Original Article

The application of methylene blue location technique in deep-seated benign breast tumor resection under endoscopy: a retrospective, single-institution analysis

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Background: Endoscopic curative excision of benign breast diseases (BBDs) can preserve the cosmetic appearance of the breast. However, endoscopic surgery is not feasible, and some challenges still need to be addressed. Traditional line marker localization methods cannot visualize tumors, and the exploration of deep tumors may lead to certain risks of accidental injury. This study aimed to investigate the value of the methylene blue location (MBL) technique in endoscopic resection of deep-seated benign breast tumors.

Methods: A total of 217 patients with benign deep breast tumors admitted to the Sixth Affiliated Hospital of Sun Yat-sen University between November 2017 and June 2023 met the inclusion criteria. Among them, 107 patients underwent endoscopic resection with a MBL, in which methylene blue was injected to guide the tumor resection endoscopically, whereas 110 patients underwent endoscopic resection with a skin mark location (SML), in which the tumor was located by a marking line on the skin. We compared patient characteristics, surgery-related data, complications, and cosmetic outcomes between the two groups.

Results: Endoscopic breast tumor resection was successfully performed in 217 patients, none of whom had undergone open surgery. The mean operation time was significantly different between the MBL and SML groups (45.70±12.508 and 49.59±10.997 min, respectively; P=0.008<0.05), and blood loss in the MBL group was significantly reduced compared with that in the SML group (11.07±5.665 and 13.83±7.918 mL, respectively; P=0.004<0.05). There were no significant differences in drainage volume, length of hospital stay, or postoperative complications between the MBL and SML groups (P>0.05). The postoperative cosmetic outcomes of the patients were noteworthy, with no statistically significant differences between the two groups.

Conclusions: The methylene blue positioning technique is safe and effective for the endoscopic treatment of deep breast tumors. It shortens operation time, reduces surgical complications, and is worthy of clinical promotion.

Keywords: Benign breast tumor; endoscopic; resection; methylene blue; ultrasound

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Introduction

Benign breast diseases (BBDs) are one of the most common diseases in the females worldwide (1,2). Among women diagnosed with invasive breast disease, 30% have a prior diagnosis of BBD (3). Benign breast lesions usually present as palpable masses or are identified on incidental screening mammography (4). These varieties of lesions include fibroadenoma, fibrocystic change, breast cysts, and breast abscesses. Most benign tumors were evaluated using the Breast Imaging-Reporting and Data System (BI-RADS) 3 or 4A, which always indicates benign lesions before the biopsy, but with the final pathological confirmation of malignancy, and proven by many studies from multiple countries (5,6), Surgical excision is the definitive procedure performed for symptomatic benign breast tumors to alleviate anxiety regarding the potential for growth, malignancy, and physical discomfort (7).

With the development of oncoplastic breast techniques that have developed over recent years, concerns regarding postoperative aesthetic outcomes have also increased (8). Endoscopy has been widely used in breast tumor surgery to achieve curative partial resection and preserve the cosmetic appearance of the breast (9,10). The appearance of endoscopy allows wide excision without compromising the aesthetic outcome of the breast (11). However, deep-seated tumors are hidden and difficult to touch, and there are still some challenges for endoscopy to explore: the conventional line marking location method cannot visualize the tumor, and exploration for deep-seated tumors may lead to a certain risk of accidental injury.

In this study, ultrasound-guided intraoperative injection of methylene blue was used to locate deep-seated breast tumors, thereby enabling visualization and precision of deep breast tumor resection under endoscopy. We discuss the application of the methylene blue location (MBL) technique in endoscopic resection of deep-seated BBD, and review the differences in surgical indices brought about by the MBL technique. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-139/rc).

Highlight box

Key findings

- The methylene blue positioning technique is safe and effective for the endoscopic treatment of deep breast tumors.

What is known and what is new?

- Methylene blue has been used in the field of surgery for decades, detecting breast tumor sentinel node biopsy, and labeling breast tumors owing to the disadvantages of radioisotopes, typically presenting a good safety profile. The conventional line marking location method cannot visualize the tumor, and exploration for deep-seated tumors may lead to a certain risk of accidental injury.
- We evaluate the application of the methylene blue location (MBL) technique in endoscopic resection of deep-seated benign breast disease.

What is the implication, and what should change now?

- MBL is a safe and effective technique with fewer complications, which shortens operation time, reduces surgical complications, and is worthy of clinical promotion.

