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Innovations in the localization techniques for non-palpable breast lesions: Make invisible visible

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ABSTRACT

Non-palpable breast cancer lesions pose a challenge for surgeons to resect cancer lesions. Making 'invisible' lesions 'visible' is the main strategy. Currently, multiple preoperative localization techniques have been applied in clinical. Among them, wire-guided localization (WGL) is the most common procedure due to its convenience and low cost. However, its limitations including discomfort, wire migration and the coupling of localization and operation procedures cause troubles for surgeons and patients. The desire for localization methods improvement, accompanied by the advance of emerging science and technology, leads to the development of a series of locating approaches for breast non-palpable lesions, aiming to improve locating accuracy while reducing adverse events. These emerging methods have undergone improvements from steel wire to functional particles, from radioactivity to non-radioactive, which help doctors and patients choose a more appropriate scheme. This review outlines the principles, procedures, advantages and disadvantages of these locating methods, and highlights the latest progress and related clinical data on innovative locating approaches. Finally, we briefly discuss the current challenges and future opportunities for the clinical application of these localization approaches.

1. Introduction

With the popularization of breast screening and the advancement of imaging technology, more and more non-palpable lesions have been detected [1]. Undoubtedly, surgery has made an important contribution to improving the prognosis of patients with early breast cancer [2–4]. However, non-palpable breast cancer lesions, which cannot be located by palpation, pose new challenges for surgery [5,6]. On the one hand, limited imaging equipment restricts the surgeon's real-time judgment of the location of the lesion, especially the displacement of the breast after changing the position. On the other hand, the fuzzy judgment of the lesion boundary increases the removal of innocent healthy breast tissue and harms the aesthetic outcome of the breast. The preoperative lesion localization technique is by implanting markers near the lesion with the assistance of imaging equipment as a signal to guide surgical resection of the lesion [7]. The emergence of preoperative localization techniques makes 'invisible' lesions 'visible'. Among them, the most classic technology is wire-guided localization (WGL) technology, which is by inserting a metal wire into the centre of the lesion to guide the surgeon in resecting lesions by tracking the path of the metal wire [8]. Although the WGL is extendedly applied, its drawbacks including binding of radiologists, surgeons and operating rooms [9], increasing pain experience of patients [10], etc., promote researchers to develop novel alternative localization to locate lesions. The past few decades have witnessed a great expansion of the locating techniques for breast non-palpable lesions, as detailed in Fig. 1. These methods have undergone improvement from the long steel wire to the functional particles that can emit signals, from radioactive particles to electromagnetic signal particles [11]. The purpose of this review is to focus on preoperative locating techniques of breast non-palpable lesions. The review summarizes the currently available breast non-palpable localization techniques, describes the procedure and discusses the advantages and drawbacks of various techniques. The current challenges and future opportunities for the clinical application of these localization techniques are deliberated briefly.

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2. Conventional methods

2.1. Wire guide localization

WGL is a localization procedure that utilizes a metal wire as a visual marker to guide surgeons in excising non-palpable breast lesions. Dodd et al. [12] completed the first-ever localization of a non-palpable breast lesion using a wire under the guidance of imaging in 1966. Subsequently, WGL was extensively used and served as the standard method for non-palpable lesion localization [13,14]. Preoperatively, the metal wire was inserted into the target lesion or adjacent lesion through a 16-20G needle under the guidance of imaging (stereotactic or ultrasound) [15,16]. Subsequently, imaging was utilized to confirm the accurate placement of the wire [17]. The exposed metal wire was fixed on the surface of the skin. To decrease the risk of wire migration, localization and surgery are always performed on the same day, and the patients are usually advised to minimize ipsilateral arm activity [18,19]. Intraoperatively, the surgeon excises the lesion with the guidance of the metal wire which is from the skin surface to the target lesion [9,13,20]. To improve the accuracy of WGL, many attempts have been made on the shape and structure of the metal wire, such as hook, barb, and pigtail [21,22]. The results of experimentally evaluated 22 types of wires found that wire with long-hooked X-shaped structures was the least likely to dislodge under external force [23]. Numerous evidences demonstrated that the WGL is an effective localization with a successful localization rate of 99.1%–100 % [8,24], which means that WGL is maneuverable. Besides, WGL is a simple and cost-effective method, which does not require additional equipment and supplies, except wire [25,26]. Moreover, wires have no risk of ionizing radiation and radioactive exposure[7]. A good clinical outcome is crucial for patients, the higher positive margin rate increases the risk of reoperation and recurrence [27]. In literature, the positive margin rate of WGL is 14–20.8 % [28–30] and the reoperation rate is 13–18.2 % [8,28,29,31]. The safer and more precise locating is still the goal to pursue. In addition, the drawbacks also impede the application of WGL. The tail of the wire is exposed to the outside of the breast, which increases the risk of wire migration [32]. Reportedly the incidence of wire migration was 4.2 % [31]. Moreover, the binding of localization and surgery constricts the coordination of radiologists and surgeons and limits the utilization of the operating unit [17,33]. Of note, the metal wire itself as the guide sign, the ideal locating path is not always the optimal surgical path, which will increase excess tissue stripping and resection, impeding the cosmetic outcome of patients [33,34]. In addition to the aforementioned, the potential adverse events of WGL include migration, surgical site infection and drainable seroma. Literature showed that the risk of migration is 4.2 % [31], surgical site infection is 15.9 %, and drainable seroma is 11.4 % [35].

