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# Real-time electromagnetic navigation for breast-conserving surgery using NaviKnife technology: A matched case-control study

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## Abstract

Breast-conserving surgery (BCS) is a mainstay in breast cancer treatment. For non-palpable breast cancers, current strategies have limited accuracy, contributing to high positive margin rates. We developed NaviKnife, a surgical navigation system based on real-time electromagnetic (EM) tracking. The goal of this study was to confirm the feasibility of intraoperative EM navigation in patients with nonpalpable breast cancer and to assess the potential value of surgical navigation. We recruited 40 patients with ultrasound visible, single, nonpalpable lesions, undergoing BCS. Feasibility was assessed by equipment functionality and sterility, acceptable duration of the operation, and surgeon feedback. Secondary outcomes included specimen volume, positive margin rate, and reoperation outcomes. Study patients were compared to a control group by a matched case-control analysis. There was no equipment failure or breach of sterility. The median operative time was 66 (44-119) minutes with NaviKnife vs 65 (34-158) minutes for the control ($P$ = .64). NaviKnife contouring time was 3.2 (1.6-9) minutes. Surgeons rated navigation as easy to setup, easy to use, and useful in guiding nonpalpable tumor excision. The mean specimen volume was 95.4 ± 73.5 $cm^3$ with NaviKnife and 140.7 ± 100.3 $cm^3$ for the control ($P$ = .01). The positive margin rate was 22.5% with NaviKnife and 28.7% for the control ($P$ = .52). The re-excision specimen contained residual disease in 14.3% for NaviKnife and 50% for the control ($P$ = .28). Our results demonstrate that real-time EM navigation is feasible in the operating room for BCS. Excisions performed with navigation result in the removal of less breast tissue without compromising postive margin rates.

KEYWORDS

breast cancer surgery, breast-conserving therapy, image-guided surgery, surgical oncology

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## 1 | INTRODUCTION

Breast cancer is the most common cancer in women worldwide.[1] Due to availability of screening programs, cancers are detected at earlier stages. As a result, up to 75% of patients can be treated by breast-conserving surgery (BCS).[2,3] In BCS, the balance between complete tumor excision and cosmetic outcome is a challenge. Attempts to save healthy breast tissue can increase the chance of leaving tumor behind. Almost a third of patients have tumor found at the margins on pathological analysis of the specimen. It is well known that a positive margin increases the risk of local recurrence,[4] making additional surgery necessary in these patients. The challenge in removing all of the tumor is multifactorial, including the fact that many tumors are not palpable, lesion targeting techniques do not offer a 3-dimensional image of the tumor within the breast, and the nature of breast tissue which deforms easily when manipulated.

Nonpalpable tumors must be marked for surgeons using various localization techniques. The most frequently used technique is a needle placed in the tumor under image guidance prior to surgery (needle localization).[5] A major limitation of this technique is that the localization needle marks only a single point in the tumor, while the surgeon needs to excise a 3-dimensional, often noneccentric contour around the needle.[6] Radioactive and magnetic seed localization methods are being used more frequently, but like needle localization, the seed only provides a single point of reference in the breast and does not give information on the tumor's margins.[7,8] Other localization techniques include intraoperative ultrasound,[9] which requires advanced sonography skills and only provides localization information when the probe is in use.

With the current strategies, positive margin rates after initial BCS are 30%-40%.[10,11] The presence of a positive margin is linked with higher local tumor recurrence rates despite adjuvant radiotherapy.[12] Even with current localization methods, around a quarter of women will undergo additional surgeries to manage the positive margin.[13]

This is the first human study using NaviKnife, which combines preoperative needle localization and ultrasound-based tumor contouring with real-time electromagnetic (EM) surgical navigation. This method successfully improved the outcomes of needle localization technique in simulated procedures.[14] The primary outcome of this study was to investigate the safety, feasibility, and surgeon experience using real-time EM surgical navigation in BCS. Secondary outcomes included specimen volume, weight, positive margin rate, and reoperation outcomes, comparing study patients to matched patients who underwent needle localized BCS without navigation.