Methods

Data source

Data of patients with primary deep-seated breast tumors who underwent endoscopic resection between November 2017 and June 2023 were retrieved from a retrospectively maintained breast tumor database at the Sixth Affiliated Hospital of Sun Yat-sen University. Data collected from the database included patient demographics, tumor characteristics, and surgical outcomes in terms of operative time, blood loss, length of hospital stay, surgical complications, and cosmetic effects. All data were collected through chart review by specially trained investigators and subsequently confirmed by the principal investigators. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University, with the approval number of 2021ZSLYEC-404. The current study included photographs of several patients who agreed and consented to the publication of their photographs. Written informed consent for the use of the clinical records was obtained from each participant.

Patient eligibility for inclusion and exclusion

Ultrasound and mammography results were used to determine the eligibility of patients enrolled in the study. Eligible patients were those who had breast tumors, the BI-RADS range from class 3 to 4A), a tumor distance from the pectoralis major of less than or equal to 5 mm or on the surface of the pectoralis major, a tumor greater than or equal to 20 mm at maximum diameter, no evidence of

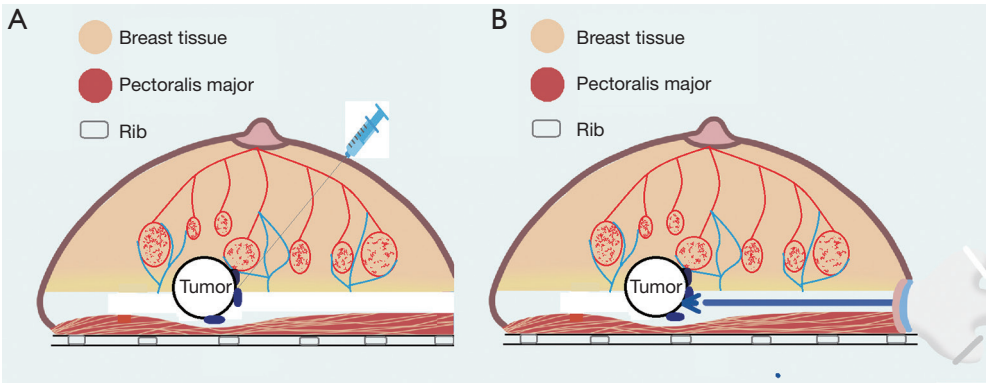


Figure 1 Multi-point injection of methylene blue was performed under ultrasound guidance before the operation, the needle was passed through the entire layer of the gland to reach the posterior space of the mammary gland, avoid passing through the tumor. The methylene blue injection sites were visible under the surgical field, and the surgery was performed under methylene blue guidance. (A) MBL sketch map; (B) endoscope resection guided by MBL (the blue arrow represents the top of the electric hook). MBL, methylene blue location.

multiple lymph node metastasis, and no evidence of skin or chest wall invasion. Patients with inflammatory breast tumors, multi-centric disease, breast tumor with chest wall or skin invasion, and breast tumors with extensive axillary lymph node metastasis (stage IIIB and above) were excluded. Patients who underwent endoscopic resection with methylene blue were allocated to the MBL group and those who underwent endoscopic resection by skin mark location (SML) were allocated to the SML group.

SML method

The tumor was palpated on the lateral side of the breast under ultrasound, marking the site of the tumor by drawing a cross-line and drawing a range that the endoscope could explore. The patients in the SML group underwent endoscopic resection using the skin-mark location method.

MBL technique

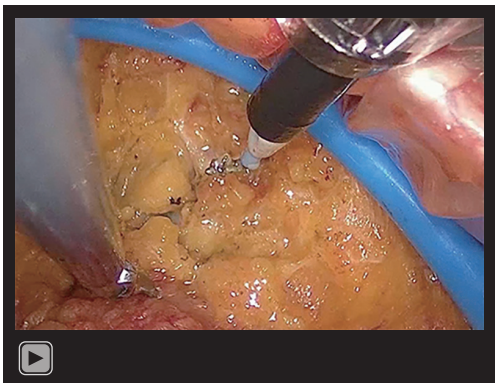
Details of the surgical techniques for endoscopic resection with a MBL are described in the surgical procedures section. A brief summary of the techniques is as follows: firstly, 0.1 mL of methylene blue was extracted with a 1 mL syringe, the syringe barrel was removed, and the needle of a 10 mL syringe was connected (the longer length of the needle of a 10 mL syringe could reach the bottom of the deep tumor).