2.2. Carbon suspension guided localization

In 1983, Svane et al. [36] described a carbon suspension localization technique for non-palpable breast lesions. A 3 % or 4 % sterile carbon suspension was injected into the lesion under the guidance of the stereotactic or ultrasound [37]. Then, as the needle was withdrawn, the carbon suspension was continuously injected to produce a visible trail from the lesion to the breast skin [38]. Subsequently, the surgeon was able to follow the carbon trail to locate and excise the lesion [36,39]. The volume of injection ranges from 0.3 ml to 3 ml, depending on the distance of the lesion to the skin [36,40]. During the procedure, an assistant needed constantly to agitate the carbon bottle to prevent precipitation [39]. Additionally, 18-21G needles are adopted to prevent blockage of the tip by carbon particles [39,41]. Carbon suspension is an ideal tracer that exhibits biological inertness and is not easily diffused into surrounding tissues [42]. A study demonstrated that there was no correlation between the dyeing area and dyeing time in carbon suspension localization [42]. Moreover, in the report of Svane et al. [36], the carbon track of one case did not diffuse for 57 days after injection. The stability of carbon means that localization and surgery can be separated, which improves the coordination between the radiologist and surgeon. This procedure is quite feasible. In literature, the success rate of localization is close to 100 % [41,42]. Besides, the procedure is economical since it does not involve cumbersome operations and special equipment and the carbon suspensions are readily obtained and inexpensive [43]. The drawbacks of the method mainly arise from the carbon particle. The aggregation of those carbon nanoparticles made it easy to clog the tip of the needle. Other than that, it is difficult to inject in dense breasts [39]. The phenomenon of residual carbon marking along the incision scar was observed and the incidence was 3.6 % [39]. In addition, the residual charcoal in the breast tissue may form granuloma and mimic malignant lesions in follow-up imaging studies [44]. Reportedly, charcoal granuloma is most commonly detected 2–3 years after surgery and occurs more frequently when the incision choice is different from the tattooed area [45].

2.3. Toluidine/Methylene blue dye

In 1976, Dietler et al. [46] first described the use of MB to localize non-palpable breast lesions with high accuracy and gratifying patient acceptance. Since then, the application of MB injection guiding the preoperative localization of non-palpable breast lesions and the biopsy of sentinel lymph nodes has gained attention [47,48]. In this procedure, by injecting MB into the breast tissue near the lesion, surgeons can

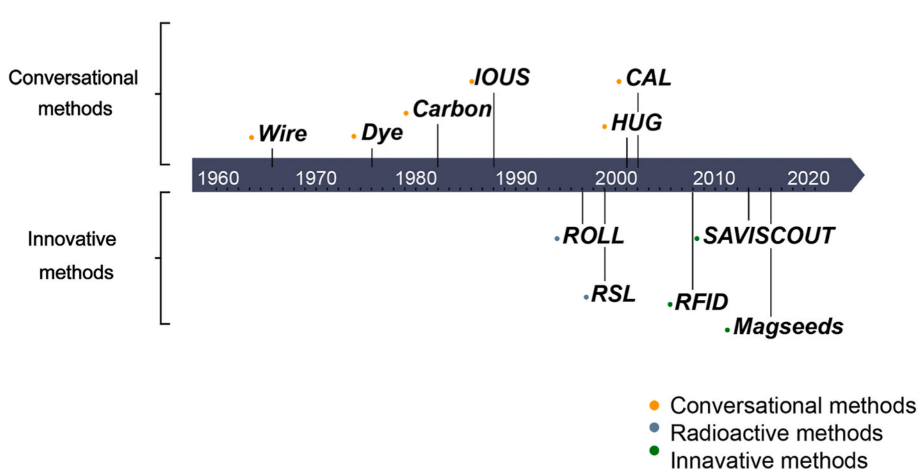

Fig. 1. The development process of localization methods for non-palpable breast lesions.

