Real-world application of Cytalux for targeted imaging of occult peritoneal disease in epithelial ovarian cancer

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Abstract. Occult disease in normal-appearing peritoneum is common in epithelial ovarian cancer (EOC), especially after neoadjuvant chemotherapy (NACT). Pafolacianine (Cytalux) is the first Food and Drug Administration-approved agent for targeted imaging of EOC occult disease. The current study presents its first out-of-trial use during cytoreductive surgery (CRS). This study analyzed three cases of Cytalux application in patients with EOC and peritoneal metastases who underwent CRS and hyperthermic intraperitoneal chemoperfusion. Targeted imaging with Cytalux was performed before CRS to confirm uptake by visible lesions and after to identify occult disease. The association between Cytalux-positive disease and pathology was evaluated. Patient A had primary EOC and patients B and C had recurrent disease. All patients received NACT. Patient A had a peritoneal cancer index (PCI) of 21 and a completeness of cytoreduction (CC) score of 1, while patients B and C both had PCI 9 and CC score of 0. Cytalux imaging was associated with all macroscopic lesions. In patient A, Cytalux identified 16 additional peritoneal lesions with 14 confirmed as metastases [true positive (TP) rate, 87.5%]. Two Cytalux-positive peritoneal areas were fulgurated until the signal loss but subsequently tested positive for cancer. In patients B and C, Cytalux detected two lesions in each case with 50.0% positive on pathology. Overall peritoneal-level TP and false positive (FP) rates were 80.0 and 20.0%, respectively. Cytalux can help identify occult EOC peritoneal disease and manage questionable areas of post-chemotherapy fibrosis. However, the FP rate is considerable. Cytalux signal navigation should not be used for energy destruction of lesions until more data are available.

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Abbreviations: BRCA, breast cancer gene; CA-125, cancer antigen 125; CC, completeness of cytoreduction; CRS, cytoreductive surgery; EOC, epithelial ovarian cancer; FDA, Food and Drug Administration; FP, false positive; HIPEC, hyperthermic intraperitoneal chemotherapy; HIPAA, Health Insurance Portability and Accountability Act; IRB, Institutional Review Board; NACT, neoadjuvant chemotherapy; NIR, near-infrared; PCI, peritoneal cancer index; POD, postoperative day; PSS, prior surgical score; TP, true positive

Key words: peritoneal metastases, peritoneal carcinomatosis, ovarian cancer, Pafolacianine, occult disease, imaging, clinical implication, surgical oncology, gynecological oncology

Introduction

Up to 75% of patients with epithelial ovarian cancer (EOC) present with peritoneal spread, making cytoreductive surgery (CRS), with or without hyperthermic intraperitoneal chemotherapy (HIPEC), a cornerstone of treatment (1,2). The best disease control is achieved through the complete removal of all macroscopic tumor (3). Systemic chemotherapy is also frequently utilized, especially in patients unsuitable for upfront resection (4). The response to neoadjuvant chemotherapy (NACT) can be substantial with the peritoneum displaying scarring, adhesions, or even completely normal appearance, despite prior tumor presence (5,6).

Occult disease-microscopic lesions in normal-appearing peritoneum-remains a significant challenge in EOC, particularly in patients after NACT (7). It occurs near visible tumor nodules in up to 46% of cases and in entirely normal-looking regions in 34% (6,7). These lesions are clinically significant and can lead to gross disease recurrence and poor survival outcomes. Visual inspection and palpation during surgery are often insufficient for detecting occult EOC disease (8). Total parietal peritonectomy has been proposed by several centers to reduce the risk of residual occult tumor; however, this approach can result in substantial surgical trauma, associated with high complication rates and increased mortality (6,9,10).

Pafolacianine (Cytalux) is the first agent approved by the Food and Drug Administration (FDA) for intraoperative tumor-targeted visualization in ovarian and lung cancer. It works through a folic acid analog tracer conjugated with indocyanine green, which targets the folate receptor overexpressed in EOC cells, and is visualized intraoperatively using near-infrared (NIR) fluorescence imaging (11-13). Data from phase II and III trials showed promising results, leading to FDA approval in 2021; however, it has not yet been widely adopted, and no real-world data are currently available (14,15).

