Intraoperative imaging of residual ovarian cancer after neoadjuvant chemotherapy using indocyanine green

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ABSTRACT

Objectives Interval debulking surgery has similar outcomes and less morbidity compared with primary debulking in advanced ovarian cancer. However, there is controversy regarding the selection of chemotherapy-resistant clones. Complete resection is an essential prerequisite, and near-infrared surgery combined with various techniques for highlighting malignant foci strives to achieve actual complete resection. This study investigated the role of indocyanine green (ICG) in identifying additional residual malignant foci during interval debulking of apparently intact peritoneum not deemed clinically suspicious under white light inspection.

Methods Patients diagnosed with stage III or IV high-grade serous ovarian carcinoma, older than 18 years of age, with satisfactory hepatic and renal functions who underwent neoadjuvant chemotherapy according to the institutional protocol and were scheduled to undergo interval debulking surgery between 2020 and 2022 were deemed suitable for inclusion after agreeing to the study protocol and acknowledging no contraindications for the administration of the ICG product. After laparotomy and white light inspection, using bolus administration of ICG, additional suspect peritoneal samples in near infrared (defined by clinical hyper- or hypointensity areas compared with surrounding ICG fluorescence using the Zeiss Opmi Pentero 800 surgical microscope, that were not deemed clinically suspicious under white light) were excised. Descriptive statistics were inferred and the chi-square test was used for the comparison of excised areas. The Kaplan–Meier method was deployed for computing the overall survival and progression-free survival of the cohort. All statistical analyses were performed using IBM SPSS Statistics software.

Results Fifteen patients with a median age of 56 years were included. Most cases (n=10, 66.7%) were International Federation of Gynecology and Obstetrics (FIGO) stage III, and all patients received four to seven cycles of neoadjuvant platinum chemotherapy, with 40% of regimens using bevacizumab. The mean interval between neoadjuvant treatment and surgery was 39 (median 42, range 20–78) days. A total of 39 suspect additional peritoneal samples were analyzed, with 41% confirming malignant foci. The positive predictive value (PPV) for malignant foci was 30% in ICG hyperintense areas and 46% in ICG hypointense areas. Germline BRCA1/2 mutant patients and using neoadjuvant bevacizumab led to a higher PPV for ICG hypointense areas (60% and 72.7%, respectively). Overall, the number of additionally resected pathologically confirmed malignant lesions through ICG fluorescence increased by 25%.

Conclusions The use of ICG was associated with an increase in the resection of samples with residual malignant foci. Overall, hypointense areas had a higher positive PPV for malignant foci in comparison with hyperintense ICG areas (46% vs 30%), which could be interpreted in the context of dynamic changes in the tumor

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior research showed that targeted fluorescence imaging with a folate receptor alpha probe allowed for the visualization and resection of more tumor deposits compared with standard white light surgical procedures, while only one specific folate receptor alpha-targeted probe, pafolacianine, is US Food and Drug Administration (FDA)-approved for clinical use following positive results of a phase III trial, currently unavailable in Europe. Indocyanine green (ICG) is a readily available, non-specific fluorophore with both FDA and European Medicines Agency clearance for clinical use in angiography and a good tolerability profile. Thus far, few studies have investigated the use of ICG in ovarian cancer peritoneal carcinomatosis.

WHAT THIS STUDY ADDS

⇒ The use of ICG was associated with an increase in the resection of samples with residual malignant foci. The positive predictive value for malignant foci was 30% in ICG hyperintense areas and 46% in ICG hypointense areas. Overall, the number of additionally resected pathologically confirmed malignant lesions through ICG fluorescence increased by 25%.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ ICG could serve as a fluorophore for folate receptor alpha-negative patients and a platform for future drug development. The present analysis could stand as a pillar for future research on a larger scale, investigating the capabilities of such fluorophores to detect otherwise non-suspicious peritoneal areas in white light inspection during surgery for ovarian cancer.

microenvironment or enhanced permeability and retention effect following neoadjuvant chemotherapy.

