ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

LumiSystem for intraoperative tumour margin assessment following breast-conserving surgery

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Contents

Summary of Key Points

- Breast cancer accounts for 30% of all female cancers diagnosed in Singapore.
- While breast-conserving surgery (BCS) is the standard of care for patients with early-stage breast cancer (e.g. ductal carcinoma in situ [DCIS], invasive cancer), positive margins often necessitate reoperation due to incomplete tumour removal.
- The current gold standard method for margin assessment is postoperative pathological margin assessment, which is associated with costly reoperation if positive margins are found. Intraoperative techniques that examine the excised specimens are limited by poor sensitivity, especially in DCIS cases, and by pathological assessment, which is time and labour intensive.
- LumiSystem (Lumicell. Inc), a drug-device combination product (optical imaging agent LUMISIGHT and a fluorescence imaging device), enables real-time *in vivo* detection of residual breast cancer tissue in the lumpectomy cavity wall during BCS through fluorescence imaging.
- Based on five mostly diagnostic accuracy studies, LumiSystem was found to be generally safe and effective in detecting residual tumours which are missed by standard pathological assessment.
    - A low rate of serious adverse events (0% to 0.74%) was reported with LUMISIGHT, with only one device-related adverse event (AE). All AEs resolved without sequelae.
    - LumiSystem demonstrated moderate tissue-level sensitivity (49.3% to 84%) and specificity (73% to 86.2%) when referenced to standard postoperational pathological assessment. While it demonstrates higher tissue-level sensitivity (69.4% *vs.* 38.2%) compared to standard pathology assessment, its lower specificity (70.4% *vs.* 91.2%) and low positive predictive value (8.7% to 16.6%), highlight the potential of LumiSystem to falsely identify residual tumour (with a false positive rate of 76%).
    - Following standard-of-care BCS, LumiSystem detected additional residual tumour in 6.4% to 7% of cases missed by postoperative pathological margin assessment. This reduced the need for a second surgery in 15% to 25% of patients, with minimal cosmetic impact.
- Key limitations of the evidence include the lack of comparison with other intraoperative tumour margin assessment tools and unclear impact of LumiSystem on longer-term patient outcomes, such as tumour recurrence and survival.
- Cost effectiveness of the technology is uncertain, with LUMISIGHT reported to cost S$19,401 for ten vials of stock (39mg) powder. On average, two vials are required for a patient undergoing imaging with LumiSystem
- Although integration of LumiSystem demonstrated minimal workflow disruption in a major US hospital, a local clinician opined that significant workflow modifications and interference with sentinel lymph node (SLN) biopsy procedures would be anticipated.

- Despite a need for an accurate tool that can better detect residual tumour, a local clinician expert shared that LumiSystem may not present a clear advantage over current available intraoperative tools, with its additional costs.

I.Background

Breast cancer is the most common cancer diagnosed in women worldwide, with an age-standardised rate of 46.8 per 100,000 people (based on 2022 data).[1] Global forecasts for the period 2020–2050 estimate the economic cost of breast cancer to be the third highest among all cancer types, accounting for 7.7% of the total cancer cost.[2] In Singapore, it is the predominant malignancy among women, constituting about 29.6% of all female cancers diagnoses and 17.1% of all female cancer-related deaths between 2018 to 2022.[3] Pathologically, breast cancer commonly begins in the ductal epithelium (i.e. ductal carcinoma in situ [DCIS]) or in the breast lobules (i.e. lobular carcinoma).[4] Early-stage breast cancer can either be non-invasive (in situ), where cancer cells remain in their original site, or invasive, where cancerous cells spread beyond the original location to surrounding normal tissue or lymph nodes.[5]

Treatment for breast cancer is guided by various factors including the disease stage, pathology, patient preference and available resources, with options including surgery, axillary lymph node management, hormonal therapy, chemotherapy, and radiotherapy.[4] In patients with early-stage breast cancer, breast-conserving surgery (BCS) is considered a standard treatment when the tumour size allows for adequate resection with clear margins.[6] Also referred to as a lumpectomy or partial mastectomy, BCS involves removing the tumour with a surrounding margin of normal breast tissue.[6] However, local recurrence after lumpectomy is reported to occur in nearly 40% of cases without radiation at 15 to 20 years, with the risk of local recurrence directly related to incomplete tumour removal during surgery.[7]

In Singapore, between 1960 and 2019,BCS was performed in 27.7% of patients with invasive breast cancer and 51% of patients with DCIS (Personal communication, Senior Consultant from Sengkang General Hospital, 7 April 2025). About 10% to 30% of these patients would require additional surgery due to incomplete tumour removal as indicated by positive margins (Personal communication: Head & Senior Consultant from Ng Teng Fong General Hospital, Senior Consultant from Sengkang General Hospital, 25 September 2024).

At present, the gold standard for margin assessment is post-operative pathological evaluation, which may lead to reoperation if positive margins are found, resulting in additional costs and potential complications.[8] Locally, various intraoperative margin assessment tools are used during BCS, however, they all rely on *ex vivo* examination of the excised specimen, presenting challenges with specimen deformation and orientations.[9] Current intraoperative assessment methods include imaging approaches such as specimen X-ray and ultrasound, which show poor sensitivity in certain breast cancer subtypes (i.e. DCIS),

while other common approaches such as frozen section analysis and imprint cytology require experienced pathologists and are both labour-intensive and time-consuming.[10] As such, there remains a need for an intraoperative margin assessment method that is more accurate, easy to use and can rapidly identify the exact location of the residual tumours.

II.Technology

LumiSystem (Lumicell, Inc) is a drug-device combination product that provides fluorescence imaging to detect breast cancer tissue in the surgical cavity after primary specimen removal during BCS (Figure 1). It consists of (i) an optical imaging agent, LUMISIGHT that is administered intravenously (1 mg/kg) two to six hours before imaging (See Figure A1 in Appendix A), and (ii) a fluorescence imaging device, Lumicell Direct Visualisation System (DVS) that is used to excite the imaging agent, and capture and display real-time fluorescence images that may indicate residual cancer tissue (See Figure A2 in Appendix A).