We report, to our knowledge, one of the first national out-of-trial experiences using Cytalux, evaluating its utility in detecting occult disease following complete macroscopic resection during CRS/HIPEC in patients with primary and recurrent EOC with peritoneal metastases.

Materials and methods

Study design. A case series study was conducted to describe and analyze the outcomes of Cytalux application in out-of-trial settings.

Participants, data source, and setting. We identified patients with primary or recurrent EOC and peritoneal dissemination who underwent CRS/HIPEC with the use of Cytalux for detecting occult disease. Patient demographic, surgical, and outcome data were extracted from a prospectively collected institutional database, encompassing cases from 2018 to 2024. This study complied with the ethical principles outlined in the Declaration of Helsinki (2013 revision) and received approval from the Institutional Review Board (IRB-24-1573) on October 7, 2024. All patients provided written informed consent for participation in research and inclusion in prospective CRS/HIPEC database, including use of their intraoperative imaging and de-identified clinical data in research projects conducted using it. Before study inception, the IRB granted a waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization (45 CFR 164.512(i) (2)(ii)), confirming that no additional patient consent was required. No biological samples were collected for research purposes-histopathological analyses were performed as part of standard clinical care, and only de-identified surgery and pathology reports were retrospectively reviewed.

Variables. Prior surgical score (PSS) was used to quantify surgical history with PSS-2/3 considered extensive previous surgeries (16). Tumor burden was measured using the peritoneal cancer index (PCI), with scoring from 0 to 39 (17). Completeness of cytoreduction (CC) score was used post-CRS to record the amount of residual tumor, with CC-0/1 indicating complete cytoreduction (18).

CRS/HIPEC. All procedures were performed by a surgical oncologist experienced in the CRS/HIPEC for various peritoneal surface malignancies. Cytalux was administered in a dose of 0.025 mg/kg in the preoperative area within 1 h before the procedure. After laparotomy in the lithotomy position, the abdominal cavity was explored and the PCI was recorded. The Stryker 1788 imaging system was used to confirm Cytalux uptake by visible tumor lesions prior to resection. Multiple organ resections and peritonectomies were then performed with the goal of achieving macroscopically complete tumor removal. All anastomoses were performed before the chemoperfusion. Once CRS was concluded, the CC-score was recorded, and HIPEC was performed with 150 mg of cisplatin using a closed technique, with perfusion for 90 min at a target temperature of 41-42˚C.

Follow-up. The first follow-up appointment occurred at 2-3 weeks post-discharge and included a physical examination and wound check. Subsequent surveillance included physical examination, CA-125 level assessment, and imaging of the chest, abdomen, and pelvis every 6 months for 5 years, or sooner if patients experienced symptoms.

Results

Patient and disease characteristics. Out of 96 patients in the database, 3 met the inclusion criteria. Age was 64 years in Patient A, 68 in Patient B, and 62 years in Patient C (Table I). All 3 patients had preoperative pathology consistent with high-grade serous ovarian adenocarcinoma in all included patients. BRCA-2 mutations were present in patients B and C. Patient A had primary stage IIIc ovarian cancer and underwent 6 cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel, with a significant response based on imaging. Patients B and C had recurrent ovarian cancer, which was first diagnosed 6 and 3 years prior, respectively. Their previous treatment and disease courses are described in detail in Table I.

Treatment characteristics and surgical outcomes. After abdominal exploration, PCI was 21 for patient A and 9 for patients B and C. A CC-1 score was achieved for patient A, while patients B and C had CC-0. The length of surgery was 977, 735, and 573 min for patients A, B, and C, respectively. Estimated blood loss was 1,500 ml for patient A, 350 ml for patient B, and 600 ml for patient C, with all patients requiring intraoperative blood transfusions.