visually locate and remove the target lesion during surgery [49]. The literature reported that the sentinel lymph node identification rate was 89–100 % [50–52]. There are many advantages of MB dye localization technology. First, the material is easily accessible and inexpensive [53,54]. Second, it does not require specific equipment and radioactive materials and is more suitable for patients and healthcare systems with financial constraints [51]. Last, it also allows for direct visualization of the lesion during the procedure, reducing the incidence of positive margins and unnecessary sacrifice of healthy breast tissue [42]. Compared to wire localization, MB dye has similar results on diagnostic accuracy [55]. But MB dye eliminates the need for wire handling and potential wire dislodgement. However, MB dye has a small molecular weight and can easily spread to surrounding tissues after injection, contaminating the surgical area and damaging lymphatic vessels and lymph nodes [56,57]. Compared to nanocarbon injection, the staining time of the MB dye group was 2–20 h, and the staining area and staining intensity decreased with the increase of staining time [42]. Therefore, the optimal injection time is within 6 h before surgery, which greatly limits the timing of surgery [42]. Previous studies have shown that complications of MB dye include allergic reactions [58], fat necrosis [59], damaged skin [60] and mycoplasma infection [61]. MB dye has emerged as a valuable technique for localizing occult breast lesions [62]. Its cost-effectiveness, real-time visualization, and simplicity make it an attractive option for surgeons and patients. However, careful patient selection, intraoperative visualization, and radiological guidance are necessary to ensure optimal outcomes. Further research and refinement of the technique are warranted to explore its full potential and enhance its role in breast cancer surgery.

2.4. Cryo-assisted localization

Tafra et al. [63] first proposed cryoprobe-assisted localization(CAL) for non-palpable breast lesions in 2003, which was derived from cryosurgery. The procedure utilizes cryogenic technology to transform a non-palpable lesion into a palpable "ice ball" [64]. Preoperatively, after administering anaesthesia, the cryoprobe is inserted along the long axis of the lesion through a 3 mm skin nick under the guidance of ultrasound [65]. Subsequently, the entire lesion and estimated adjacent normal tissue are frozen into an "ice ball" by ultra-cold argon gas. The size of the "ice ball" can be precisely controlled by adjusting the flow of argon [63]. Of critical importance to the successful localization is the placement of the probe through the centre of the lesion. Tafra et al. [63] reported that the positive margin rate of CAL was 16.7 % in a small series, but among patients who had more than 6 mm ice created around the tumour, the rate fell to 5.7 %. In their subsequent randomized controlled study ($n = 310$), the positive margin rate was 28 % and the positive margin status had no difference between CAL and WGL when the ice around the tumor was more than 8 mm [64]. The advantage of the procedure is that the "ice ball" could serve as a template, which had clear visualization and allowed the surgeon to rapidly dissect tissue, especially typical fatty tissue [63,64]. Besides, locating and surgery were integrated. It does not require additional operation for locating, allowing the patient to avoid excess trauma. The potential drawback is that freeze causes changes in the tumor and interferes with the interpretation of ancillary immunohistochemical studies [65,66]. Careful consideration should be given when immunohistochemical results are needed to formulate a follow-up treatment scheme. CAL is an attempt at a new approach and displays more interest in academic research. More evidences are still needed to prove the clinical value of CAL.

2.5. Intraoperative ultrasound guidance localization

Intraoperative ultrasound localization(IOUS) of non-palpable breast lesions was first described by Schwartz et al., in 1988 [67], and its localization potential emerged in subsequent studies [68,69]. This procedure does not require additional operations. Preoperatively, a linear array transducer is used to detect the lesions. The depth and size of the lesions, and the relationship between the projection of lesion on the breast surface and the skin surface markers were recorded [70,71]. Subsequently, based on the guidance of ultrasound, the optimal surgical incision and area were drawn on the skin surface [68]. To continuously obtain information feedback from the lesion, the transducer was first draped with a sterile glove containing sterile acoustic gel and then covered with a sterile plastic sheath [68]. Numerous studies demonstrated that IOUS is a safe and highly effective localization method for non-palpable breast lesions [72–74]. Reportedly, its identification rate is close to 100 % [75,76]. Besides, IOUS is also a safe method. In literature, the positive margin rate ranges from 2.5% to 13 % [74,77–80], and the reoperation rate varies between 2.5 and 7% [77,78,80]. Compared to WGL, the results suggest that the IOUS was superior in positive margin status and reoperation [79,81]. It is worth noting that IOUS has many practical advantages. First, it does not increase the patient's preoperative anxiety and secondary trauma because it is non-invasive [5]. Second, it is more flexible, as it is performed directly in the operation room before surgery and carried out completely by the surgeon himself [75]. It grants surgeons full liberty in choosing the surgery incision. Last, compared with other localization methods, IOUS is cost-effective since it does not involve cost-increasing materials (such as radioactive markers, and metal wires) and special equipment or devices [79]. However, it also presents challenges for surgeons as it requires them to be familiar with ultrasound [71,82]. Of note, there are still some drawbacks impeding the application of it. Air is a strong beam reflector. The air infiltration between the skin and probe may impede visualization and produce possible refraction problems when the probe is scanning the irregular wound [5]. Furthermore, when the probe was inserted into the wound, the adjacent tissue was compressed which may induce the surgeon to misjudge the distance from the resection site to the edge of the tumor [5]. The main limitation of this technique is that it can only be applied to lesions visible on the ultrasound. When the lesion is not visible on ultrasound, alternative methods can be combined to enhance the visualization during intraoperative ultrasound.