Multi-point injection of methylene blue was performed under ultrasound guidance before the operation, and the incision and tumor line were used as the injection routes (*Figure 1A*). A virtual connection was made between the tumor and the incision; the connection line was across the edge of the tumor, and a syringe with 1% methylene blue was inserted at the cross point. The needle was passed through the entire layer of the gland to reach the posterior space of the mammary gland, avoid passing through the tumor. The tumor markings were on the lateral side and at the bottom of the tumor. Methylene blue was injected into the deep side of the gland for localization, and methylene blue was injected into the retromammary space approximately 5 mm from the cross point to determine the proximal and distal incisal margins of the tumor.

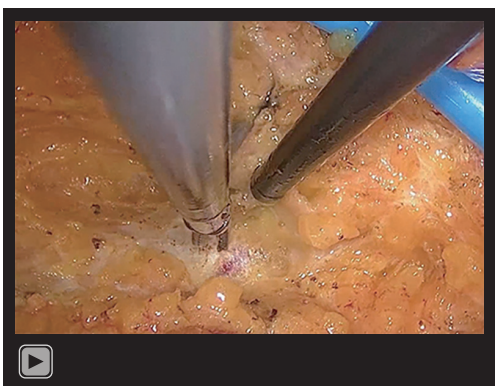
The patients were placed under intraoperative ultrasound guidance and methylene blue was clearly observed during intraoperative endoscopy. Surgery was performed under methylene blue guidance (*Figure 1B*), and none of the patients underwent open surgery.

The specific surgical procedures

(I) The patient was placed in full supine position after anesthesia. (II) The length of 2.5 cm incision was made in the axillary fold, and established an air chamber with a pressure of 8 mmHg was established. (III) The posterior space of the breast was separated by an electric hook under a single-hole endoscope along the surface of the pectoralis major. The bottom of the tumor was identified by pressing the marker above the tumor in SML group, while the location of the tumor in MBL group was confirmed by



Video 1 The posterior space of the breast was separated using an electric hook under a single-hole endoscope along the surface of the pectoralis major; the location of the tumor in the MBL group was confirmed by the methylene blue point, and the methylene blue injection sites were visible under the surgical field. MBL, methylene blue location.



Video 2 The surgeon incised the gland behind the tumor, exposed the tumor envelope, and then separated the tumor forward and upward to the initial point until the tumor was completely exposed in the air cavity.

the methylene blue point, the methylene blue injection sites were visible under the surgical field (*Video 1*). The surgeon incised the gland behind the tumor, exposed the tumor envelope, and separated the tumor forward and upward from the initial point (*Video 2*). The separation was continued to the distal end until the tumor was completely exposed in the air cavity (*Figure 2A*,*2B*, *Video 3*). (IV) The tumor was resected (*Figure 2C*,*2D*, *Video 4*), and the wound was rinsed with 0.9% saline and a drainage tube was placed. (V) The incision was closed with absorbable thread. The duration of localization and dissection were recorded.

Postoperative process

The tumor was resected using a methylene blue-guided endoscope, and pressure bandages were applied postoperatively. The drainage tube was removed when the daily drainage volume was less than 25 mL postoperatively (*Figure 3*), and breast elastic underwear was used to replace the bandages. Blood loss, drainage volume, and length of hospitalization were recorded.

Follow-up

All patients were followed up at the outpatient clinic 1 week, 1 month, 3 months, and 6 months after surgery, and the doctor assessed the status of recovery and postoperative complications. The ABNSW scoring system was used to evaluate cosmetic effects after 6 months and consisted of five items: asymmetry (A), breast shape (B), nipple shape (N), skin condition (S), and wound scars (W). Each item was evaluated in four steps (0, poor; 1, fair; 2, good; 3, excellent). The scores were then summed up. On a scale of 15 points, the results were as follows: excellent, 15 points; good, 11–14 points; fair, 6–10 points; and poor, ≤5 points (12).

Statistical analysis

Data on demographic factors (age, body mass index, and sex), tumor-related elements (tumor location, pathologic type, tumor size, and depth), surgery-related elements (duration of endoscopic surgery, intraoperative blood loss, drainage volume, hospitalization, and postoperative stay), complications, and patient-reported cosmetic results were collected. All statistical analyses were performed using SPSS version 25.0. software (SPSS Inc., Chicago, IL, USA). The degree of significance was set at a P value of less than 0.05. Comparisons between groups were performed using an unpaired Student's *t*-test.