INTRODUCTION

Ovarian cancer is the second deadliest gynecological cancer in industrialized countries, and most patients are diagnosed with advanced-stage disease.[1] Given the lack of adequate tools for effective screening,[2] optimizing the current treatment of advanced ovarian cancer represents a significant topic of interest. Surgical cytoreduction of advanced-stage ovarian cancer remains the cornerstone of initial treatment. There is also general agreement that adding chemotherapy after complete cytoreductive surgery is the most effective first approach, given that complete upfront debulking to no visible tumor residuals is the ultimate goal of any ovarian cancer surgery and treatment, whenever deemed feasible.[3] Macroscopically complete resection often necessitates extensive upper abdominal surgery with multi-visceral resections and can be achieved in only up to 60% of patients.[4] Such results are primarily achieved in experienced centers with a considerable number of patients where a significant impact on overall survival has been observed.[5]

The use of neoadjuvant chemotherapy followed by debulking surgery in advanced ovarian cancer is a viable alternative, having a higher rate of R0 resection and less morbidity (meaning fewer post-operative serious adverse effects, and fewer bowel resections or stoma formations) without any added significant differences in respect of the overall survival or progression-free survival.[6] However, previous studies had significant surgical limitations, and inconsistent data have been published regarding the impact on the quality of life; the results of the TRUST trial are eagerly awaited.[7] There is also controversy regarding selecting chemotherapy-resistant clones following neoadjuvant chemotherapy. Recent data indicate that the chemoresistant clones were already present in the tumor cells before undergoing neoadjuvant chemotherapy. These clones were then selectively favored and adapted in response to neoadjuvant treatment, which supports the hypothesis of adaptive resistance. Additionally, an increase in the polarization of M1 and M2 macrophages was observed, together with a substantial drop in the fraction of the CD8+ naive T cell subpopulation linked to protective immunity, after neoadjuvant therapy. The findings indicate the existence of a chemoresistant microenvironment in the remaining tumors after neoadjuvant therapy.[8] Hence, complete resection is an essential prerequisite, and near-infrared surgery combined with various techniques for highlighting malignant foci strives to achieve proper complete resection. Following this hypothesis, a combination of neoadjuvant chemotherapy and a method for detecting intraoperative residual tumors could represent a breakthrough in the current treatment of ovarian cancer, minimizing comorbidities and maximizing the effects of surgical debulking.

Near-infrared fluorescence imaging is an attractive method for aiding in the immediate detection of malignant tumors during surgery. This method utilizes near-infrared fluorescence light (700–900 nm) produced by contrast compounds when stimulated by an imaging device capable of capturing this near-infrared fluorescent signal.[9] Van Dam et al pioneered demonstrating tumor detection in ovarian cancer using a folate receptor alpha-targeting drug. Such studies may be costly and time-consuming,[10] and US Food and Drug Administration (FDA)-approved agents for ovarian cancer, such as pafolacianine, have not yet entered the European Union market.[11] Hence, it is necessary to use and evaluate the role of therapeutically accessible contrast agents, such as indocyanine green (ICG).

ICG fluorescence can be used to evaluate tissue perfusion, which is traditionally assessed quickly using visual indicators. The signals are subjective, while near-infrared imaging using ICG can provide a vivid representation of tissue perfusion and has shown high effectiveness in reconstructive surgery.[12] Conversely, ICG attaches to blood proteins and functions like a macromolecule in the bloodstream that concentrates in tumor cells because of enhanced vascular permeability and impaired drainage. The enhanced permeability and retention effect is prevalent in solid tumors. However, the heterogeneity of solid tumors might affect the accumulation of macromolecules in tumor tissue, and it is uncertain if all initial findings may be applied to clinical settings.[13]

The primary objective of the study was to evaluate the feasibility of near-infrared fluorescence imaging based on ICG in a homogeneous cohort of advanced high-grade serous ovarian cancer patients who underwent neoadjuvant chemotherapy with or without bevacizumab. Areas of apparently intact peritoneum not deemed clinically suspicious under white light that were either hyper- or hypointense during subsequent fluorescence imaging were sent for pathological evaluation to confirm if they harbored residual tumor foci.

METHODS

The inclusion criteria for this study were adult female patients aged over 18 years diagnosed with advanced high-grade serous ovarian cancer with initial International Federation of Gynecology and Obstetrics (FIGO) stage III or IV. All patients had to receive neoadjuvant chemotherapy according to the institutional protocol, followed by interval debulking surgery and in agreement with the study protocol. Exclusion criteria were contraindications for the use of the ICG diagnostic product, Verdye, disagreement with the proposed study, no intent of undergoing interval debulking surgery, planned primary debulking surgery, impaired renal function (creatinine>1.5×), impaired hepatic function (ALT/AST>3×, total bilirubin>1.5×), or enrollment in another clinical trial.