2.6. Hematoma ultrasound-guided localization

In 2001, Smith et al. [83] introduced a hematoma-directed ultrasound-guided localization(HUG) technique as an alternative to WGL. 2–5 ml of blood from the patient was injected into the lesion under image guidance. Afterwards, the hematoma was identified by intraoperative ultrasound to guide surgery [83]. It is similar to IOUS, but the difference is that the hematoma is utilized as the target in this procedure, not the lesion. The method is maneuverable and the learning curve of this procedure is gradual [84]. Previous research reported that the success rate of localization is nearly 100 % [84,85]. Reportedly, HUG is a more accurate and safer localization method compared to WGL [85–87]. The positive margin rate is 4.4%–24 % in the literature [78,84–86,88]. A retrospective study of 455 cases showed that HUG had a lower margin positive rate (24 % vs 47 %, $P < 0.05$) than WGL [85]. The comparison results of excision volume suggest that HUG is superior to WGL [84,88]. The advantages of the methods contain the following aspects. First, the procedure is cost-effective and feasible since it does not require additional operations and equipment [85,89,90]. A retrospective study of 569 patients demonstrated that HUG could save $497 per procedure compared to wire-guided localization and a total of $94,430.00 for the study period [91]. Second, the hematoma in this procedure can be derived from biopsy, which helps it avoid additional trauma [92]. Last, the hematoma in the body can present for about 5 weeks, which provides more flexible scheduling options for patients and surgeons [85]. Nevertheless, it is necessary to confirm the presence of the hematoma before surgery. Its disadvantages are similar to those of IOUS. However, the difference is that the hematoma can be created under the guidance of non-ultrasound, which effectively overcomes the problem that IOUS cannot be applied in ultrasound-invisible lesions.

3. Radioactive methods

3.1. Radio-guided occult lesion localization

Luini et al. [93]. first described radio-guided occult lesion localization (ROLL) in 1997. The procedure involves injecting particles with a diameter of 10–150 μm of human serum albumin labelled with approximately 3.7 MBq of radioactive tracers (^{99}mTc) into the lesion under the guidance of imaging [94,95]. Afterwards, the correct inoculation is verified by a scintigraphy scan of the breast. Intraoperatively, a gamma-detecting probe is utilized to precisely locate the lesion and assist the surgeon in determining the optimal surgery incision [93,96]. Despite being radioactive, there is negligible radiation hazard for patients and hospital staff [97,98]. Previous studies demonstrated that the mean absorbed dose to the abdomen of the patient was 0.45 mGy, and the mean absorbed dose to the hands of surgeons after 100 operations was 0.45 mGy, and the mean effective dose was 0.09 mSv [97]. The absorbed dose to all individuals involved in the procedures was well below the recommended annual limits stipulated by the International Commission on Radiological Protection [99]. ROLL is a safe and effective technique to localize non-palpable breast lesions [100,101]. Literature reported that its success rate of localization is 94 %–100 % [24,31,102,103]. The positive margin rate is 6.5 %–11.8 % [104–107] and the reoperation rate is 11.8 %–12 % [31,104]. Previous studies demonstrated that ROLL had a lower positive margin rate compared with WGL [6,108,109]. However, ROLL did not show an advantage in resection volume and resection tissue weight compared with WGL [6]. The result of the questionnaire on satisfaction for patients indicated that ROLL is superior to WGL [31,110]. As for the economic cost, ROLL does not reduce the total cost. Postma et al. [104] reported that although ROLL can reduce the cost of localization, it has no superiority in total medical costs because of the treatment and care of postoperative complications. The advantage of ROLL is that the optimal surgical incision can be determined based on the feedback signal, which avoids stripping and excising excessive tissue because the optimal localization path is not always the best surgical path [111]. In order to ensure adequate tracer effect, the surgery should be performed within 24 h after localization [100]. In the comparison of the day-before and same-day schemes of ROLL, there was no difference in pathological diagnosis and positive margin status between the two schemes [98]. The latter alleviates slightly the contradiction but the injection amount of 99mTc was inevitably increased due to the half-life of the radioactive tracer. ROLL also has some potentially adverse events including the spreading of radioisotope away from the localization site, hematoma, vasovagal episodes, and pain. Moreover, the addition of radioactive materials has increased the pressure on medical nuclear management and the training of related personnel.