Results

Clinical demographics of breast tumor patients

Of 738 patients with benign breast tumors who underwent surgery between November 2017 and June 2023, 217 met the inclusion criteria. There were 107 patients whose endoscopic resection was guided by the methylene blue position, and 110 patients underwent endoscopic resection by SML preoperatively (*Table 1*). The MBL group consisted of 65

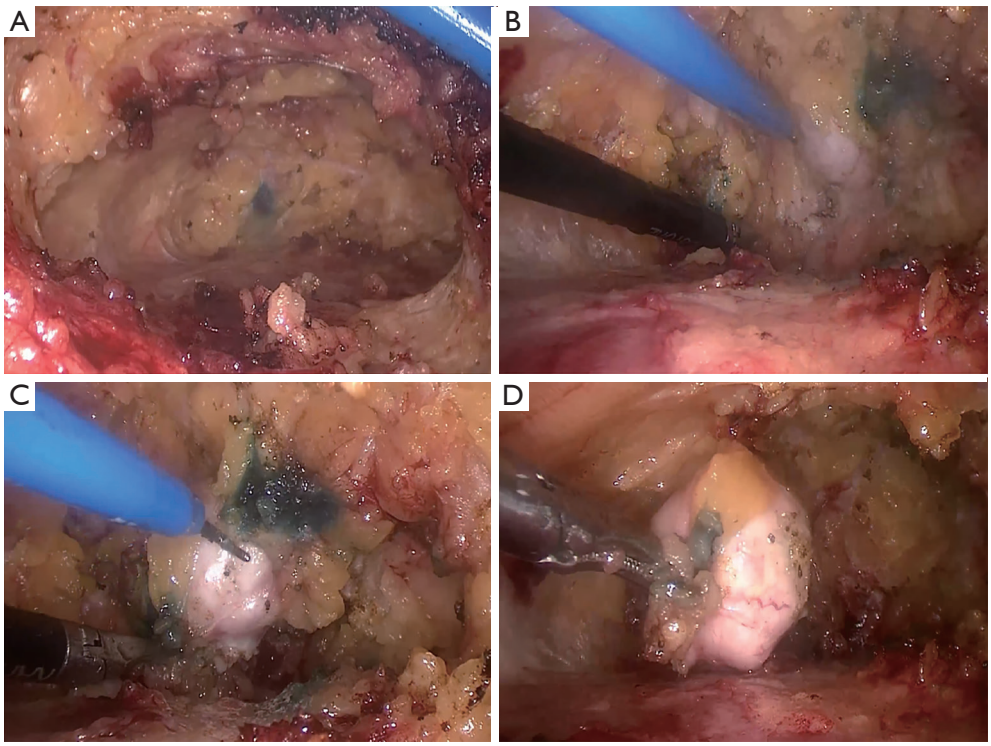
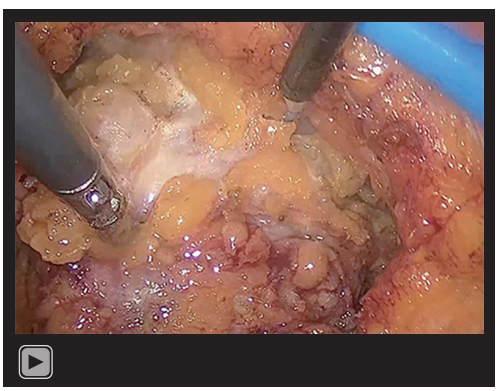
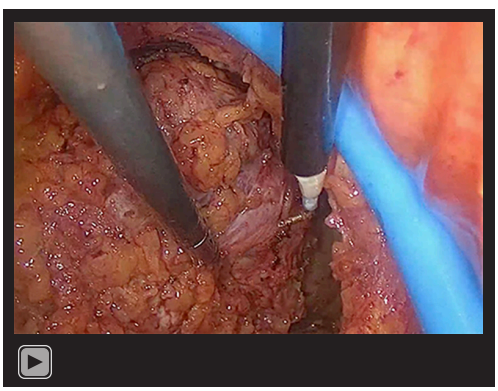


Figure 2 The surgeon incised the gland behind the tumor, exposed the tumor envelope under the guide of methylene blue. The separation was conducted from initial to the distal end until the tumor was completely exposed in the air cavity, then the tumor was resected. (A,B) The staining of the tumor base of tumor under the endoscopic field; (C) the tumor was resected around the marked resection margins; (D) the tumor was completely resected.