After interval debulking surgery, patients had adjuvant chemotherapy followed by maintenance treatment with bevacizumab, olaparib, and bevacizumab/olaparib according to their molecular and clinical status, per the standard of care protocols. Use of neoadjuvant bevacizumab was allowed at the clinician's discretion. Patients were chronologically included in the study protocol from June 2020 until June 2022. Following neoadjuvant chemotherapy with or without bevacizumab, all patients were deemed operable for interval debulking surgery. After laparotomy the first step was inspection of the peritoneal cavity, with the identification of lesions under normal white light and palpation deemed as resectable. The second step was the near-infrared fluorescence imaging protocol.

Under sterile conditions, the ICG diagnostic product, Verdye, 25 mg as powder, was reconstituted with 5 mL water for injections and used immediately. ICG administration was performed via a peripheral venous line as a rapid bolus of 0.1 mg/kg body weight and immediately followed by a bolus of 10 mL normal saline, with

a maximum of two bolus administrations/patient, after excluding all package insert contraindications. The absorption maximum of ICG at 800 nm and the emission maximum at 830 nm places them both in the near-infrared range. The imaging system used was a Zeiss Opmi Pentero 800 equipped with intraoperative fluorescence module Infrared 800, designed for an excitation range of 700–780 nm and emission detection in the range 820–900 nm, assuring ICG compatibility as a fluorescent dye.[14]

After each bolus of ICG, the peritoneal surface was immediately inspected for anomalies in fluorescence intensity, defined as either hypointense or hyperintense fluorescence areas compared with surrounding ICG fluorescence. After area annotation, in the third step previously defined hypo- or hyperintense areas of the peritoneum were excised and sent for pathological examination by a senior pathologist (these areas under white light appeared as intact peritoneum not deemed clinically suspicious). In the fourth step the surgical intervention continued with the removal of all resectable clinically suspicious lesions identified under white light during the first step, as per the standard operating principles.

The study complied with the Declaration of Helsinki, all guidelines, and applicable laws in Romania. An independent ethics committee approved the protocol and informed consent ("Prof. Dr. Ion Chiricuță" Institute of Oncology, Cluj-Napoca, Cluj, Romania Ethics Committee decision evaluation number 116/12.12.2018). All patients provided written informed consent, and all patient data were anonymized.

Following descriptive statistics, overall survival and progression-free survival were computed since diagnosis. The Kaplan–Meier method[15] was used to estimate overall survival and progression-free survival. The significance level p was set to 0.05 for any statistical comparison and interval confidence evaluation.[16] The chi-square test was used to compare percentages. Since this study was a feasibility study, no actual sample size could be inferred. All statistical analyses were performed using IBM SPSS Statistics software (version 26).

RESULTS

A total of 15 patients were included in the study. The median age at initial pathological diagnosis was 56 (range 38–71) years. According to the FIGO 2014 classification system, 10 cases were stage IIIB-C (66.7%) and five were stage IVA-B (33.3%). The histological subtype included only high-grade serous ovarian cancer (n=15, 100%). After molecular characterization, seven patients were found to have a BRCA1 or BRCA2 mutation (46.6%), and eight patients were germline BRCA 1 or BRCA2 wild-type (53.3%). Analyzing homologous recombination deficiency (HRD) status, eight patients were HRD-positive (53.3%), and seven were unknown (46.6%). Patient characteristics are presented in Table 1.

All patients underwent a median of five neoadjuvant chemotherapy cycles (range 4–7), and six (40%) patients additionally received a median of four cycles (range 4–6) of bevacizumab during neoadjuvant chemotherapy. The mean duration of neoadjuvant treatment was 91 days (SD 28 days, median 86, range 63–153 days), and the mean time from the last chemotherapy cycle to interval debulking surgery was 39 days (SD 17 days, median 42, range 20–78).

All interval debulking surgeries were performed by two experienced surgeons trained in surgical oncology, with surgeon A performing 12 surgeries (80%) and surgeon B performing three surgeries (20%). The mean operative time was 135 (SD 32) minutes. After neoadjuvant chemotherapy, one patient had a tumor limited to one ovary (6.6%), one had microscopic extrapelvic peritoneal involvement (6.6%), eight had macroscopic peritoneal metastasis beyond the pelvis ≤2 cm in the most substantial dimension (53.3%), and five had macroscopic peritoneal metastasis beyond the pelvis >2 cm in the most substantial dimension (33.3%). Complete peritoneal debulking was achieved in 11 patients (73.3%).

