREVENTIVE MASTECTOMY

Prophylactic or preventive mastectomy is an operation that involves the removal of both breasts in order to prevent the development of breast cancer. Of the available surgical techniques, skin and nipple sparing mastectomy is most often used with immediate breast reconstruction with implants. Any patient who opts for this operation should be advised by a multidisciplinary team for breast disease since the decision must be examined from medical, ethical, and psychosocial aspects [44]. Indications are primarily positive immediate family history (mother, sister who developed disease under 50 years of age), and women with proven BRCA1 and BRCA2 gene mutations, then women with LCIS which is a sign of increased risk for morbidity of invasive breast carcinoma, as well as women with biopted suspicious lesions whose pathohistological findings suggest atypical ductal hyperplasia, and at the same time who have a positive family history [45,46]. Prophylactic mastectomy is not a 100% guarantee that operated patients will not develop breast cancer (although this outcome is significantly reduced), since the operation can never 100% remove breast tissue (usually some tissue remains in the axillary or submammary areas), which must be explained to the patient. Of radiological techniques in monitoring patients who underwent prophylactic mastectomy with reconstruction with implants, the importance of magnetic resonance is emphasised. An alternative to this surgical procedure is the regular monitoring of women with increased risk, or the use of tamoxifen (antiestrogen) in women with proven LCIS.

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