Video 3 The separation was continued to the distal end until the tumor was completely exposed in the air cavity.



Video 4 The tumor was resected.

women with fibroadenoma, 10 with adenosis of the mammary glands, 15 with fibrocystic breast disease, seven with tissue hyperplasia, three with foliate tumors, five with papilloma, and two with sclerosing adenosis. There were no differences between the two groups in terms of tumor location and type.

The surgical features between the two groups

All 107 patients in the MBL group underwent tumor resection and the tumor specimen envelope was complete. There were no significant differences in drainage volume,

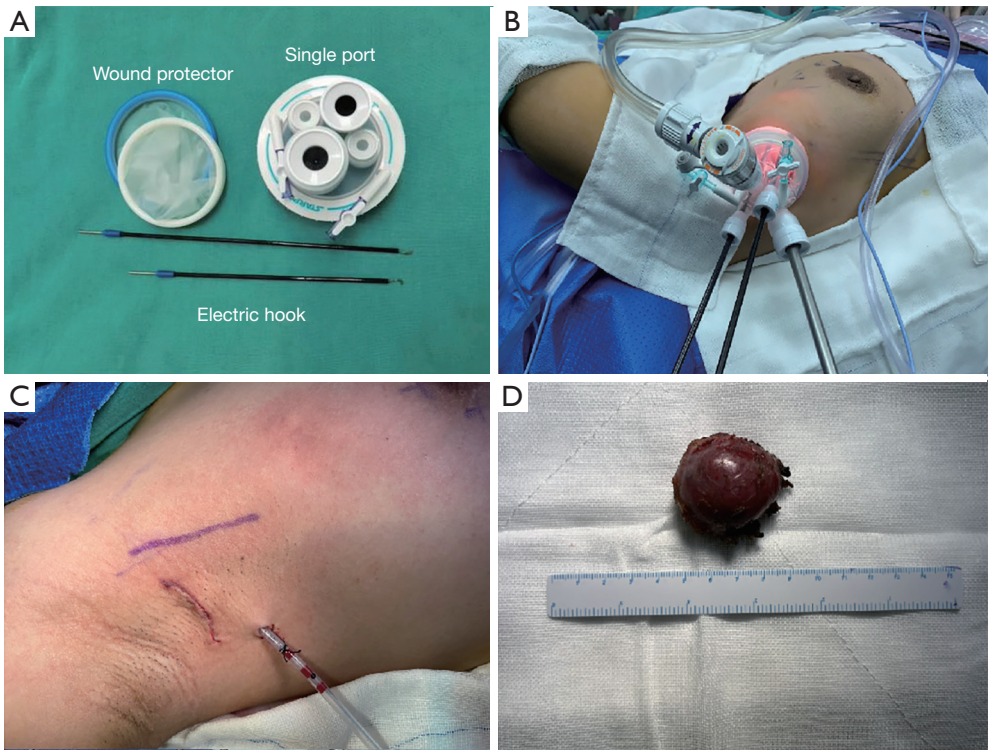


Figure 3 The surgeon used a single-hole endoscope to remove a deep benign tumor with a diameter of 38 mm. (A) Surgical instruments; (B) surgery image; (C) the appearance of incision after the surgery; (D) resected tumor.

hospitalization stay, or complications between the two groups (*Table 2*). However, the surgical results reflected a decreased tendency towards the duration of localization and dissection in the MBL group compared to the SML group. There were significant differences in terms of the duration of endoscopic surgery, with a value of 45.70±12.508 min in the MBL group compared to 49.59±10.997 min in the SML group (P=0.008<0.05). Blood loss in the MBL group was significantly reduced compared to that in the SML group, which was 11.07±5.665 and 13.83±7.918 mL (P=0.004<0.05).

The surgical complications between the two groups

There were no significant differences in postoperative complications between the two groups (*Table 3*), and each group had a few cases of seroma and incision infection. None of the groups showed paresthesia of skin, poor wound healing, or ischemic necrosis of the nipple or areola. There were five cases of seroma in the MBL group and seven cases in the SML group; there was one case of incision infection in the MBL group and three cases in the SML group. Both groups presented with a similar incidence of seroma, which improved after the syringe puncture and extraction.