## 2 | MATERIALS AND METHODS

### 2.1 | Study protocol

The study protocol was approved by the Research Ethics Board at Queen's University. Informed consent was obtained from all NaviKnife participants. Patients with a single, ultrasound visible, nonpalpable, biopsy-proven invasive breast cancer, with planned BCS were enrolled in this study from 2016 to 2018. Patients underwent BCS using needle localization and NaviKnife technology. Patients were excluded if they had previous breast surgery or radiation therapy to the affected breast, or multifocal disease. Retrospective case-match control analysis was done in a 2:1 fashion by selecting patients who were treated according to our institution's standard of care with non-navigated needle localized BCS for ultrasound visible, single foci, invasive breast cancer at our institution between 2016 and 2018. Cases were also matched for tumor size. Intraoperative ultrasound was not used in the matched control group.

Study patients underwent ultrasound-guided needle localization in the radiology department as per standard of care at our institution. Following anesthesia induction, NaviKnife was setup and surgery was performed using the navigation display to guide resection. All patients underwent routine follow-up after surgery. Primary outcomes of case completion using NaviKnife, sterility, and duration of operation and tumor contouring time were recorded. Surgeon feedback was collected looking at ease of setup, ease of use, and if they felt the technology was useful in guiding excision of nonpalpable tumors. Qualitative data and a quantitative 5-point Likert scale were used to comment on various aspects of the procedure. Secondary outcomes of specimen weight and volume, positive margin rate, and reoperation outcomes were gathered from the pathology reports. A positive margin was defined as tumor on ink for invasive pathology and <2 mm for ductal carcinoma in situ as per consensus guidelines.[15,16] Patient characteristics and surgical outcomes were compared to the case-matched control group.

### 2.2 | Navigation system and surgical workflow

The navigation system consists of an ultrasound machine, an EM position tracker, a navigation computer/tablet, and a navigation display (Figure 1). An EM sensor was attached to the localization needle and tumor contouring was performed in a sterile fashion using tracked ultrasound and a touchscreen tablet (Figure 2A). The resulting images were displayed on the mounted display. The real-time position and distance of the cautery device relative to the tumor were visible (Figure 2B). Through real-time navigation, the surgeon is provided with constant visual feedback. The green tumor model turns red when the cautery tip breaches the tumor contour, indicating the need to perform a wider resection. The excised specimen included the localization needle and was sent for imaging confirmation, then to pathology per institutional protocol.

The navigation system overcomes breast deformation during surgery by defining the tumor contour relative to the position of the localization needle in real time. As the needle is anchored in the tumor, the 3-dimensional tumor contour moves with the needle and accurately shows the tumor position throughout the surgery. Technical details of the system and validation on synthetic breast models have been previously published.[14] The navigation software uses the open-source SlicerIGT software platform.[17] The EM field generator for position tracking is placed under the drape opposite the surgeon. The patient, cautery, ultrasound, and localization needle are instrumented with EM sensors.