3.2. Radioactive seed localization (RSL)

Dauway et al. initially proposed an alternative to WGL by using radioactive seed in 1999 [112]. The technique was carried out with a titanium seed containing .29 mCi of ^{125}I, with a size of 4.5 mm × 8 mm [113]. The seed was placed within an 18G needle, the tip of which was occluded with sterile bone wax [114]. The needle was then guided to the lesion, and a stylet was utilized to displace the seed into the breast parenchyma at the site of the lesion [115]. Subsequently, the needle was withdrawn, and the position of the seed was confirmed with mammography [113]. A handheld gamma probe set to an energy of 27-keV was supplied to detect the seed intraoperatively [116]. The point of greatest signal marked the site closest to the lesion and indicated that the position could serve as the incision of surgery. Feedback on the signal changes could help the surgeon estimate the distance from the lesion and avoid excessive dissection and tissue loss. The surgery concluded with the complete removal of the seed by detecting the ^{125}I radioactivity source within the excised specimen and wound [115]. The localization success rate of RSL is 92.8%–100 % [117,118]. The implementation of RSL also has a shortened learning curve [119]. The positive margin rate of RSL is 6.8%–42 % [120–124]. In the comparison of RSL and WGL, both had similar positive margin rates and reoperation rates [125,126]. Taking into account the cost of localization and the specific costs related to radiation safety in the budget analysis, RSL, which uses the pre-loaded radioactive seed, is more expensive than WGL [26], however, using the seed loaded by radiologist can save about $869 per case [127]. Due to ^{125}I having a half-life of 60 days [113], the time between the insertion of the seed and the surgery removal could be up to 60 days [115], which improves the flexibility and coordination between the localization and surgery [127]. The patients who underwent RSL had higher convenience compared to WL [128]. However, the ^{125}I source of radioactivity increases the risk of radiation exposure for all staff involved in the procedure [33], although previous studies have confirmed that such radioactivity is safe [115]. Meanwhile, It increases the pressure on the management of radioactive sources and the education of the personnel in the hospital [115]. This stringent nuclear radiation management limits the use of this technology in smaller hospitals. Finally, it has a limitation that it cannot be redeployed or retrieved after placement. Occasionally, the seed may migrate from the target and need additional surgery to remove it.

4. Innovative methods

4.1. Radiofrequency identification tags guiding localization

Reicher et al. [129]. attempted to locate breast lesions with radiofrequency identification tags (RFID) using an opaque sonography breast phantom and isolated chicken in 2008. Their results indicated that the combination of RFID tags and a detector showed promise for image-guide breast lesion localization [129]. The RFID system comprises a passive 2 mm × 12 mm tag and a handheld radiofrequency identification reader [130,131]. Each tag contains a microchip that stores a unique identification number and an antenna that responds to access by the reader [132]. The RFID reader sends a radiofrequency signal to the tag, which then receives, modifies, and re-emits the signal back to the reader [133]. Subsequently, the reader can capture the signal emitted by the tags through two different modes, one using a 6-cm-range loop probe and the other using a 3-cm-range pencil probe [130], and respond with the combination of an LCD display and audio signal [129]. The screen of the LCD shows a bar indicating the distance from the tags and emits an audio tone that increases in volume and pitch as the reader approaches the tag, which benefits the surgeon in determining the site of the lesion [134]. The success location rate of RFID is 92%–100 % [130,135–138]. The positive margin rate was 3%–27 % [130,135,139] and reoperation is 3.1%–27 % in the literatures [130,135,137,139–141]. There was no significant difference between RFID and WGL in terms of positive margin status and reoperation [139]. Other than that, RFID does not increase the volume or weight of excised specimens and operation time compared with WGL [141]. Regarding cost aspects, the result of a small series study demonstrated that RFID is more expensive than WGL [142]. It is not surprising, as RFID increases the required consumables and equipment. Current evidence indicates that RFID is an alternative that is not inferior to WGL. The advantage of this procedure is that decouples the location and surgery since the tag was licensed for long-term implantation before surgery [136]. Besides, there is no risk of radiation exposure and no pressure on the management of radioactive materials. The disadvantages of RFID include signal interference [141], artefact [130,140] and limitation of detection range [136]. If two tags are placed closer than 1.8 cm, the unique ID will disappear due to the signal interference, making it difficult for the surgeon precisely to locate the breast lesion [141]. Another drawback is the tag causes a 2-cm bloom artefact on MRI, which will compromise the evaluation of tumor [140]. The detection range of the system is limited to 6 cm, potentially causing issues in large volume breasts and deep lesion [136].

Moreover, a common limitation is that it cannot be repositioned or withdrawn.