After receiving a bolus of ICG, the abdominal cavity was immediately inspected using fluorescence imaging for areas that were either hyper- or hypointense against the average background fluorescence intensity of the peritoneum. A mean number of 1.6 (SD 0.5) ICG boluses were given for each patient. After each bolus, the mean intraoperative fluorescence time for identifying suspect areas was 3.59 (SD 1.39) minutes. Each patient had a combined mean fluorescence time of 5.74 (SD 2.4) minutes. The mean time between the first and second ICG bolus was 7 (SD 2.5) minutes. For each case, a mean of 2.6 (SD 1.12) additional suspect peritoneal samples were identified using fluorescence imaging and sent for pathological examination, depicted in Figure 1. The mean size of suspect peritoneal samples was 15.9 (SD 0.96) mm.

The number of surgical specimens removed during standard surgery using white light was 101, with 64 (63.3%) confirming malignancy. A total number of 39 suspect additional peritoneal samples were identified using the ICG protocol, with 16 (41%) confirming microscopic malignant foci of high-grade serous ovarian cancer. Hence, the total number of resected lesions increased by 38% (from 101 to 140) and the number of resected pathologically confirmed malignant lesions increased by 25% (from 64 to 80). Across all patients, true-positivity for malignant foci was found in 4 of 13 (30.8%) hyperintense areas and 12 of 26 (46.2%) ICG hypointense areas, detailed in Table 2.

An exploratory subgroup analysis according to BRCA status demonstrated that true-positivity for malignant foci was found in 1 of 6 (16.7%) ICG hyperintense areas and 6 of 16 (37.5%) ICG hypointense areas in gBRCA1/2 wild-type patients. In comparison, true-positivity for malignant foci was found in 3 of 7 (42.9%) ICG hyperintense areas and 6 of 10 (60%) ICG hypointense areas in gBRCA1/2 mutant patients. Similarly, according to the neoadjuvant use of bevacizumab, in patients who did not receive neoadjuvant bevacizumab true-positivity for malignant foci was found in 1 of 9 (11.1%) ICG hyperintense areas and 4 of 15 (26.7%) ICG hypointense areas, in contrast to patients who did receive neoadjuvant bevacizumab where true-positivity for malignant foci was found in 3 of 4 (75%) ICG hyperintense areas and 8 of 11 (72.7%) ICG hypointense areas, the latter being statistically significant ($p<0.05$), detailed in Table 3.

The median follow-up time was 36.6 months (95% CI 32.2 to 40.9). During follow-up, seven patients relapsed (46.7%) and three patients died (20%). Mean progression-free survival was 34.2 months (95% CI 27.1 to 41.4) and mean overall survival was 42.4 months (95% CI 37.1 to 47.7).

Table 1 Patient characteristics

Characteristic	n	%
Age, median (range)	56 (38–71)	
Histology		
High-grade serous carcinoma	15	100.0
Initial FIGO stage		
IIIB	3	20.0
IIIC	7	46.7
IVA	3	20.0
IVB	2	13.3
BRCA status		
Mutant	7	46.7
Wild-type	8	53.3
HRD status		
HRD positive	8	53.3
HRD unknown	7	46.7
Neoadjuvant chemotherapy		
Number of patients receiving chemotherapy	15	100.0
Number of chemotherapy cycles, median (range)	5 (4–7)	
Number of patients receiving bevacizumab	6	40.0
Number of bevacizumab cycles, median (range)	4 (4–6)	
Mean duration of neoadjuvant chemotherapy, days (SD)	91 (28)	
Mean duration from last neoadjuvant chemotherapy to IDS, days (SD)	39 (17)	
IDS details		
Mean operative time, minutes (SD)	135 (32)	
Post-operative pathological staging		
Tumor limited to one ovary, ypT1a	1	6.6
Microscopic extrapelvic involvement, ypT3a	1	6.6
Macroscopic metastasis beyond the pelvis ≤2 cm, ypT3b	8	53.3
Macroscopic metastasis beyond the pelvis >2 cm, ypT3c	5	33.3
Complete peritoneal debulking	11	73.3
ICG fluorescence microscopy		
Mean number of ICG bolus per patient, n (SD)	1.6 (0.5)	
Mean intraoperative fluorescence time per bolus, minutes (SD)	3.59 (1.39)	
Mean fluorescence time per patient, minutes (SD)	5.74 (2.4)	
Number of additional suspect peritoneal samples per patient, n (SD)	2.6 (1.12)	
Survival outcomes		
Relapse	7	46.7
Mean PFS, months (95% CI)	34.2 (27.1 to 41.4)	
Death	3	20
Mean OS, months (95% CI)	42.4 (37.1 to 47.7)	
Mean follow-up, months (95% CI)	36.6 (32.2 to 40.9)	

BRCA, BReast CAncer gene; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ICG, indocyanine green; IDS, interval debulking surgery; OS, overall survival; PFS, progression-free survival.