Patient A's recovery was complicated only by a pleural effusion that required thoracentesis. Patient B developed bilateral pulmonary embolism, necessitating reintubation on postoperative day (POD) 3. She was later discharged to a rehabilitation facility but was readmitted with aspiration pneumonia on POD 27 and expired on POD 36 after her family elected to withdraw care. Patient C had a relatively uneventful recovery after a brief re-intubation for stridor (POD 2-4).

Cytalux application. Cytalux imaging correlated with all macroscopic lesions in all three cases. In patient A, post-CRS Cytalux revealed 16 additional positive peritoneal areas. Of these, 3 had no palpable or visible abnormalities even upon close inspection: the parietal peritoneum in the right flank and lower quadrant, the left flank and lower quadrant, and the left diaphragm. One area, initially suspected to be post-chemotherapy fibrosis, was Cytalux-positive and later confirmed as malignant by pathology. Cytalux-positive areas of parietal peritoneum were extensively fulgurated with argon plasma for over 20 min, until the NIR signal was lost, and then resected; however, pathology confirmed cancer. The other 13 Cytalux-visualized lesions, missed during the initial abdominal exploration, were very small and identified only after targeted imaging. They included 11 mesenteric peritoneum nodules (9 positive and 2 negative for cancer), a 1 right upper quadrant lesion (positive), and about 30 cm of colon with multiple millet-sized lesions, all confirmed as cancer (Fig. 1). A single Cytalux-positive retroperitoneal lymph node near the inferior vena cava was removed but found negative for carcinoma. Among 16 Cytalux-guided peritoneal samples, 14 (87.5%) were positive for cancer, and 2 (12.5%) were found negative.

Table I. Patient characteristics.

Variable	Patient A	Patient B	Patient C
Age, years	64	68	62
BRCA 2 mutations	-	+	+
PSS	2	2	3
Disease	Primary	Recurrent	Recurrent
Prior course	• Carboplatin + Paclitaxel (6 cycles)	• Suboptimal CRS • Carboplatin + Paclitaxel (6 cycles) • Olaparib (4 years) Recurrence	• Carboplatin + Paclitaxel (3 cycles) • CRS • Carboplatin + Paclitaxel (3 cycles) • Niraparib (1 year) Recurrence: • Carboplatin + Paclitaxel (8 cycles) • Bevacizumab (maintenance)
PCI	21	9	9
CC-score	CC-1	CC-0	CC-0
Length of surgery, min	977	735	573
EBL, ml	1,500	350	600
Blood transfusion	+	+	+
Length of hospital stay, days	14	19	8
Cytalux-positive occult peritoneal disease	16 lesions: • 11 mesenteric lesions (9 path+) • 5 parietal peritoneum lesions (5 path+)	2 lesions: • Appendix (path+) • Segment of small bowel (path-)	2 lesions: • Right lateral abdominal wall lesion (path-) • Parietal peritoneum of anterior abdominal wall below umbilicus (path+)
True positive lesions	14 (87.5%)	1 (50.0%)	1 (50.0%)
False positive lesions	2 (12.5%)	1 (50.0%)	1 (50.0%)

BRCA, breast cancer gene; CC, completeness of cytoreduction; CRS, cytoreductive surgery; EBL, estimated blood loss; path, pathology; PCI, peritoneal cancer index; PSS, prior surgical score.