During surgery, the handheld probe is used to scan the tumour bed for activated LUMISIGHT by delivering an excitation light and measuring the fluorescence emission signal using a camera. Data from the handheld probe is transmitted to a proprietary real-time image processing system that analyses the data using proprietary software to highlight regions within the resection cavity that may contain residual cancer.

LumiSystem offers a novel *in vivo* approach that overcomes the limitations of current intraoperative imaging methods by providing higher sensitivity for tumour detection. It rapidly assesses the entire lumpectomy cavity, to precisely identify sites of residual cancer in the lumpectomy cavity wall after primary specimen removal during BCS. Unlike conventional *ex vivo* methods that examine the excised specimen, this real-time cavity assessment may enable the removal of additional remaining cancer tissue during the initial surgery, potentially reducing the need for reoperations.

Figure 1: Overview of LumiSystem *Figure from: https://lumicell.com/lumicells-cutting-edge-imaging-platform-receives-historicfda-approval-to-illuminate-residual-breast-cancer/*

III.Regulatory and Subsidy Status

Lumicell DVS was granted breakthrough device designation by the US Food and Drug Administration (FDA) in March 2018, followed by Fast Track designation in 2020 for LUMISIGHT.

In April 2024, Lumicell DVS received premarket approval (P230014) from the FDA for use in adults with breast cancer as an adjunct for the intraoperative detection of cancerous tissue within the resection cavity following removal of the primary specimen during lumpectomy surgery. In the same month, LUMISIGHT received a new drug application approval (NDA214511) from the FDA for fluorescence imaging to be used together with Lumicell DVS in the approved indication mentioned above.

IV.Stage of Development in Singapore

☒	Yet to emerge	☐	Established
☐	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐	Established *but* modification in indication or technique
☐	Nearly established	☐	Established *but* should consider for reassessment (due to perceived no/low value)

V.Treatment Pathway

Local clinical practice follows the National Comprehensive Cancer Network (NCCN) guidelines for pathological tumour margin evaluation in patients following BCS for breast cancer, to determine the presence of residual tumour at the radial margins.[9] Based on the type of cancer (i.e. invasive cancer or DCIS) and margin status, further surgery (re-excision or mastectomy) may be recommended (see Table B1 and Table B2 in Appendix B):

- Further surgery is recommended if invasive cancer with or without DCIS is present at the edge of the tissue that was removed during surgery ('tumour on ink'; 0 mm).
- Further surgery is recommended if DCIS with or without microinvasion is present within 2 mm between the edge of the cancer and the outer edge of the removed tissue.

As part of consideration for further surgery, healthcare professionals should discuss benefits and risks with patients, taking into account the individuals' circumstances, needs and preferences, any comorbidities and other potential treatment options such as radiotherapy.

In local clinical practice, various techniques for intraoperative tumour margin assessment following BCS are applied alongside the gold standard of post-operative pathological evaluation, to improve the chance of achieving a clear margin and reducing the need for further surgery. . The introduction of LumiSystem into current practices would serve as an

alternative tool for intraoperative assessment of tumour margins (see Table B3 in Appendix B).

VI.Summary of Evidence

This assessment was conducted based on the Population, Intervention, Comparator and Outcome (PICO) criteria outlined in Table 1. Literature searches were conducted in relevant international health technology assessment (HTA) databases, Cochrane Library and Embase. The key evidence base comprises five studies, including one pivotal trial[7], three single-arm studies[10-12] and one cohort study.[13] All studies included patients with a mix of breast cancer subtypes, including invasive ductal carcinoma (with and without DCIS components), invasive lobular carcinoma, and pure DCIS cases. It should be noted that while the pivotal trial involved randomisation, it is not intended to provide a control group for evaluating device performance, as only outcomes from patients in the LumiSystem arm were used to assess its performance. An FDA summary of Safety and Effectiveness Data (SSED) was included as supplementary evidence.[14] The study design and characteristics of the key and supplementary evidence sources are presented in Table C1 and Table C2 in Appendix C.

Table 1: PICO criteria

Population	Patients undergoing breast-conserving surgery for breast cancer
Intervention	LumiSystem
Comparator	Primary comparator: Intraoperative imaging (e.g. specimen X-ray or ultrasound) for margin assessment Secondary comparator: Other intraoperative margin assessment tools Reference standard: Postoperative histopathological assessment
Outcome	Safety (e.g. adverse events), clinical effectiveness (e.g. detection rate, accuracy, reoperation rate, conversion to mastectomy, survival rate, quality-of-life), cost and cost-effectiveness

Safety

Across five studies, LUMISIGHT was found to be generally safe, with a low rate of treatment-related serious adverse events (SAEs; 0% to 0.74%) reported, including anaphylaxis, hypersensitivity, and allergic reactions (Table 2).[7, 11] In two studies, blue chromaturia (a transient and expected AE due to the blue fluorescence dye) was the most common adverse event (AE) reported (90.1% to 100%). Other LUMISIGHT-related AEs included superficial thrombophlebitis, transient transaminitis, post-traumatic stress disorder, allergic reactions, mild hypersensitivity, nausea and extravasation, all of which resolved without sequelae.[7, 11, 13]

In addition, haematoma was reported as a device-related AE in one patient (out of 45 participants) in one study and resolved without intervention.[10]

Table 2: Summary of LUMISIGHT-related adverse events

Safety outcomes	Hwang et al. (2022)[11]	Smith et al. (2023)[7]	Smith et al. (2020)[10]	Smith et al. (2018)[13]	Lanahan et al. (2021)[12]
SAEs, % (n/N)	**0.43% (1/234)**	**0.74% (3/406)**	**0% (0/45)**	**0% (0/10)**	—

Anaphylaxis	0.43% (1/234)	0.25% (1/406)	—	—	—
Hypersensitivity	—	0.25% (1/406)	—	—	—
AEs, % (n/N)	**1.28% (3/234)**	**90.6% (368/406)**	**4.44% (2/45)**	**100% (10/10)**	**—**
Chromaturia	—	90.1% (367/406)	—	100% (10/10)	—
Other AEs	1.28% (3/234)[a]	0.99% (9/406)[b]	4.44% (2/45)[c]	—	—

Notes:

[a] LUMISIGHT-related AEs reported include superficial thrombophlebitis, transient transaminitis, and post-traumatic stress disorder (in the same patient who experienced anaphylaxis).