4.2. Radar reflector guiding localization

SAVI SCOUT is a novel surgery guidance system (Cianna Medical, Inc., Aliso Viejo, CA) and has been approved by the FDA in 2014 [143]. The SCOUT system combines electromagnetic wave technology with infrared light to provide real-time direction and proximity guidance during surgery [144]. SCOUT system consists of an infrared-activated, electromagnetic wave-reflective reflector, a detector handpiece and a console [145]. Preoperatively, the reflector was percutaneously implanted into the target lesion through a 16G delivery needle under the guidance of imaging. Intraoperatively, the detector emits electromagnetic and infrared light towards the reflector, which then receives the infrared light and reflects the electromagnetic waves. Subsequently, the detector in turn receives the electromagnetic waves reemitted by the reflector and transforms them into acoustic signal output at the console [144]. This procedure is similar to RFID. The localization success rate is close to 100 % [146–149]. The positive margin rate is 1.5%–14.9 % [144,146–148] and the reoperation rate is 7.4%–16.8 % [146–148]. In positive margin status and reoperation rates respect, current data suggest that this novel technique is comparable to WGL [139,150,151]. In comparison to the volume or weight of the excised specimen, SAVI SCOUT has no significant advantage [150]. The advantage of the procedure is that the reflector can be inserted with no time limits prior to surgery, which gives radiologists, surgeons and patients full-time freedom [146]. In addition, this technology abandons radioactive substances and avoids radiation exposure while providing real-time information. In addition, the reflector has less interference with the MRI signal, measuring <5 mm [146,151,152]. However, there are many disadvantages to this procedure. First, its detection range is limited to 6 cm, which means that there are challenges in the application of large volume or deep lesions [143]. Second, it is expensive due to the cost of the reflector, start-up costs of the SAVI SCOUT system, and the costs of disposables [153]. Third, the signal may be accidently lost, due to the accidental hit of the electrocautery device [148], or the hematoma interference during localization [153]. Finally, a common limitation of this procedure is that it cannot be repositioned or withdrawn. If accidently placed away from the target, additional surgical resection is required [153].

4.3. Magnetic seed localization

Magnetic seed localization (MSL) is a novel technique approved by the FDA in 2016 [9]. The technique uses Magseed® marker (Endomagnetics, Cambridge, UK) as a visual marker for non-palpable lesions, which consists of a 5 mm × 1 mm cylindrical, non-radioactive, paramagnetic surgical steel marker and is preloaded into an 18G needle [25]. This procedure is similar to RSL, but it is not radioactive [154]. After the seed is inserted, the Sentimag® probe, which generates an alternating magnetic field to instantly magnetize the seed and then measures the magnetic field emitted by the seed, is utilized to locate the seed's site [155,156]. Signal feedback from the probe helps the surgeon select the optimal incision and estimate the distance from the lesion. The placement of seed initially was approved by the FDA for up to 30 days before surgery and has now been extended to long-term implantation in Europe and the USA [9,157]. Based on the long-term efficacy of the seed, it is easier to coordinate the schedules of radiologists and surgeons and improves operating room efficiency [158]. The success rate of localization is 93 %–100 % [8,159–162], and the accuracy rate is 97.5 %–99.86 % [8,161,163]. The seed migration is an important factor affecting the accuracy of localization. Mercifully it is a low-probability event and numerous studies have shown that the risk of seed migration is about 2.2 %–2.5 % [159,160,163]. MSL is an effective and non-inferior alternative to WGL that overcomes many of the limitations of the latter. The positive margin rate is 5 %–24 % [8,25,156,163–166] and the reoperation rate is 5.1 %–12.3 % [8,159,161]. There was no significant difference between MSL and WGL in positive margin status and reoperation [8,161]. Moreover, the volume and weight of the excised specimen and complications of the MSL are similar to that of the WGL [8]. MSL breaks the link between localization and surgery and improves the flexibility and coordination of patient, radiologist and surgeon. In addition, MSL avoids the risk of radioactive exposure [167]. Whereas, in clinical practice, Morgan et al. [168] found that difficult percutaneous detection of the magnetic signal was associated with patients with dense or large volume breast tissue after localization. It is not recommended to perform an MRI after MSL is completed, as the Magseed causes a 4 cm bloom artefact due to its iron content, which may limit the diagnostic accuracy of breast imaging [25]. Besides, non-ferromagnetic surgical instruments are required as the ferromagnetic surgical instruments will interfere with the signal when the probe is working [25,163]. Signal interference also is a thorny issue for MSL [155]. A distance of more than 25 mm between the two markers is recommended as cross-signal interference from multiple Magseed® markers is considered less common when the markers are spaced more than 25 mm apart. Owe to the signal crosstalk caused by the close distance between the markers, a distance of more than 25 mm between the two markers is recommended [25]. There are two contraindications to Magseed: one is nickel allergy, as the seed consists of stainless steel, and the other one is the presence of a pacemaker due to the magnetic induction by Sentimag [163,169].