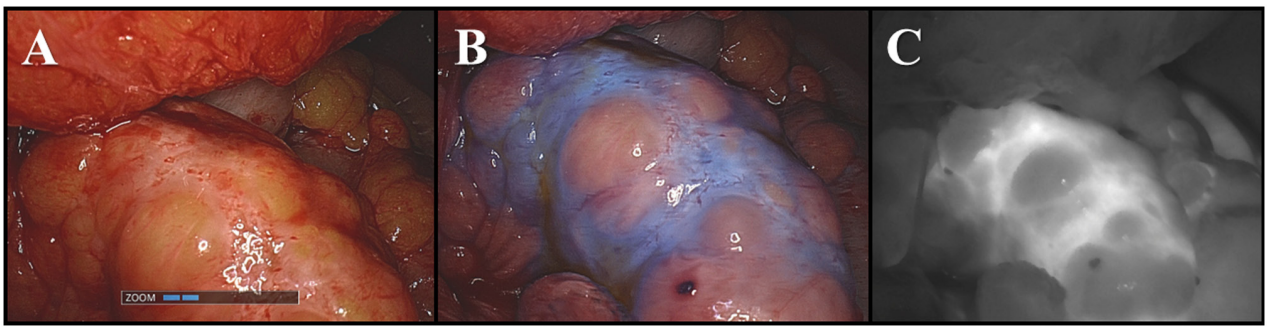

Figure 1. Intraoperative targeted imaging of occult peritoneal disease in Patient A. (A) Grossly visible disease on the descending and sigmoid colon illuminated with (B) Cytalux and (C) near-infrared fluorescence.

For patient B, Cytalux imaging identified two areas of concern for occult disease: the appendix (Fig. 2), which was later confirmed to be a metastasis of high-grade ovarian carcinoma, and a segment of small bowel previously adherent to the right lower quadrant tumor but dissected off it before resection. The resected segment came back negative for malignancy. Additionally, Cytalux showed uniform uptake inside the gallbladder, with no visible surface disease. The true positive (TP) and false positive (FP) rates were both 50.0%.

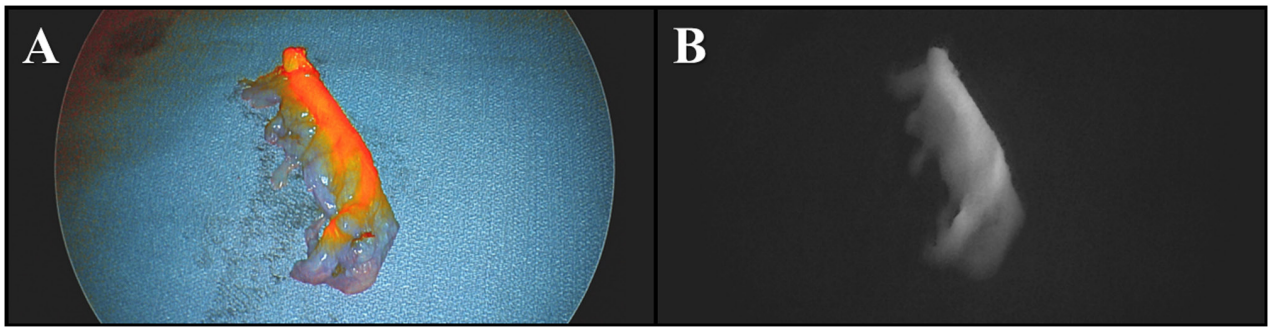

Figure 2. Postoperative targeted imaging of occult peritoneal disease in Patient B. The removed appendix with occult not grossly visible disease highlighted with (A) Cytalux and (B) near-infrared fluorescence.

In patient C, Cytalux highlighted the entire small bowel on initial imaging after all visible tumors were removed. As the imaging intensity decreased, two positive areas with no visible lesions on close inspection were identified: one on the abdominal wall on the right posterior rectus sheath, which was later found negative for cancer, and a large area of parietal peritoneum of the abdominal wall below the umbilicus, which was positive. Both TP and FP rates were 50.0% each.

Overall, at the peritoneal lesion level, the TP rate was 80.0% (16/20) and the FP rate was 20.0% (4/20). Included patients experienced neither intra-nor postoperative known Cytalux-related complications.

Oncology outcomes. Final pathology for patient A confirmed papillary serous carcinoma with 25% PD-L1 expression. She was started on adjuvant therapy with nivolumab and shows no laboratory or imaging signs of disease 8 months after CRS/HIPEC. Pathology for patients B and C revealed high-grade serous carcinoma. Patient C was started on post-operative liposomal doxorubicin and remains disease-free 3 months post-procedure.