[b] LUMISIGHT-related AEs reported included allergic reaction, mild hypersensitivity, nausea, and pegulicianine extravasation.

[c] Of the two AEs, one was LUMISIGHT-related (i.e. pegulicianine extravasation) and one was device-related (i.e. hematoma).

Abbreviations: AE, adverse events; SAEs, serious adverse events

Effectiveness

Effectiveness outcomes were reported in five studies. However, the studies lacked comparative analysis between LumiSystem and other intraoperative assessment techniques.

Diagnostic Accuracy

Using postoperative pathological assessment as the reference standard in two studies, LumiSystem showed moderate tissue-level sensitivity (49.3% to 84%) and specificity (73% to 85.2%) as summarised in Table 3.[7, 10] Another study by Hwang et al. (2022) compared the performance of LumiSystem against standard postoperative pathological assessment. This was achieved by comparing the pathologic assessment of margin status (positive or negative) for each orientation on the main specimen with the pathologic assessment (tumour vs no tumour) of the subsequent corresponding shave, using a hierarchy of truth standards as reference (see Table C2 and Table C3 in Appendix C).[11] The study showed that LumiSystem demonstrated higher tissue-level sensitivity (69.4% *vs.* 38.2%) but lower specificity (70.4% *vs.* 91.2%) in detecting residual tumour in the lumpectomy cavity (Table 3). Similarly, patient-level assessment showed a higher sensitivity (76.3%) and a notably lower specificity (24.0%) for LumiSystem (see Table D1 in Appendix D).[11] However, despite the higher sensitivity than standard pathological assessment in Hwang et al. (2022), LumiSystem's performance in the pivotal study failed to meet the pre-set performance goal for sensitivity, which required the lower bound of the 95% confidence interval to exceed 40% (Table 3).[7]

At both tissue- and patient-level, low positive predictive value (PPV; 8.7% to 16.6%) and high negative predictive value (NPV; 83.6% to 98.2%) were reported consistently across two studies (see Table 3 and Table D1 in Appendix D). The low specificity and PPV, reflected in the high false positive rate of 76% reported by Hwang et al. (2022), highlight the potential of LumiSystem to falsely identify residual tumour.[11]

Table 3: Tissue-level diagnostic accuracy of LumiSystem for detecting residual cancer in the lumpectomy cavity

Study	N	LumiSystem, % (95% CI)				Standard pathology assessment, % (95% CI)			
		Sen	Spe	PPV	NPV	Sen	Spe	PPV	NPV
Hwang et al. (2022)[11]	230	69.4% (56.3% to 80.4%)[a]	70.4% (68.1% to 72.7%)[a]	8.7% (6.4% to 11.6%)[a]	98.2% (97.3% to 98.9%)[a]	38.2% (27.2% to 50.0%)[b]	91.2% (88.3% to 93.5%)[b]	40.3% (28.9% to 52.5%)[b]	90.5% (87.5% to 92.9%)[b]

Smith et al. (2023)[7]	357	49.3% (37.0% to 61.6%)[c]	85.2% (83.7% to 86.6%)[c]	9.2% (6.4% to 12.6%)	98% (97.7% to 98.8%)	—	—	—	—
Smith et al. (2020)[10]	45	84% (NR)[d]	73% (NR)[d]	—	—	—	—	—	—

Notes:

[a] Each LumiSystem image was compared with a truth standard hierarchy as the reference standard as histopathology of the imaged tissue was not always available (e.g. a guided shave was not taken).

[b] Each margin orientation on the main lumpectomy section was compared with pathological assessment of the corresponding shave as reference standard.

[c] Each LumiSystem image was compared to histopathology results of the respective lumpectomy specimen margin as the reference standard.

[d] Diagnostic accuracy results were scored relative to histopathology results of the shaved specimen obtained at the margin, if no specimen was taken from the cavity wall at the site of positive Lumicell image, histopathology of the outer surface of the specimen excised from the cavity orientation was used as the reference standard.

Abbreviations: CI, confidence interval; NPV, negative predictive value; NR, not recorded; PPV, positive predictive value; sen, sensitivity; spe, specificity.

Of note, LumiSystem was reported to be able to distinguish cancer tissues from normal tissues for all breast cancer subtypes (e.g. invasive ductal carcinoma, invasive lobular carcinoma, invasive carcinoma with mixed ductal and lobular features, and DCIS), regardless of breast density and menopausal status.[12]

Clinical Utility

Across two studies, LumiSystem demonstrated the ability to guide the removal of additional tumours in 7.6% to 11.3% of all study participants following standard-of-care (SOC) BCS, exceeding the pre-specified performance goal of 3% in the pivotal study (Table 4).[7, 11] It is worth noting that LumiSystem-guided removal of residual tumour included tumour deposits (i.e. discrete collection of cancer cells found in the lymph nodes or other tissues adjacent to the primary tumour site) in women over 70 years of age.[7] This is of particular importance as current guidelines conditionally recommend omitting radiation therapy in these patients with invasive breast cancer when prespecified negative margins are achieved.[15] Notably, in patients initially deemed to have negative margins after SOC BCS, LumiSystem-guided shaves revealed residual cancer in 6.4% to 7% of cases, indicating the ability of LumiSystem to detect residual tumour that could have been missed by the standard pathology assessment (see Table D2 in Appendix D).[7, 11]