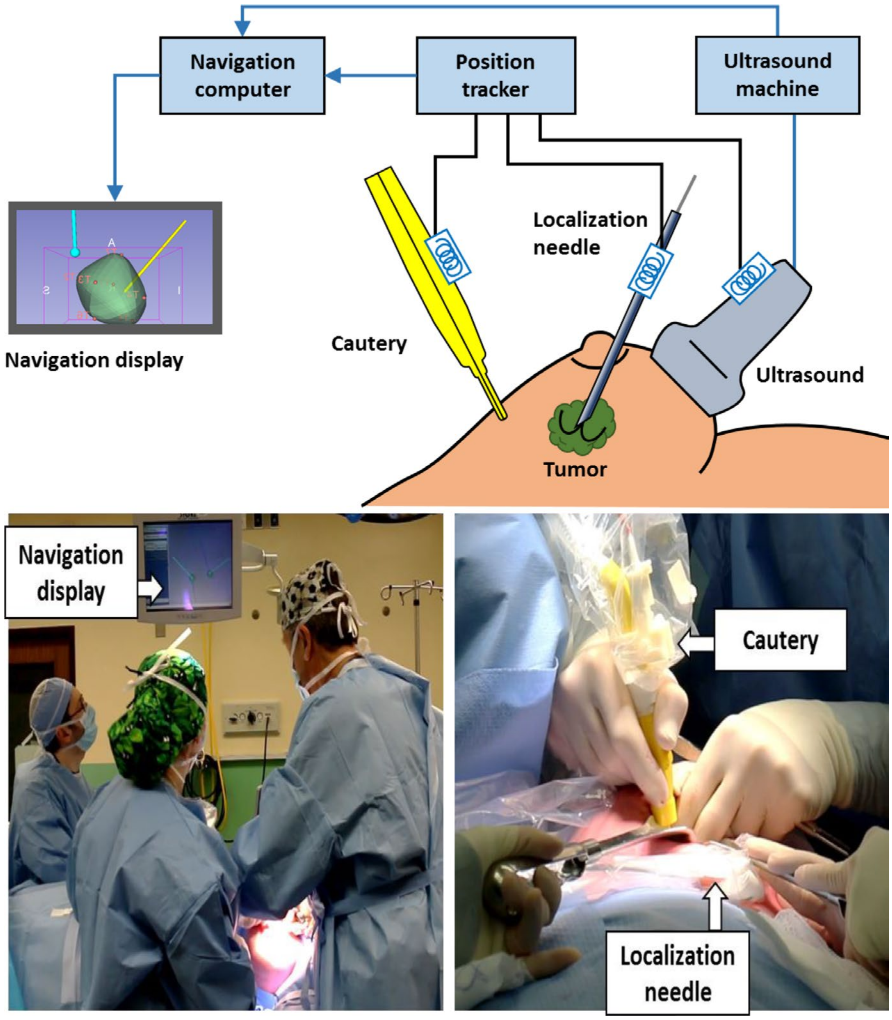


**FIGURE 1** Schematic of the navigation system (upper image). Electromagnetic (EM) sensors are represented by blue coils. Navigation system in the operating room (lower images) [Colour figure can be viewed at wileyonlinelibrary.com]

### 2.3 | Statistical analysis

Statistical evaluation was conducted using MedCalc(R) version 9.2.1.0. Operative time, specimen volume, and specimen weight were compared using independent *t*-test or Mann-Whitney *U* test. Positive margin rate, re-excision rate, and presence of residual disease on re-excision were compared using Fisher's exact test. Results were displayed as mean ± standard deviation (SD) for parametric data or median (range) for nonparametric data. Statistical significance was set as $P < .05$.

## 3 | RESULTS

A total of 40 patients were recruited to the study from 2016 to 2018 and underwent needle localized BCS with EM navigation. A total of 80 non-navigated needle localized BCS controls from the same time-period were case-matched for ultrasound visibility, single foci, invasive carcinoma, and tumor size (Table 1).

There was no equipment failure or breach of sterility during surgery. All surgeons stated that the additional instruments were not cumbersome and did not interfere with the surgical procedure in any of the cases. Most found it easy to setup and use the navigation system. Surgeons agreed that EM navigation was useful in guiding excision of nonpalpable tumors (Figure 3).

The median operative time was 66 (44-119) minutes for the NaviKnife group and 65 (34-158) minutes for the control group ($P = .64$). Median tumor contouring time was 3.2 (1.6-9.0) minutes. The positive margin rate was 22.5% with NaviKnife and 28.7% in the control group ($P = .52$). Seven of 9 (77.8%) patients underwent re-excision in the NaviKnife group, compared to 8 of 23 (34.8%) patients in the control group ($P = .04$). Re-excision specimens contained residual disease in 14.3% of the NaviKnife patients and 50% of the control group patients ($P = .28$). The mean specimen volume was 95.4 ± 73.5 $cm^3$ with NaviKnife and 140.7 ± 100.3 $cm^3$ in the control group ($P = .01$). The median specimen weight was 37.5 (17-95) g with NaviKnife and 50.0 (3-238) g in the control group ($P = .01$; Table 2).