DISCUSSION

Summary of Main Results

Overall, following fluorescence imaging, 39 suspect additional peritoneal samples were analyzed, with 41% confirming microscopic malignant foci of high-grade serous ovarian cancer. The positive predictive value (PPV)/true-positivity rate of ICG hypointense areas was higher than that of ICG hyperintense areas (46.2% vs 30.8%), in favor of our initial presumption. Interestingly, in a subgroup analysis we observed that the

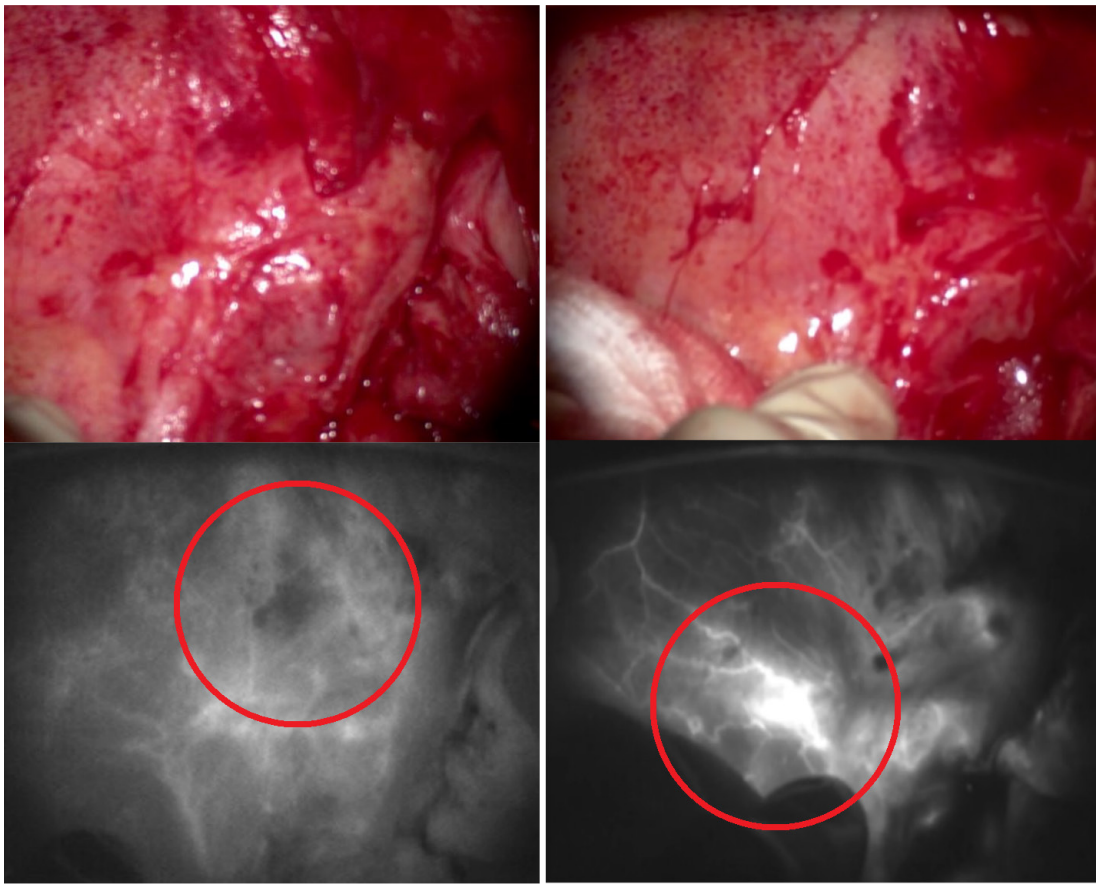

Figure 1 Optical and corresponding near-infrared imaging of suspect peritoneal lesions. Left upper and lower quadrant depicting white light appearance (not deemed clinically suspicious) of corresponding near-infrared hypointense area. Right upper and lower quadrant depicting white light appearance (not deemed clinically suspicious) of corresponding near-infrared hyperintense area.