Patient-reported cosmetic results

The ABNSW scoring system was used to assess cosmetic results 6 months after surgery (*Figures 4,5*). There were no significant differences in symmetry, breast shape, nipple appearance, breast skin condition, wound scar, or total score between the two groups (P>0.05, *Table 4*).

Discussion

Herein, we report our preliminary experience with MBL in the management of benign breast tumors. In our study, ultrasound-guided preoperative staining was used to locate and guide deep-seated breast tumors by visualizing the surgical path and resection margins using endoscopy. In our analysis of MBL procedures performed in 107 patients with benign breast lesions, we found that all patients in the MBL group underwent ultrasound-guided multi-point positioning, and the tumor was resected successfully. The

Table 1 Clinical characters of the patients

Variables	MBL (n=107)	SML (n=110)	P value
Age (years)	35.32±10.148	37.82±10.473	0.08
BMI (kg/m^2)	21.35±3.042	21.82±3.518	0.29
Tumor location, n (%)			0.93
Unilateral			
Lateral upper quadrant	56 (52.3)	55 (50.0)	
Lateral lower quadrant	13 (12.1)	15 (13.6)	
Medial upper quadrant	15 (14.0)	17 (15.5)	
Medial lower quadrant	12 (11.2)	10 (9.1)	
Bilateral	11 (10.3)	13 (11.8)	
Pathologic type, n (%)			0.49
Fibroadenoma	65 (60.7)	54 (49.1)	
Adenosis of mammary glands	10 (9.3)	7 (6.4)	
Fibrocystic breast disease	15 (14.0)	23 (20.9)	
Tissue hyperplasia	7 (6.5)	10 (9.1)	
Foliate tumor	3 (2.8)	5 (4.5)	
Papilloma	5 (4.7)	9 (8.2)	
Sclerosing adenosis	2 (1.9)	2 (1.8)	

Data are presented as mean ± standard deviation or n (%). MBL, methylene blue location; SML, skin mark location; BMI, body mass index.

age of the patients ranged from 19 to 68 years, with a mean age of 35.32 years, 59% of the lesions were located in the lateral upper quadrant of the breast, and fibroadenoma was the most common finding in 60.7% of the patients. The discovery of a breast mass may cause significant anxiety in patients, which needs to be evaluated to exclude the possibility of malignancy, and the doctor must decide whether to remove or reserve the mass (13,14). The MBL technique provides a field of vision to reduce accidental injury, which shortens the operation duration. Compared with 110 patients in SMP group, the time of localization and surgical resection was significantly shortened, and the overall surgical time was reduced, in which the localization time with a mean of 15.87 min in MBL group compared to 17.59 min in SML group, the dissection time with a mean of 29.83 min in MBL group compared to 32.35 min in SML group, the operation time with a mean of 45.7 min in MBL group compared to 49.59 min in SML group. There was no statistically significant difference in terms of cosmetic outcome between the two groups, with a total score of 14.56 points in the MBL group and 14.45 points in the SML group, which is considered to be a good cosmetic effect with the methylene blue technique.

Vacuum-assisted breast biopsy (VABB) is used to remove small benign breast masses, and patients can avoid general anesthesia and have a small incision (15,16), and international guidelines recommend the use of vacuum-assisted excision for breast lesions with a maximum diameter of 25 mm (17,18), while endoscopic surgery has the advantage in the resection of benign tumors with a diameter greater than 25 mm or multiple benign tumors, and can achieve complete resection of the tumor along with its envelope (19), and remove a small amount of normal breast tissue to avoid residual tumor envelope and recurrence (20,21). For deep-seated breast tumors with a large diameter, endoscopic surgery may destroy the supporting structure when the instrument goes deep into the bottom of the breast. In our study, we observed that the MBL technique reduced the risk of injury with the guidance of methylene blue, and cut down the blood loss during the operation; the MBL group had a lower volume of blood loss than the SML group, in which the blood loss with a mean of 10.07 mL in the MBL group compared to 13.83 mL in the SML group (P=0.004<0.05), the drainage volume with a