Table 4: Tumour removal guided by LumiSystem after SOC BCS

Study (year)	N	LumiSystem-guided removal of residual tumour, % (95% CI); n/N
Smith et al. (2023)[7]	357	7.6% (5.0% to 10.8%); 27/357
Hwang et al. (2022)[11]	230	11.3% (NR); 26/230

Abbreviations: BCS, breast-conserving surgery; CI, confidence interval; NR, not reported; SOC, standard of care

Among patients with a positive margin following SOC BCS, LumiSystem-guided shave led to a final negative margin in 14.5% to 25% of cases, reducing the need for a second surgery in these patients (Table 5).[7, 10, 11] In the pivotal trial, 10% (35 of 357) of patients reported benefit from LumiSystem, either from the removal of residual tumour (n=27) or avoidance of second surgery (n=9), with one patient falling into both categories.[7]

Table 5: Avoidance of second surgery

Study (year)	N	Number of patients with positive margins following SOC BCS	Potential avoidance of second surgery by LumiSystem, % (n/N)
Smith et al. (2023)[7]	357	62	14.5% (9/62)
Hwang et al. (2022)[11]	230	38[a]	19% (6/32)
Smith et al. (2020)[10]	45	8	25% (2/8)

Notes:

[a] Six patients had a positive LumiSystem signal but LumiSystem-guided excisions were not taken based on surgeon judgement.

Abbreviations: BCS, breast-conserving surgery; SOC, standard of care

Additionally, LumiSystem led to an average of 1 to 1.1 additional shaves per patient, resulting in 6.5% to 9.4% (median, 0 cm^3 to 4 cm^3) more tissue removed compared to total resection volume (Table 6). Acknowledging the potential for a higher rate of additional margin excision guided by LumiSystem, it was argued that the additional tissue volume removed would likely have minimal cosmetic impact, with the benefit of maximising residual tumour removal .[11] Supplementary evidence from the FDA SSED reported no difference in overall satisfaction between patients with or without LumiSystem-guided shaves, although this outcome was not statistically powered.[14]

Table 6: Tissue volume of LumiSystem-guided excision

Study (year)	Total N	Mean number of LumiSystem-guided shaves (mean ± SD)	Median volume of LumiSystem-guided shaves	Contribution of LumiSystem shaves to total resection volume
Smith et al. (2023)[7]	357[a]	1.0 ± 1.4	0 cm^3 (IQR: 0.0 to 14.1 cm^3)[a]	9.4% (14.1%)[b,c]
Hwang et al. (2022)[11]	230	1.1 ± 1.2	4.0 cm^3 (95% CI: 0.0 to 102.8 cm^3)	6.5% (95% CI: 0.0 to 55.9)

Notes:

[a] This is due to no additional margin excision being performed in 54% of patients who underwent LumiSystem-guided surgery.

[b] Reported in mean (standard deviation)

[c] Value based on FDA SSED

Abbreviations: CI, confidence interval; FDA, Food and Drugs Administration; IQR, interquartile range; SSED, summary of safety and efficacy data.

Cost-effectiveness

No cost-effectiveness studies for LumiSystem were identified. There may be potential cost savings arising from the conversion of a positive margin to a negative margin, avoiding the need for reoperation and improving patient outcomes, all which could result in reduced overall healthcare costs. However, this remains to be validated.

Ongoing trials

No ongoing trial was identified from the ScanMedicine database. However, one recently completed RCT (NCT04440982; n=98) was identified that evaluates the performance of LumiSystem for intraoperative detection of residual tumour in patients with breast cancer with and without neoadjuvant therapy.[16] While this study assessed key outcomes including

safety, reduction in residual tumour and patient-reported outcomes and preferences, it is unclear when the results may be published. Notable evidence gaps remain unaddressed, such as comparative effectiveness against standard intraoperative assessment tools and the impact of LumiSystem use on longer-term patient outcomes like local recurrence and survival.

Summary

Based on the available evidence, LumiSystem was found to be generally safe for intraoperative margin assessment following BCS. The rate of LUMISIGHT-related SAEs was low (0% to 0.74%) and common AEs resolved without sequelae. One device-related AE was reported, that also resolved without complications. In general, LumiSystem demonstrated moderate tissue-level sensitivity (49.3% to 84%) and specificity (73% to 86.2%). When compared with postoperative pathological assessment at the tissue-level, a higher sensitivity (69.4% *vs.* 38.2%) but lower specificity (70.4% *vs.* 91.2%) was reported. Its low PPV (8.7% to 16.6%) and high false positive rate (76%) highlight the potential for LumiSystem to falsely identify residual tumour.

Following SOC BCS, LumiSystem was reported to detect additional residual tumour in 6.4% to 7% of cases missed by standard pathological assessment, and result in the avoidance of a potential second surgery in 15% to 25% of patients. Despite its potential for a higher rate of additional margin excision due to the low PPV, it was argued that the additional volume of tissue removed would likely have minimal cosmetic impact, with the benefit of maximising removal of residual tumour. The cost-effectiveness of the technology remains unclear.

The evidence should be interpreted with caution. Key evidence gaps include the lack of a direct comparison with other intraoperative tumour margin assessment tools and unclear impact on how improved margin assessment translates to longer-term patient outcomes such as local recurrence and survival rates, and quality-of-life. It is also worthwhile highlighting that of the five studies that formed the evidence base, two were funded by Lumicell, while two other studies were written by authors who received remuneration and stock ownership from Lumicell.