5. Conclusion and prospect

Preoperative localization techniques play an essential role in the surgery of non-palpable breast lesions. Accurate localization of the lesion provides the guarantee to reduce the risk of the positive margin and remain innocent tissue. In this review, we discuss the various methods for locating nonpalpable lesions, summarizing the characteristics of each technique as outlined in Table 1 and presenting the estimated costs of the different methods in Table 2. Notably, although there are many drawbacks in WGL, it can ignore the depth of the lesion, and allow replacement, which is currently the most broadly used localization technology. Among the other conventional techniques, IOUS is an ideal alternative because it is non-invasive, economical, and completely operated by surgeons which allows surgeons to determine the surgical path and achieve better clinical outcomes. Nevertheless, it remains a restriction in ultrasound invisible lesions. Radioactive material-based localization techniques get rid of the limitation of the metal wire and attempt to use the signal from the radioactive material to guide the resection of the lesion in real time. However, the potential risks and management burden of radiation limit its use. Subsequently, multiple innovatory techniques without radiation including RFID, SAVI SCOUT system and MSL, are developed as signal sources to guide surgeons to resect lesions. These emerging approaches greatly improve the drawbacks of the above methods and provide a real-time signal to guide the surgery, showing a potential application prospect. Strikingly, signal interference between different signal sources, accidental loss of signals during surgery, and artefacts generated on MRI will cause some trouble for surgeons.

Numerous efforts are required to optimize the coordination between different signal sources, address signal interference, and ensure stable signal transmission during surgery. Additionally, issues such as signal loss, particularly due to the impact of surgical instruments, may affect the surgery. Developing more advanced signal enhancement technologies to ensure stable signal transmission in complex surgical environments is crucial. Notably, with the advancement of artificial intelligence and machine learning, combining intelligent algorithms with existing signal source technologies could lead to the development of adaptive surgical navigation systems. These systems would analyze real-time data from various signal sources during surgery and dynamically adjust the surgical approach, may helping enhancing the precision and safety of

Table 1
Features of various localization techniques.

Feature	Classification Of Localization Techniques					
	Conventional methods					
	WGL	**Carbon Suspension**	**Methylene Blue Dye**	**CAL**	**IOUS**	**HUG**
Delivery needle gauge(G)	16–20	18–21	–	None	None	–
Depth limitation	None	None	None	None	–	–
Additional equipment requirements	None	None	None	Visica Cryoablation System	Ultrasound instruments	Ultrasound instruments
The maximal duration of implantation(day)	<1	No exact data	<1	0	–	<35
Advantages	Low cost; Convenient; No depth limitation; No signal interference; No additional equipment;	Low cost; Biological inertness; Scheduling flexibility; Simplicity of operation; No additional equipment; No diffusing to the surrounding tissue;	Low cost; Biological inertness; Simplicity of operation; No additional equipment;	Easy to dissect; Scheduling flexibility;	Low cost; No invasion; No additional procedures; Scheduling flexibility; High autonomy for a surgeon;	Low cost; Scheduling flexibility; High autonomy for a surgeon; No application limitation;
Disadvantages	Scheduling inflexibility; Discomfortable; Wire migration; Coupling of locating path with operation path; Many adverse events;	Risk of needle blockage; Risk of carbon residue; Risk of charcoal granuloma; Coupling of locating path with operation path;	Scheduling inflexibility; Easy diffusing to the surrounding tissue; Coupling of locating path with operation path;	Additional equipment required; Risk of changing immunohistochemical results;	Air infiltration interference; Application limitation, lesions visible only by ultrasound; Learn curve of ultrasound skills; Additional equipment required;	Additional procedure required; Air infiltration interference; Learn curve of ultrasound skills;
Reference	[15,16,32–35]	[36,39,41,44]	[51,53,54,56,57]	[63–65]	[5,71,75,82]	[85,89,92]