Discussion

This report presents the first out-of-trial experience using Cytalux-based intraoperative imaging to detect occult disease in EOC with peritoneal spread during CRS/HIPEC. Cytalux uptake correlated with visible tumors and identified at least one additional non-visible lesion post-CRS in each of the three patients. The overall true positive rate for occult peritoneal lesions after CRS was 80%, with a false positive rate of 20%. Notably, Cytalux imaging revealed one area of post-chemotherapy fibrosis, later confirmed as malignant by pathology. Additionally, 2 Cytalux-positive peritoneal areas underwent extensive argon plasma fulguration for over 20 min until the NIR signal was lost, but both were still positive for cancer, suggesting caution in using Cytalux imaging for this purpose. These findings validate previously published data from clinical trials on Cytalux efficacy in real-world settings while also highlighting critical new challenges associated with its intraoperative use.

All patients in our study demonstrated Cytalux uptake in grossly visible tumors, confirming high folate receptor expression in all EOC cases. Previous studies have shown that EOC cells can express folate receptors at levels 10-100 times higher than normal tissues, making them an attractive target for imaging occult disease (12,13,19). In a phase III trial, 109 out of 150 patients who received infusion with Cytalux had confirmed folate-receptor-positive EOC (15). This high uptake is likely because of Cytalux targeting folate receptor alpha, present in up to 90% of EOC, rather than the less frequently expressed folate receptor beta, found in about 20% of EOC. Two patients in our study had high-grade serous carcinoma, and one had papillary serous carcinoma, indicating that even different EOC subtypes can express folate receptors and show appropriate Cytalux uptake. In the phase III trial, up to 18% of patients with folate-receptor-positive disease had less common EOC variants than high-grade serous carcinoma (15). Both our and previous data suggest that Cytalux has a high affinity for tumor cells in the majority of EOC patients, but its uptake should be confirmed at the beginning of the procedure before tumor removal.

Interestingly, the first antibody-drug conjugate targeting folate receptor alpha, mirvetuximab soravtansine, was recently approved by FDA for treatment of platinum-resistant ovarian cancer. Its interaction with Cytalux is unclear but competitive blockade of folic receptors alpha can potentially interfere with Cytalux uptake and accuracy of the imaging, warranting further investigation.

Achieving complete cytoreduction is crucial in EOC, as the presence of residual occult disease worsens patient outcomes. Therefore, total parietal peritonectomy has been proposed by several centers outside the United States to cope with occult disease yet it can significantly increase morbidity while the impact on survival is unclear (6,9,10). The concept of using Cytalux for targeted imaging is a precise identification of occult lesions that offers a more selective approach and potentially reduces the need for highly morbid procedures such as total peritonectomy. In our study, the TP rate for Cytalux-positive lesions was 80%, consistent with 83% reported in the clinical trial, where 395 of 531 lesions were TP (15). Notably, Cytalux identified additional occult lesions in all patients in our cohort. In the original trial, the rate of additionally detected lesions by Cytalux that were confirmed by pathology but not initially planned for resection was 39.7% for interval CRS and 17.1% for primary CRS (15). Our findings reinforce the clinical utility of Cytalux in guiding and achieving more thorough cytoreduction by enhancing intraoperative lesion detection beyond standard visual and tactile assessment, thereby potentially improving long-term EOC patient outcomes.

There are several limitations to the use of Cytalux. A significant FP rate, leading to unnecessary resections, has been previously reported. In our study, the FP rate was 20%, which is lower than the 32.7% reported in the phase III trial (15). The FP rate can vary significantly depending on the interpretation of imaging. For patient C, nearly the entire small bowel surface was highlighted with Cytalux at the beginning of the case, which resolved with a decrease in imaging gain. Fluorescence can occur in normal tissues, including areas of the bowel, kidneys, lymph nodes, lungs, and inflamed tissue, leading to potential interpretation errors. This underscores the importance of fluorescence standardization and surgeon training to optimize imaging interpretation and minimize unnecessary resections. Additionally, the presence of company representatives during the first several cases may be necessary for accurate imaging interpretation and navigation.