VII.Estimated Costs

Based on available information from an unofficial source, LUMISIGHT is supplied as a powder in a 39 mg/vial for reconstitution to a solution (10 mg/mL). The estimated cost for 10 vials is US$13,488 (S$17,751)[a], with the per-patient cost varying according to the required volume. Based on the recommended dose of 1 mg/kg, two vials would be required, on average, for a patient undergoing imaging with LumiSystem.[17] The cost of Lumicell DVS remains unclear. To note, the accuracy of the above information remains to be verified.

As a reference, the cost of BCS ranges from S$2,484 (subsidised) to S$8,448 (unsubsidised) at local public healthcare institutions.[18] Information shared by a local public hospital indicates

[a] Based on the Monetary Authority of Singapore exchange rate as of May 2025: US$1=S$1.31603. Figures were rounded to the nearest dollar.

minimal to no additional charges for intraoperative margin assessment methods that include gross inspection, tumour palpation, specimen radiography, and ultrasound (Personal communication: Senior Consultant from Tan Tock Seng Hospital, 28 May 2025).

VIII.Implementation Considerations

Published evidence showed that the clinical adoption of LumiSystem in a major US hospital was associated with minimal organisational impact, negligible disruption to routine preoperative protocols, minimal added time to surgical procedures, and did not delay specimen delivery to the pathology lab or affect the results of standard histopathology, immunohistochemistry or fluorescent *in situ* hybridisation analyses.[12]

However, a local clinician opined that the technology would involve significant implementation considerations when adopted into local clinical practice. There may be changes to the existing surgical workflow given that LUMISIGHT needs to be administered two to six hours prior to BCS. As a result, patients would need to be admitted to the hospital earlier, rather than the current one-hour pre-surgery admission time. As such, the use of LumiSystem would extend the surgery time by up to an hour following the completion of tumour resection and cavity imaging (Personal communication: Senior Consultant from Tan Tock Seng Hospital, 28 May 2025).

Moreover, the use of LumiSystem may interfere with any sentinel lymph node (SLN) assessment conducted during BCS to determine the extent of cancer spread. As indicated in the instructions for use, dyes for SLN mapping should not be administered before imaging the BCS cavity with LumiSystem. The dyes used in SLN (e.g. isosulfan blue and methylene blue) fluoresce at wavelengths similar to LUMISIGHT's excitation spectrum, potentially interfering with imaging accuracy.[12] Although unlikely, this may result in increased risk of non-identification rate for SLN assessment, requiring patients to have further axillary dissection for staging (Personal communication: Senior Consultant from Tan Tock Seng Hospital, 28 May 2025).

Given the risk of anaphylaxis associated with the imaging agent, it is also important to ensure the availability of emergency resuscitation equipment and trained personnel on site.[14]

IX.Concurrent Developments

Currently, LumiSystem is the only FDA-approved fluorescence imaging technology for intraoperative tumour margin assessment following BCS. However, several comparable technologies are in early stages of development (see Table E1 in Appendix E).[19-22]

Aside from fluorescent probes, other techniques have been developed for real-time intraoperative management of breast margins, including spectroscopy, tomography, magnetic resonance imaging, microscopy and multimodal imaging techniques. Some notable technologies that conduct *ex vivo* examination of the excised specimen include MarginProbe,

which utilises electromagnetic field and OTIS, which employs optical coherence tomography (Table 7).

Table 7: Concurrent development of other imaging modalities for intraoperative tumour margin assessment for breast cancer

Technology (Manufacturer)	Imaging modality	Brief description	Status
MarginProbe System (Dune Medical Devices)[23]	Electromagnetic field	The device analyses the reflection based on the tissues' dielectric properties to identify cancerous tissue at the margins of the main *ex vivo* lumpectomy specimen, providing real-time binary classification to guide surgical decision during BCS.	FDA cleared and CE marked
OTIS (OncoRes Medical)[24]	OCT	The device combines QME and OCT technologies to provide a quantitative measure and high-resolution image to guide *ex vivo* identification of residual cancer on the excised human tissue.	Granted FDA BDD
Abbreviations: BCS, breast conserving surgery; BDD, Breakthrough Device Designation; CE, Conformité Européenne; FDA, Food and Drug Administration; OCT, optical coherence tomography; QME; quantitative micro-elastography			

X.Additional Information

Local clinician feedback indicates that the current intraoperative imaging techniques (e.g. ultrasound and specimen X-ray) have limitations in detecting positive margins on final histology, particularly for DCIS cases. An accurate and cost-effective intraoperative tool that can better detect residual tumour and reduce repeat surgery would be useful (Personal communication: Senior Consultant from Sengkang General Hospital, 7 April 2025).

While the accuracy of LumiSystem is comparable with existing methods (e.g. intraoperative specimen X-ray and ultrasound), local clinician experts opined that it did not provide a clear advantage over current available intraoperative methods. This is further coupled with the significant cost increase to use LumiSystem, which would potentially exceed the total surgical cost for subsidised patients (Personal communication: Senior Consultant from Tan Tock Seng Hospital, 28 May 2025).

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Appendix

Appendix A: Device appearance and mechanism

Figure A1: Mechanism of LUMISIGHT activation in breast cancer imaging[25]