## 4 | DISCUSSION

To our knowledge, this is the first study investigating real-time EM navigation technology in patients with nonpalpable breast cancer. One of the primary challenges that surgeons face with existing

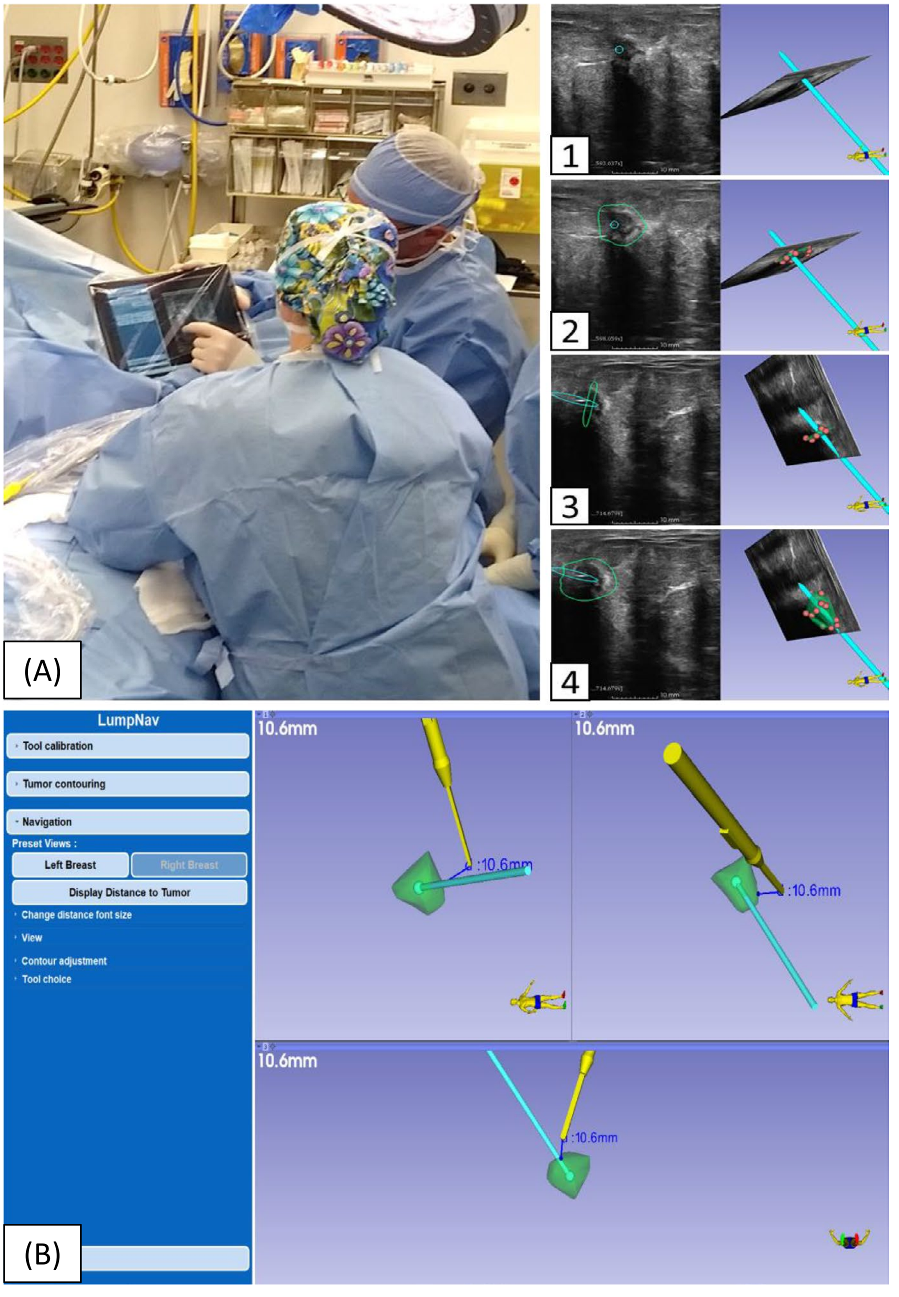


**FIGURE 2** A, Tumor contouring on a touchscreen (left). Tumor contouring in sagittal (1-2) and axial (3-4) images (right). Contour points (red dots) create a 3-dimensional tumor contour (green). B, Screenshot of navigational display. Tumor contour (green), localization needle (cyan), and cautery (yellow) are visible from 3 different orientations. The distance between cautery tip and tumor margin is shown [Colour figure can be viewed at wileyonlinelibrary.com]

techniques is the attempt to excise a 3-dimensional tumor using 1 or 2-dimensional localization techniques. We developed an EM navigation technique to improve the accuracy of nonpalpable breast cancer excisions by providing the surgeon with a 3-dimensional image of the lesion to target. This is the first patient study on nonpalpable BCS to confirm the safety and feasibility of EM navigation in the clinical setting.