Feature	Classification Of Localization Techniques				
	Radioactive methods		Innovative methods		
	ROLL	**RSL**	**MSL**	**RFID**	**Radar Reflector**
Delivery needle gauge (G)	–	18	18	12	16
Depth limitation	None	None	4 cm	<6 cm	<6 cm
Additional equipment requirements	Delivery needle; Gamma probe;	Delivery needle; Gamma probe; Console;	Delivery needle; Sentimag® probe; Console;	Delivery needle; RFID tags; Radiofrequency identification reader;	Delivery needle; Reflector; Detector; Console;
The maximal duration of implantation(day)	<1	<60	Long-term implantation	Long-term implantation	Long-term implantation
Advantages	Real-time signal feedback; Scheduling flexibility (slightly); Uncoupling of locating path with operation path;	Real-time signal feedback; Scheduling flexibility (significantly); Uncoupling of locating path with operation path;	Real-time signal feedback; No radioactive exposure; Scheduling flexibility (significantly);	Real-time signal feedback; Scheduling flexibility (significantly); No radioactive exposure;	Real-time signal feedback; Scheduling flexibility (significantly); No radioactive exposure; Less interference with the MRI signal;
Disadvantages	Expensive; Risk of radioactive exposure; Additional equipment required; The heavy burden of radioactive material management; Additional surgical resection (misplacement);	Expensive; Risk of radioactive exposure; Additional equipment required; The heavy burden of radioactive material management; Additional surgical resection (misplacement);	Expensive; A 4-cm bloom artefact on MRI; Depth limitation; Additional equipment required; Risk of cross-signal interference; Risk of allergy to nickel; Nonferromagnetic surgical instruments required; Additional surgical resection (misplacement);	Expensive; Additional equipment required; A 2-cm bloom artefact on MRI; Depth limitation; Risk of cross-signal interference; Additional surgical resection (misplacement);	Expensive; Additional equipment required; Depth limitation; Risk of accidental signal loss; Additional surgical resection (misplacement);
Reference	[94,96,100,111]	[114–116]	[130,131,136,140,141]	[143,145,148,153]	[25,154,155,163,169]

Table 2
The estimated cost of the various localization methods.

Localization Techniques	Estimated Cost (USD)	Cost Breakdown	Reference
WGL	$148-$311	localization needle and wire, and imaging guidance (ultrasound or mammography)	[26]
Carbon Suspension	without explicit data available	sterile carbon suspension, needles and imaging guidance	[170]
MB dye	without explicit data available	MB dye, needles and imaging guidance	[171]
HUG	$497-$587	imaging guidance (ultrasound machine) and sterile probe cover	[91]
CAL	without explicit data available	cryoablation device, and imaging guidance	[63]
ROLL	$250-$311(containing the cost of complications and reinterventions:$322-$593)	radioactive tracer (^{99}mTc), associated equipment and imaging guidance	[104]
RSL	$245-$517	radioactive seed (^{125}I), associated equipment and imaging guidance	[26]
IOUS	cheaper than WGL, without explicit data available	imaging guidance (ultrasound machine) and sterile probe cover	[172]
MSL	magnetic seed ($110 - $550) intervention costs $2928.2	Magnetic seeds, associated equipment and imaging guidance	[33]
RFID Tags Localization	$292.04	RFID tags, associated equipment and imaging guidance	[142]
Radar Reflector Localization	Expensive than WGL, without explicit data available	Reflector and associated equipment	[144, 153]

Localization Techniques	Estimated Cost (USD)	Cost Breakdown	Reference
WGL	$148-$311	localization needle and wire, and imaging guidance (ultrasound or mammography)	[47]
Carbon Suspension	without explicit data available	sterile carbon suspension, needles and imaging guidance	[48]
MB dye	without explicit data available	MB dye, needles and imaging guidance	[49]
HUG	$497-$587	imaging guidance (ultrasound machine) and sterile probe cover	[50]
CAL	without explicit data available	cryoablation device, and imaging guidance	[18]
ROLL	$250-$311(containing the cost of complications and reinterventions:$322-$593)	radioactive tracer (^{99}mTc), associated equipment and imaging guidance	[51]
RSL	$245-$517	radioactive seed (^{125}I), associated equipment and imaging guidance	[47]
IOUS	cheaper than WGL, without explicit data available	imaging guidance (ultrasound machine) and sterile probe cover	[52]
MSL	magnetic seed ($110 - $550) intervention costs $2928.2	Magnetic seeds, associated equipment and imaging guidance	[3]
RFID Tags Localization	$292.04	RFID tags, associated equipment and imaging guidance	[53]
Radar Reflector Localization	Expensive than WGL, without explicit data available	Reflector and associated equipment	[38,54]

the procedure.

Regarding clinical practice, although the emergence of these innovative technologies has given patients and surgeons more choices, it should be noted that there is no one technique is perfect. Making a clinical decision needs to comprehensively consider the economic cost, breast aesthetic outcomes, and the characteristics of the lesions, including the number and location of lesions, the volume of the breast, etc. Therefore, it is necessary to consider both the individual characteristics and disease-specific factors of each patient to formulate the optimal scheme, choosing the most suitable techniques or combining multiple techniques.

CRediT authorship contribution statement

Quankun Lin: Writing – original draft, Visualization, Data curation. **Qiwen Hou:** Writing – original draft, Visualization, Data curation. **Chenyu Zhang:** Writing – original draft, Visualization, Data curation. **Wei Zhai:** Data curation. **Baosan Han:** Writing – review & editing, Funding acquisition.

Conflict of interest

The authors declare no conflict of interest.

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