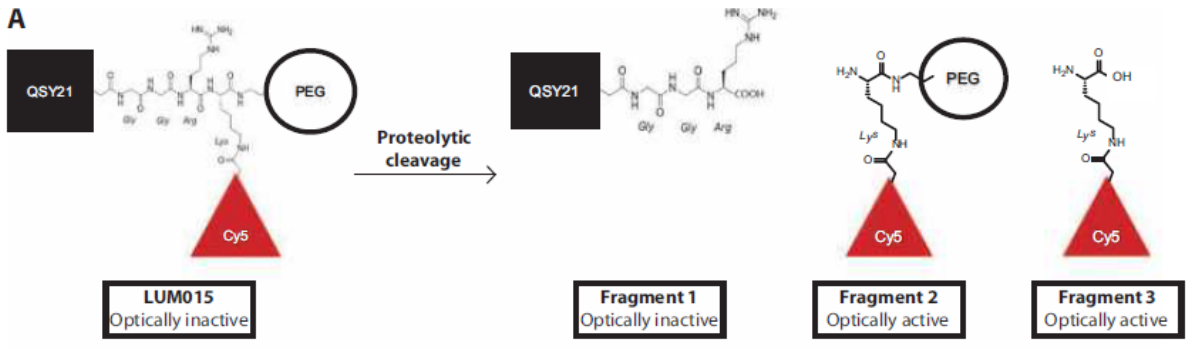
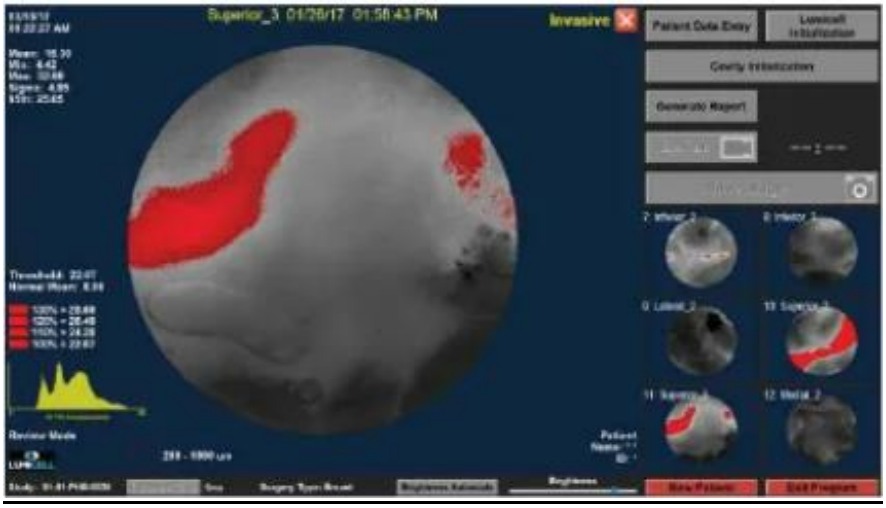
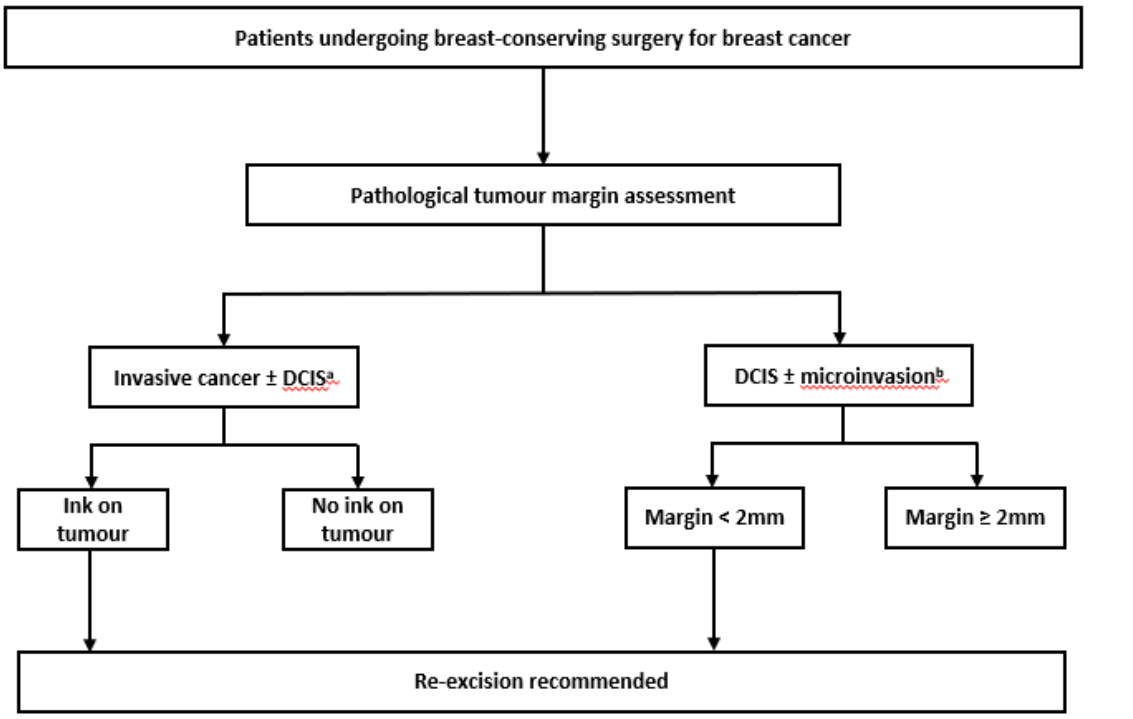


Figure A2: User interface for LumiSystem decision software. Regions highlighted in red indicate areas suspected to have tumour[11]



Appendix B: Clinical pathways

Table B1: Clinical pathway according to NCCN Guidance for Early Breast Cancer



[a] Refers to invasive breast cancer with or without DCIS or extensive DCIS. For these patients, no ink on tumour is recommended for either DCIS or invasive cancer cells.

[b] Refers to pure DCIS or DCIS with microinvasion. For patients with pure DCIS treated with BCS with or without radiotherapy, tumour margin of at least 2 mm is recommended to reduce risk of ipsilateral breast tumour recurrence.

Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; NCCN, National Comprehensive Cancer Network

Table B2: NCCN margin status recommendations after BCS for invasive cancers and DCIS

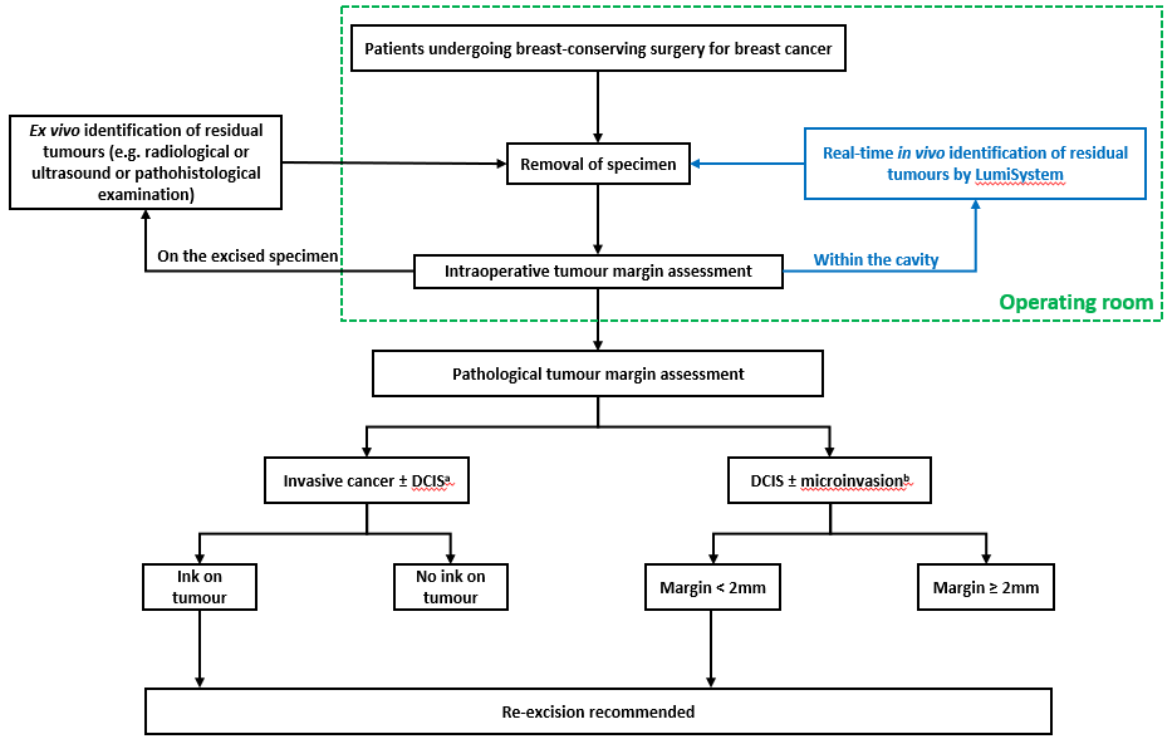
	No ink on tumour	2-mm margin	No margin necessary
Invasive breast cancer	×		
Invasive breast cancer + DCIS	×		
Invasive breast cancer + extensive DCIS	×		
Invasive breast cancer (treated with neoadjuvant chemotherapy followed by breast-conservation therapy)	×		
Pure DCIS		×	
DCIS with microinvasion		×	
Classic LCIS[a] at surgical margin			×
Atypia at surgical margin			×

Notes:

a. For pleomorphic LCIS, the optimal with of margins is not known

Abbreviations: BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; NCCN, National Comprehensive Cancer Network

Table B3: Proposed place of LumiSystem in clinical workflow



[a] Refers to invasive breast cancer with or without DCIS or extensive DCIS. For these patients, no ink on tumour is recommended for either DCIS or invasive cancer cells.

[b] Refers to pure DCIS or DCIS with microinvasion. For patients with pure DCIS treated with BCS with or without radiotherapy, tumour margin of at least 2 mm is recommended to reduce risk of ipsilateral breast tumour recurrence.

Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ

Appendix C: Studies included and study design

Table C1: List of included studies

Type of Study	Key evidence base	Supplementary evidence base
Published studies	5	—
FDA summary of Safety and Effectiveness	—	1

Note:

1. Inclusion criteria
   a. Studies that fulfil the PICO criteria listed in Table 1.
2. Exclusion criteria
   a. Studies only available in abstract form.
   b. Duplicate studies.
   c. Non-human studies.

Table C2: Design and characteristics of included studies

Study	N	Study design	Population	Comparator	Reference standard	Outcome reported
Smith et al. (2018)[14]	15	Prospective non-randomised cohort study	Patients with invasive breast cancer ILC or DCIS	NA	● Standard histopathologic margin assessment	● Safety ● Clinical utility (Mean tumour-to-normal tissue fluorescence ratio)
Smith et al. (2020)[11]	45	Prospective, single-arm study	Patients with invasive breast cancer ILC or DCIS	NA	● Standard histopathologic margin assessment	● Safety ● Diagnostics accuracy (sensitivity, specificity) ● Clinical utility (Reduction in re-operation rate)
Lanahan et al. (2021)[13]	55	Prospective, single-arm study	Patients with invasive breast cancer ILC or DCIS	NA	● Standard histopathologic margin assessment	● Safety ● Clinical utility (Mean tumour-to-normal tissue fluorescence ratio)
Hwang et al. (2022)[12]	234	Prospective, single-arm study	Patients with invasive breast cancer or DCIS	Standard histopathologic margin assessment[a]	● Truth standard hierarchy (Table C3)	● Safety ● Diagnostics accuracy (sensitivity, specificity, PPV, NPV) ● Clinical utility (Reduction in re-operation rate)
Smith et al. (2023)[7]	406	Randomised controlled trial[b]	Patients with stages 0-3 breast cancer	NA	● Standard histopathologic margin assessment	● Safety ● Diagnostics accuracy (sensitivity, specificity, PPV, NPV) ● Clinical utility (Reduction in reoperation rate)