Our EM navigation system builds on two existing tumor localization methods, needle localization (current gold-standard) and intraoperative ultrasound. Most tumors have sonographic visibility,[13] and intraoperative ultrasound was previously found to successfully reduce the positive margin rate in BCS.[18] A study comparing needle localization, intraoperative ultrasound, and radio-guided occult lesion localization (ROLL) found a significantly lower positive margin rate when using intraoperative ultrasound (3.7%), vs needle localization (21.3%) and ROLL (25%).[19] However, intraoperative ultrasound alone is limited to 2-dimensional cross-sectional images, and the image is only available when the transducer is on the patient. This requires the surgeon to pause the excision to re-localize the lesion. With our novel navigation method, an ultrasound based 3-dimensional rendering of the tumor is displayed on a screen, allowing the surgeon to see the tumor location in real-time throughout the excision. This makes the contour from the intraoperative ultrasound easily accessible to surgeons without additional cognitive load or interruption of excision for imaging as the surgeon does not need to repeatedly place the ultrasound transducer on the patient during the case.

We demonstrated that NaviKnife is easy to use in the operating room. There were no equipment failures or breach of sterility.

**TABLE 1** Patient demographics

| | NaviKnife (n = 40) | Matched control (n = 80) | *P*-value |
|---|---|---|---|
| Age | 66.7 ± 6.5 | 65.1 ± 9.5 | .37 |
| Laterality | | | |
| Left breast | 16 (40%) | 42 (52.5%) | .25 |
| Right breast | 24 (60%) | 38 (47.5%) | |
| Tumor pathology | | | |
| Invasive only | 19 (47.5%) | 36 (45%) | .85 |
| Invasive + DCIS | 21 (52.5%) | 44 (55%) | |
| Size of invasive lesion ($cm^3$) | 1.1 (0.04-4.32) | 1.2 (0.06-4.53) | .60 |

Abbreviation: DCIS, Ductal carcinoma in situ.

**TABLE 2** Outcomes of NaviKnife compared to control

| | NaviKnife (n = 40) | Matched control (n = 80) | *P*-value |
|---|---|---|---|
| Positive margin | 9/40 (22.5%) | 23/80 (28.7%) | .52 |
| DCIS | 5 (12.5%) | 15 (18.7%) | |
| IDC | 4 (10%) | 7 (8.87%) | |
| ILC | 0 | 1 (1.25%) | |
| Re-excision | 7/9 (77.8%) | 8/23 (34.8%) | .04 |
| Re-excision-residual disease | 1/7 (14.3%) | 4/8 (50.0%) | .28 |
| Specimen volume ($cm^3$) | 95.44 (±73.5) | 140.67 (±100.3) | .01 |
| Specimen weight (g) | 37.5 (17-95) | 50.0 (3-238) | .01 |
| Operative time (min) | 66 (44-119) | 65 (34-158) | .64 |
| Contouring time (min) | 3.2 (1.6-9) | n/a | |

Abbreviations: DCIS, ductal carcinoma in situ, IDC, invasive ductal carcinoma, ILC, invasive lobular carcinoma.

Surgeons found the setup and implementation easy. Computerized navigation has been successfully implemented in the routine surgical practice of certain specialties, such as neurosurgery[20] and orthopedic surgery,[21] where the bony structures provide a rigid frame. Real-time surgical navigation is challenging in more deformable tissues, such as the breast. Our proposed method overcomes the challenge of breast deformation and movement by tracking the localization needle directly inside the tumor. When the localization needle is used as a frame of reference, it allows both contouring and navigation of the tumor despite breast movement and deformation. Due to the high incidence of breast tumors, the potential benefit of such a navigation system is significant.

The current positive margin rate for BCS is approximately 30%.[13] Accurate excision of the tumor at first attempt would reduce the need for a second or third surgery. This not only reduces the cost of care, but also decreases anxiety and provides a better cosmetic outcome for the patient.[22] A recent study has shown that patients undergoing re-excision for a positive margin have a higher rate of local recurrence, reinforcing the importance of a one-step lumpectomy.[4] Numerous alternative techniques have been devised to assist in tumor localization including implanted radioactive seed localization,[7,11] intraoperative radiography,[23] and intraoperative cavity shaving,[24,25] each with their unique advantages and disadvantages. None of the existing techniques offer the real-time image guidance that NaviKnife does.