Table 2 Surgical features of the patients in the two groups

Variables	MBL (n=107)	SML (n=110)	P value
Tumor diameter (mm)	25.82±8.224	25.12±8.755	0.54
Tumor depth from pectoralis major (mm)	10.60±9.545	11.81±7.264	0.29
Duration of endoscopic surgery (min)	45.70±12.508	49.59±10.997	0.008
Unilateral	43.55±11.177	46.90±6.983	0.01
Bilateral	64.45±6.362	72.69±8.528	0.02
Duration of localization (min)	15.87±4.874	17.59±6.159	0.02
Unilateral	14.81±3.582	15.74±2.888	0.048
Bilateral	25.09±5.069	31.38±6.640	0.02
Duration of dissection (min)	29.83±9.908	32.35±7.642	0.04
Unilateral	28.74±9.776	31.15±6.389	0.043
Bilateral	39.36±4.610	41.31±10.266	0.57
Drainage time (days)	2.77±0.681	2.80±0.661	0.71
Intraoperative blood loss (mL)	11.07±5.665	13.83±7.918	0.004
Unilateral	10.47±5.384	13.00±7.920	0.01
Bilateral	16.36±5.519	22.69±6.651	0.02
Drainage volume (mL)	52.77±22.210	58.63±23.321	0.059
Unilateral	49.04±19.735	55.20±18.422	0.03
Bilateral	85.27±15.285	93.85±27.046	0.36
Hospitalization stay (days)	5.79±1.387	5.94±1.103	0.37
Postoperative stay (days)	3.21±0.922	3.29±0.770	0.51

Data are presented as mean ± standard deviation. MBL, methylene blue location; SML, skin mark location.

Table 3 The complications of the patients in the two groups

Complications	MBL (n=107)	SML (n=110)	P value
Seroma	5 (4.7)	7 (6.4)	0.77
Poor wound healing	0 (0.0)	0 (0.0)	–
Incision infection	1 (0.9)	3 (2.7)	0.62
Paresthesia of skin	0 (0.0)	0 (0.0)	–
Ischemic necrosis	0 (0.0)	0 (0.0)	–
Relapse	2 (1.9)	4 (3.6)	0.68

Data are presented as n (%). MBL, methylene blue location; SML, skin mark location.

mean of 85.27 mL in the MBL group compared to 93.85 mL in the SML group, the MBL technique may support the breast tumor patients to attain a higher quality of life after the resolution of their diagnosis.

With the development of minimally invasive concepts, Kitamura *et al.* first reported the application of endoscopic resection for benign breast tumors in 1998 (22). In recent years, breast endoscopy has been developed from the classic 3-hole aeration method to a concealed single-incision design (23). The breast endoscopy not only achieves the