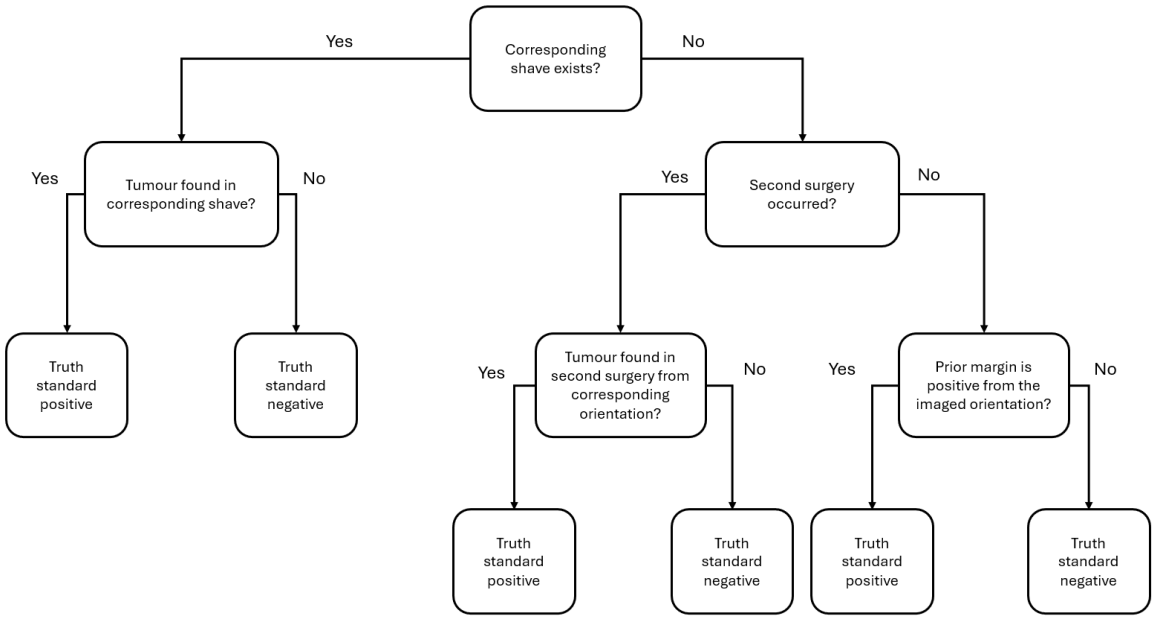
Notes:

[a] The ability of standard pathologic margin assessment to predict residual disease in the cavity was determined by comparing the pathologic assessment of margin status (positive or negative) for each orientation on the main specimen with the pathologic assessment (tumour vs no tumour) of the subsequent corresponding shave (SOC, guided shave, or re-excision).

[b] 10:1 randomization was designed primarily to prevent surgeon bias. The study evaluated patients in the LumiSystem group using paired before-and-after data points.

Abbreviations: BCS, breast conserving surgery; CI, confidence interval; DCIS, ductal carcinoma in situ; ILC, invasive lobular cancer; IV, intravenous; NA, not available; NPV, negative predictive value; PPV, positive predictive value; SOC, standard of care

Table C3: Definition of truth standards as the reference standard



Appendix D: List of supplementary tables

Table D1: Diagnostic accuracy summary on patient-level for predicting residual cancer in the lumpectomy cavity

Study	N	LumiSystem, % (95% CI)			
		Sen	Spe	PPV	NPV
Hwang et al. (2022)[12]	230	76.3% (NR)[a]	24.0% (NR)[a]	16.6% (NR)[a]	83.6% (NR)[a]

Notes:

[a] Each LumiSystem image was compared with a truth standard hierarchy as the reference standard.

Abbreviations: CI, confidence interval; NR, not reported; NPV, negative predictive value; PPV, positive predictive value; sen, sensitivity; spe, specificity.

Table D2: Detection of residual cancer in SOC-negative margins with LumiSystem

Study (year)	Total n	Number of patients with negative margins following SOC excision	Patients with SOC-negative margins found to have residual cancer with LumiSystem, % (n/N)
Smith et al. (2023)[7]	357	295	6.4% (19/295)[a]
Hwang et al. (2022)[12]	230	192	7% (14/192)

Notes:

[a] Based on FDA SSED.

Abbreviations: SOC, standard of care

Appendix E: Early-stage fluorescence imaging technology for intraoperative tumour margin assessment

Table E1: Concurrent development of fluorescence imaging technologies for intraoperative tumour margin assessment for breast cancer

Technology (Manufacturer)	Brief description	Status	Remarks
Bevacizumab-IRDye800CW (University Medical Center, Groningen)[19]	Investigate the use of the tracker bevacizumab-IRDye800CW, for both *in vivo* and *ex vivo* intraoperative imaging of tumour tissue in resected tissue samples and cavity in breast cancer patients.	Undergoing clinical trial	Trial ID: NCT05939310 Estimated completion: December 2024
PRODIGI and Eagle Imaging device (University Health Network, Toronto)[20]	Investigate the use of fluorescent contrast drug 5-ALA, a hand-held optical imaging device PRODIGI and Eagle Imaging device to visualise tumour margins, both *in vivo* and *ex vivo*, on the surgical sample and within the surgical bed during BCS.		Trial ID: NCT01837225 Estimated completion: August 2025
PD G 506A and Eagle V1.2 Imaging System (SBI ALApharma Canada, Inc.)[21]	Investigate the use of PD G 506A (ALA hydrochloride) and Eagle V1.2 Imaging System for *in vivo* visualisation of carcinoma within the surgical cavity during BCS.		Trial ID: NCT04815083 Estimated completion: June 2026
PhLIP ICG (Memorial Sloan Kettering Cancer Center)[22]	Investigate the use of pHLIP ICG for both *in vivo* and *ex vivo* intraoperative imaging of tumours in excised specimens and cavity in breast cancer patients undergoing BCS.		Trial ID: NCT05130801 Estimated completion: November 2026
Abbreviations: ALA, aminolevulinic acid; BCS, breast conserving surgery; ICG, indocyanine green; SLN, sentinel lymph node.			