true-positivity rate of ICG hypointense areas was higher in gBRCA1/2 mutant than in gBRCA1/2 wild-type patients (60% vs 37.5%). Similarly, the true-positivity rate of ICG hypointense areas was higher in patients who received bevacizumab than those who did not (72.7% vs 26.7%, $p<0.05$). This could be explained by the enhanced platinum sensitivity of tumor cells in BRCA1/2 mutant patients[17] and the anti-angiogenic properties of bevacizumab.[18 19]

Results in the Context of Published Literature

Within the scope of this feasibility research, we explored the use of near-infrared fluorescence imaging in conjunction with the non-specific fluorescent tracer ICG in patients with high-grade advanced ovarian cancer who had undergone neoadjuvant chemotherapy followed by interval debulking surgery. Since ICG is used to evaluate tissue perfusion[12] and can concentrate in tumor cells through the enhanced permeability and retention effect,[13] we sought to analyze the value of both hyper- and hypointense fluorescence areas of apparently intact peritoneum. We presumed that if ICG predominantly reflected tissue perfusion in the first minutes after bolus administration, hypointense near-infrared areas could reflect residual tumorous scars after chemotherapy with decreased

Table 2 Cross-tabulation of suspect peritoneal areas with near-infrared imaging

Parameter			Near-infrared appearance*		Total
			Hypointense	Hyperintense	
Malignant†	No	Number	14	9	23
		Percentage without malignancy	60.9%	39.1%	100.0%
	Yes	Number	12	4	16
		Percentage with malignancy	75.0%	25.0%	100.0%

*Samples under white light not deemed clinically suspicious grouped by near-infrared status.
†Pathological confirmation of malignancy for samples identified based on the near-infrared protocol.

Table 3 Cross-tabulation of suspect peritoneal areas with near-infrared imaging according to BRCA status and neoadjuvant bevacizumab use

Parameter			Near-infrared appearance* Hypointense	Hyperintense	Total	Near-infrared appearance* Hypointense	Hyperintense	Total
BRCA status			gBRCA1/2 wild-type			gBRCA1/2 mutant		
Malignant†	No	Number	10	5	15	4	4	8
		Percentage without malignancy	66.7%	33.3%	100.0%	50.0%	50.0%	100.0%
	Yes	Number	6	1	7	6	3	9
		Percentage with malignancy	85.7%	14.3%	100.0%	66.7%	33.3%	100.0%
Use of neoadjuvant bevacizumab			Neoadjuvant bevacizumab - No			Neoadjuvant bevacizumab - Yes		
Malignant†	No	Number	11	8	19	3	1	4
		Percentage without malignancy	57.9%	42.1%	100.0%	75.0%	25.0%	100.0%
	Yes	Number	4	1	5	8	3	11
		Percentage with malignancy	80.0%	20.0%	100.0%	72.7%	27.3%	100.0%

*Samples under white light not deemed clinically suspicious grouped by near-infrared status.
†Pathological confirmation of malignancy for samples identified based on the near-infrared protocol.

blood flow. If the enhanced permeability and retention effect were prevalent and microscopic foci of tumor cells accumulated ICG they would appear as hyperintense near-infrared areas.

We have demonstrated that using a minimum dose of ICG (0.1 mg/kg per bolus) and for a limited period (mean fluorescence time of 5.74 minutes per patient, following a mean number of 1.6 bolus administrations per patient), the total number of resected lesions increased by 38% (from 101 to 140). The total number of resected pathologically confirmed malignant lesions increased by 25% (from 64 to 80). This is a smaller value than the one reported with folate receptor alpha-targeted near-infrared, where pafolacianine identified additional cancer in tissue not planned for resection and not detected by white light assessment among patients who underwent interval debulking surgery with a rate of 39.7%.[20]