We demonstrated that NaviKnife significantly reduces the excised specimen volume and weight. NaviKnife also resulted in a reduction in the positive margin rate, although this was not statistically significant as our study was not powered for this outcome. This demonstrates that NaviKnife technology may improve the accuracy of targeting tumor and sparing healthy breast tissue. Of our re-excision specimens, six of seven specimens contained no residual disease, and the pathologically detected positive margin was likely a result of cautery effect. More than 50% of our positive margin rate was due to the presence of ductal carcinoma in situ (DCIS). DCIS detection using ultrasound is difficult due to nonspecific imaging characteristics.[26] Furthermore, DCIS at the tumor periphery is often not a well-organized mass, and thus the precise margin is not visible on ultrasound. Enlarging our contour resection margin in the presence of DCIS should decrease the rate of positive margins. Preoperative adjuncts such as mammographically or MRI placed marking clips may

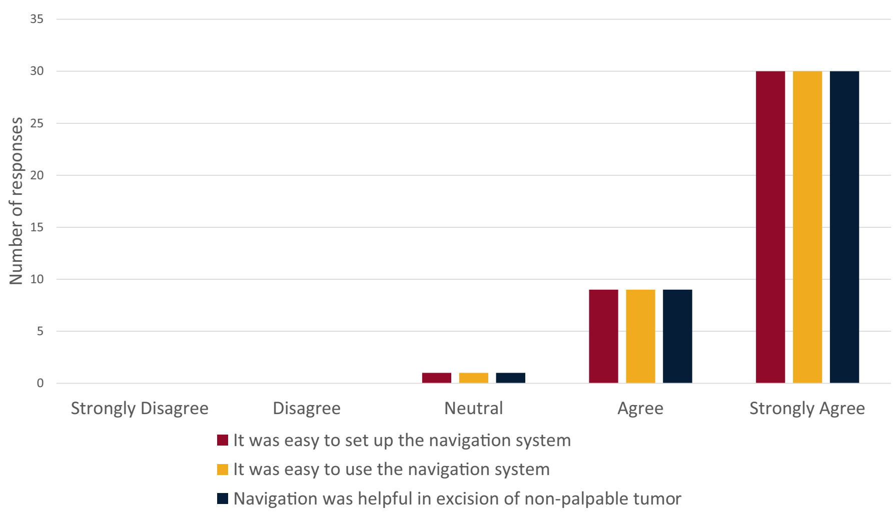


**FIGURE 3** Summary of results from the surgeons' questionnaire [Colour figure can be viewed at wileyonlinelibrary.com]

also help with intraoperative ultrasound identification of the extent of the tumor.[27] Preoperative clipping also has the potential to help expand the technology for use with nonultrasound visible tumors. We plan to explore these options in future studies. As this was a feasibility study, it was not powered to detect a significant difference in positive margin rate.

Limitations of the study include the small sample numbers and the qualitative surgeon assessment of the navigation system. Surgeons were asked to rate the navigation system on a scale of five. These results are subjective and could not be performed in a blinded fashion. We relied on the experience and judgement of the surgeons for this study, but we have also previously performed a more objective evaluation of the same navigation method using synthetic breast models, with a demonstrated accuracy within 1.5 mm.[17,28] The promising results of this feasibility study should be assessed in a multi-institution study as the next step.

We confirmed that navigation was safe to use in the operating room, despite the addition of new components near the surgical site. There were no technical failures of the system. We attached the sensors to the localization needle and the cautery by 3-D printed custom clamps. Future work includes built-in sensors, which would reduce setup time and seamlessly integrate the system into the surgical workflow. Work is also being done to eliminate the use of the localization needle and create an implantable tracker similar to the seed localization technique.

In conclusion, this feasibility study shows that navigation is easy and safe to use intraoperatively in breast-conserving surgery. EM navigation provides useful real-time feedback to surgeons regarding tumor location and has the potential to improve treatment outcomes.

## CONFLICT OF INTEREST

All authors declare no personal, commercial, or financial conflicts of interest.

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