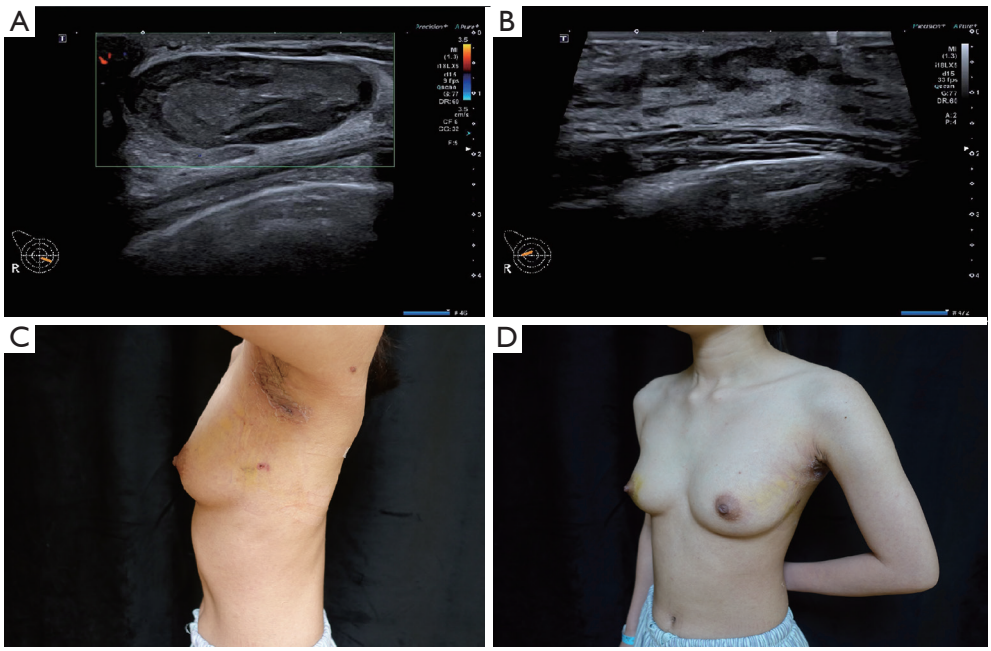


Figure 4 Female, 32 years old, the tumor was in the left-D area. The tumor was 5 cm deep from the nipple of right breast at 10 points, ultrasound showed 25 mm × 14 mm (BI-RADS type 3), tumor was resected under endoscopic, no staining remains on the breast surface after 3 months of surgery. (A) Preoperative ultrasound image; (B) postoperative ultrasound image; (C,D) the appearance of breast and incision 1 week after surgery. BI-RADS, Breast Imaging-Reporting and Data System.

therapeutic effect of invasive surgery but also conserves the aesthetic appearance of the breast. Endoscopic resection of breast tumors has more advantages than open surgery, because it does not damage the breast glands, and the incision is transferred to the hidden armpit. Endoscopic oncoplastic breast surgery is a safe excision technique for tumors that preserves breast shape. It has a less noticeable scar, excellent cosmetic outcomes, and a high patient satisfaction rate (24). Endoscopic surgery transfers the incision to the armpit and other hidden places and directly reaches the posterior space of the breast, and the tumor is removed without damaging the tumor surface and reducing surgical complications. However, the long visual distance in endoscopic surgery makes it difficult to touch the tumor, limiting the widespread use of this technique (25). Therefore, breast endoscopic surgery must seek a visual guide, which is of great significance in confirming the location and bottom of the tumor, shortening the time spent on the operation, and improving the accuracy of tumor resection.

Breast tumor localization methods generally include body surface marker localization, fine needle hook localization, and carbon or methylene blue staining localization (26). Dye marking technology has been widely used owing to its simplicity and good localization effect. Surface marker localization is not suitable for deep-seated tumors; hooky localization destroys the integrity of the tumor and breast, and carbon particles may block the needle and cause staining failure, which may cause a foreign body giant cell reaction. Methylene blue has been used in the field of surgery for decades, detecting breast tumor sentinel node biopsy, and labeling breast tumors owing to the disadvantages of radioisotopes (27,28), typically presenting a good safety profile (29), and no adverse reactions or events were noted by our patients. The methylene blue dye method can improve the localization of tumors and potentially reduce the surgical time (30). In this retrospective study, methylene blue was selected as the staining agent, and injected into the boundary between tumor and normal tissues under ultrasound guidance. The endoscope entered the breast along the methylene blue-labeled path, the tumor edge could be found at the deepest stain, and it was more efficacious to remove the tumor, allowing the surgical resection boundary to be determined quickly. The use of methylene blue dye for planning surgical margins is an ingenious method to reduce the rate of involved margins without removing excessive amounts of

Figure 5 Female, 26 years old, the tumor was in the right-D area. The benign mass with a diameter of 38 mm was successfully resected without any changes in appearance. (A,B) Preoperative images; (C,D) postoperative images.

Table 4 Patient-reported cosmetic results

Parameters	MBL (n=107)	SML (n=110)	P value
Asymmetry of breasts	2.92±0.280	2.91±0.289	0.88
Skin condition	2.90±0.306	2.85±0.354	0.36
Wound scar	2.92±0.329	2.94±0.280	0.78
Nipple deformation	2.92±0.265	2.90±0.301	0.53
Breast shape	2.90±0.306	2.85±0.363	0.27
Total score	14.56±0.649	14.45±0.644	0.21

Data are presented as mean ± standard deviation. MBL, methylene blue location; SML, skin mark location.

breast tissue. However, as methylene blue is easy to disperse, a 1 mL syringe should be selected to control the injection volume during the operation. Moreover, the 10 mL syringe needle has strong penetration and is long enough to reach the fundus of the tumor, which should be avoided during the injection process. Pressure fixation of the tumor can improve the precision of methylene blue injection.

Conclusions

Our results showed that MBL is a safe and effective technique with fewer complications, and is recommended for patients who undergo endoscopic surgery for deep-seated benign breast tumors. However, there is a limitation that the data were retrospectively collected from a single center, primarily from Chinese patients. It is difficult to generalize these results to patients of different ethnic backgrounds or those treated under different institutional conditions, which may have caused a potential bias.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-139/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-139/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-139/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University, with the approval number of 2021ZSLYEC-404. Written informed consent for the use of the clinical records was obtained from each participant.

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