Given the heterogeneity and scarcity of trials on this subject, it is challenging to make cross-study comparisons. Tummers et al analyzed cases planned for primary debulking surgery, which received a higher dose of ICG (20 mg flat dose vs 0.1 mg/kg in our study, corresponding to 6 mg in an average 60 kg female) with delayed fluorescent image acquisition. However, the false-positive rate in both studies exceeded 50% (62% in Tummers et al vs 53.80% for hypointense areas and 69.20% for hyperintense areas in our study).[21] In the study by Veys et al,[22] patients with different histological subtypes and clinical settings (primary debulking, interval debulking, relapsed) were included, with only a subgroup of patients having in vivo ICG fluorescence analyzed after neoadjuvant chemotherapy. For this subgroup of patients, the authors reported a higher PPV (57.1% in Veys et al[22] vs 46.2% for hypointense areas and 30.8% for hyperintense areas in our study). However, the delay between ICG injection and nodule resection ranged from 5 to 360 minutes in their study. In comparison, our study performed immediate ICG imaging after bolus administration. Also, it evaluated the role of ICG hypointense areas that seem to harbor more microscopic malignant foci than ICG hyperintense areas.

Strenghts and Weaknesses

The current analysis has some strengths, especially when compared with previous investigations regarding the use of ICG in ovarian cancer surgery. For example, our study proved that smaller doses (equivalent of 0.1 mg/kg) of ICG will suffice to identify suspicious foci under fluorescence in near-infrared conditions. Moreover, immediate acquisitions were performed after administering the substance, reducing the total operative time. Although false-positive rates remained high, lower rates were observed for excised hypointense areas. Furthermore, as opposed to previous publications that did not investigate this, our analysis of the hypointense areas deemed them as having a higher rate of positivity for malignant foci, results that strengthened our protocol.Given that our objective was to evaluate the feasibility of near-infrared fluorescence imaging based on ICG we included a limited number of participants, hence our sample size might not reflect real-world data regarding variables such as, but not limited to, percentage mBRCA carriers or duration of surgery. The ultimate goal would be to demonstrate that this would improve cytoreduction and survival outcomes in an adequately sized surgical trial that goes beyond the scope of our current research. However, we demonstrated a 25% increase in pathologically confirmed malignant lesions with an affordable method. The downfalls of this technique could be mitigated by using recurrent boluses and a homogenous patient population for further research. Nevertheless, since the promising results seen with targeted fluorophores, ICG seems to have been surpassed as a method to visualize malignant tumors intraoperatively, given the lack of target selectivity, presence of various factors that can influence enhanced permeability and retention,

local perfusion, and quick elimination profile, resulting in modest PPVs, ranging between 30.8% and 46.2% in our study.

Implications for Practice and Future Research

Crucial prognostic factors for survival are the response to platinum-based chemotherapy, which is improved in BRCA1/2 mutation carriers,[17] and surgical outcome. The goal of cytoreductive surgery has changed, with current guidelines recommending complete macroscopic excision.[23] However, pre-operative accurate knowledge is limited, given the low sensitivity of imaging modalities for small tumor deposits. Additionally, neoadjuvant chemotherapy can significantly decrease the size of peritoneal nodules and their detection under white light conditions. In this scenario, fluorescence-guided surgery may be an accurate tool to increase the yield of resected small peritoneal nodules up to a microscopic level that would otherwise be deemed not clinically suspicious under normal white light inspection. Recognizing that chemotherapy-resistant clones are responsible for tumor recurrence, physically removing these tumor deposits can enhance long-term survival.[24] Prior research showed that targeted fluorescence imaging with a folate receptor alpha probe allowed for the visualization and resection of more tumor deposits compared with standard white light surgical procedures.[10 20]

Currently, only one specific folate receptor alpha-targeted probe, pafolacianine, is US FDA-approved for clinical use following the positive results of a phase III trial.[20] However, this probe is currently unavailable in Europe. ICG is an easily available, non-specific fluorophore with both FDA and European Medicines Agency clearance for clinical use in angiography and a good tolerability profile. Thus far, few studies have investigated the use of ICG in ovarian cancer peritoneal carcinomatosis.[21 22] ICG could serve as a fluorophore for folate receptor alpha-negative patients and a platform for future drug development. Additionally, more extensive studies are needed to fully support our feasibility research regarding the role of ICG in this setting of precision intraoperative imaging.

CONCLUSIONS

The use of ICG was associated with an increase in the resection of samples with residual malignant foci. Overall, hypointense ICG areas had a higher PPV for malignant foci in comparison with hyperintense ICG areas (46% vs 30%), which could be interpreted in the context of dynamic changes in the tumor microenvironment or enhanced permeability and retention effect, following neoadjuvant chemotherapy. Further research is needed on larger samples to demonstrate a change in survival outcomes before expansion outside of the scope of a clinical trial.

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