An interesting finding in our study is the failure of argon beam tumor destruction under Cytalux navigation in patient A. In this case, two substantial areas, each more than 10 cm in diameter, were Cytalux-positive but had no grossly visible lesions on close inspection. These areas underwent argon fulguration for over 20 min until the Cytalux signal was lost and eschar was formed. However, when resected, these areas were confirmed to be malignant on pathology. Energy-based tumor destruction methods, including electrocautery, argon beam coagulation, ultrasonic surgical aspirator, and carbon dioxide laser, are commonly used by cytoreductive surgeons to reduce tumor burden and increase the likelihood of complete cytoreduction, particularly for implants in difficult locations (20-22). However, the efficacy of thermal tumor destruction has not been systematically studied. Based on our experience, Cytalux should not be used for guidance during thermal tumor destruction until more data are available.

This study has several limitations related to its design. First, the small sample size, with only three patients, did not allow for a comprehensive statistical analysis. Larger, multicenter prospective studies with a greater number of participants are needed to validate our results, assess patient selection criteria, and better characterize Cytalux's sensitivity and specificity in real-world clinical settings. Second, the short follow-up period prevented us from assessing the impact of Cytalux-guided cytoreduction on survival outcomes. Future studies should incorporate longitudinal follow-up to determine whether Cytalux-guided resection of occult disease improves progression-free and overall survival. Lastly, we were unable to calculate true and false negative rates, as this would require performing a total parietal peritonectomy, a highly morbid procedure that is not done routinely. Future trials could integrate biopsy mapping strategies or other validation methods to provide a more accurate assessment of the extent of occult disease missed by standard imaging techniques. Despite these limitations, our study bridges the gap between clinical trial data and real-world application, offering early insights into the feasibility, benefits, and challenges of integrating Cytalux into routine EOC management.

In conclusion, the use of Cytalux in real-world settings demonstrates significant efficacy in identifying occult peritoneal disease in a substantial proportion of EOC patients with peritoneal metastases, with a true positive rate of up to 80%. However, a notable false positive rate emphasizes the need for cautious interpretation, particularly in the context of surgical decision-making. Cytalux signal navigation should not be used for guiding thermal tumor destruction until more evidence becomes available. Routine Cytalux-guided decision-making may require standardization of fluorescence approach, implementation of special training for surgeons with learning curve to correctly identify and interpret lesions, and development of real-time lesion validation by frozen pathology. Continued collection of real-world data is critical to fully assess Cytalux utility in out-of-trial settings, ultimately guiding its broader adoption in clinical practice.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

EB conceptualized and designed the study, collected and analyzed the data, and wrote the original draft. RP collected the data, designed the methodology, and reviewed and edited the paper. RT collected and analyzed the data, and reviewed and edited the paper. JAW conceptualized and designed the study, and reviewed and edited the paper. RS conceptualized and designed the study, reviewed and edited the paper, and was the project administrator. EB and RS confirm the authenticity of all the raw data. All authors have made substantial intellectual contributions to the conception, design and execution of this study. Each author has actively participated in drafting the work, revising it critically for important intellectual content. Furthermore, all authors agree to be accountable for all aspects of the work, ensuring that questions related to any part of the work are appropriately investigated and resolved. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study complied with the ethical principles outlined in the Declaration of Helsinki (2013 revision) and received approval from the Institutional Review Board (IRB-24-1573) on October 7, 2024. All patients provided written informed consent for participation in research and inclusion in prospective CRS/HIPEC database, including use of their intraoperative imaging and de-identified clinical data in research projects conducted using it. Before study inception, the IRB granted a waiver of Health Insurance Portability and Accountability Act authorization [45 CFR 164.512(i) (2)(ii)], confirming that no additional patient consent was required. No biological samples were collected for research purposes-histopathological analyses were performed as part of standard clinical care, and

only de-identified surgery and pathology reports were retrospectively reviewed.

Patient consent for publication

All patients provided written informed consent for including their de-identified clinical data and intraoperative images in prospectively collected CRS/HIPEC database and its use for research, including this publication.

Competing interests

The authors declare that they have no competing interests.

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