Let go of the myth: safety of indocyanine green for sentinel lymph node mapping in endometrial cancer

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ABSTRACT

Objective Sentinel lymph node mapping by intracervical indocyanine green injection is the preferred method for surgical staging in endometrial cancer. Adverse reactions to indocyanine green are extremely rare, and information about the safety of this tracer in patients with a history of other allergies, asthma, or comorbidities is limited. We aim to evaluate the rate of adverse reactions to indocyanine green injected during sentinel lymph node mapping in patients with endometrial cancer and review the etiology of such reactions.

Methods All patients with endometrial cancer undergoing sentinel lymph node mapping with indocyanine green cervical stroma injection at the Mayo Clinic in Rochester, Minnesota between June 2014 and December 2018 were retrospectively evaluated. Any adverse reaction occurring intra-operatively or within 7 days after surgery was identified. A thorough chart review was performed by an allergy specialist physician for any patient with an allergic-type reaction.

Results We included 923 patients of which 565 (61.2%) had a history of allergy to antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), other medications, and/or environmental exposures. Of 490 patients who had previously received contrast media, 25 (5.1%) had a history of an adverse reaction. No immediate anaphylaxis or other allergic reactions were observed after indocyanine green injection. 10 (1.1%) patients developed a transient skin reaction within 7 days after surgery. None of these patients had a history of contrast media reaction. Based on timing and clinical/peri-operative history of affected patients, it was determined that skin reactions were likely induced by other newly prescribed medications or contact sensitivity, not administration of indocyanine green.

Conclusion Indocyanine green injection for sentinel lymph node mapping in patients with endometrial cancer caused no immediate/delayed anaphylactic or other severe allergic reactions. This included patients with a history of other allergies, asthma, and comorbidities. The myth of iodine's relationship to allergic reactions must be refuted to allow indocyanine green use in patients with a history of contrast media or shellfish allergy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sentinel lymph node mapping using indocyanine green cervical stromal injection is the preferred method for endometrial cancer surgical staging. Data regarding safety of indocyanine green, specifically as it relates to allergic reaction rate and severity, is limited. Previous studies have identified few cases with allergic reactions to indocyanine green among patients receiving the solution intravenously for other indications. Demonstration of safety of indocyanine green cervical injection is needed.

WHAT THIS STUDY ADDS

⇒ This study reinforces the evidence in favor of indocyanine green safety when administered via cervical stromal injection. We analyzed any possible adverse reaction occurring in a large series of patients with endometrial cancer receiving indocyanine green for sentinel lymph node mapping. We included a clinically heterogeneous population, including patients with history of allergies to medications/food/contrast media.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ By validating the safety of cervical injection of indocyanine green for sentinel lymph node mapping, it may be possible to remove barriers related to the use of this tracer in gynecologic oncology and to update society recommendations regarding avoidance in patients with shellfish or other contrast media allergies.

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INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in Western countries and its incidence is gradually increasing over time.[1 2] Surgical management of women with endometrial cancer has improved significantly over the past decade, and lymphatic staging by intra-operative sentinel lymph node biopsy has gradually replaced systematic pelvic and para-aortic lymphadenectomy.[3 4] Sentinel lymph node biopsy offers high accuracy in detecting nodal metastasis,[5] with a lower rate of peri-operative complications and noted oncologic safety even in patients with high-risk endometrial cancer.[6–12] The above mentioned evidence has highlighted the advantages

of using the fluorescent indocyanine green dye for sentinel lymph node mapping.[6–12]

Indocyanine green is a water-soluble, green-colored, fluorescent compound containing 5% sodium iodide. It binds to albumin and is eliminated by hepatic metabolism.[13] Although indocyanine green has been used intravenously for decades in various medical fields (cardiology, ophthalmology, hepatology, neurosurgery), its use in gynecologic oncology is more recent. Compared with other tracers, indocyanine green has shown a higher sensitivity in nodal detection[14 15] than blue dye, and has become the solution of choice for sentinel lymph node mapping. Consequently, the use of indocyanine green in the management of endometrial cancer has increased dramatically in recent years. Of note, indocyanine green has received US Food and Drug Administration approval for intravenous injection; however, interstitial injection for lymphatic mapping is still off-label.[16] Although generally considered a safe tracer,[17 18] a few cases of adverse reactions around the time of indocyanine green administration have been reported in the literature. Previous studies using intravenous injection of indocyanine green in ophthalmic practice have reported severe reactions in 0.05–0.07%,[19 20] moderate reactions in 0.2%, and mild reactions in 0.15% of patients.[19] Prospective investigations evaluating interstitial injection for sentinel lymph node evaluation in breast cancer have shown no adverse reactions attributable to indocyanine green.[21 22]

Despite the rapid and consistent expansion of its use for sentinel lymph node mapping, data on the risk of indocyanine green-related allergic reactions are still scarce.[5 23] Authors from Memorial Sloan Kettering Cancer Center investigated indocyanine green use in patients with a documented indocyanine green or contrast reaction and found an exceedingly low likelihood that severe adverse events were due to indocyanine green.[24] To our knowledge, this prior study is the only analysis that specifically evaluated indocyanine green-related allergic events when the tracer is administered by cervical stromal injection. There is a belief perpetuated among physicians that patients with a history of shellfish allergy or contrast media allergic-like reactions should not be administered indocyanine green or should receive premedication before administration, but there is no known evidence for this.[25]

Our study aims to evaluate the rate and severity of allergic events in all patients with endometrial cancer undergoing surgical staging with intra-operative cervical stromal injection of indocyanine green for sentinel lymph node mapping. We also review the etiology and physiology of allergic reactions specific to contrast media, shellfish, and indocyanine green.

METHODS

The Mayo Clinic Institutional Review Board approval was obtained (IRB ID: 20-000174), and only patients who granted research authorization were included. Consecutive patients with endometrial cancer who underwent primary surgery (hysterectomy with/without salpingo-oophorectomy) including sentinel lymph node assessment at the Mayo Clinic, Rochester, Minnesota, between June 2014 and December 2018 were included. Patients who received injection of tracers other than indocyanine green were excluded. The electronic medical record was used to abstract data regarding relevant patient factors, including age, body mass index, history of drug, food, or contrast media reactions, and volume of indocyanine green injected.

Box 1 European Academy of Allergy and Clinical Immunology 2021 and Sampson clinical criteria[26 27] for the diagnosis of anaphylaxis.

Anaphylaxis is likely when any of the following three criteria are fulfilled:

1. Acute onset (minute to several hours) of skin and/or mucosa involvement (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE of the following:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin–mucosal tissue (eg, generalized hives, itch-flush, swollen lips–tongue–uvula
   b. Respiratory compromise (eg, dyspnea, wheeze–bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia, syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   For adults: systolic BP <90 mm Hg or >30% decrease from that person's baseline

BP, blood pressure; PEF, peak expiratory flow.

Cervical injection of indocyanine green was primarily conducted in accordance with international guidelines.[4] The process involved diluting a 25 mg vial of indocyanine green powder in 20 mL of sterile water for injection. Subsequently, a unit of 4 mL was administered into the uterine cervix at the 3 and 9 o'clock positions: 1 mL superficially (1–2 mm) and 1 mL deeply (1–2 cm), totaling 4 mL (total dose of indocyanine green 5 mg; concentration 1.25 mg/mL). However, during the study period, many surgeons transitioned to solely performing a superficial injection at the 3 and 9 o'clock positions. This shift was attributed to the deep injection yielding excessive dye in the field background, thereby complicating the identification of the sentinel lymph node.

Anaphylaxis (Box 1) and severity of allergic reactions (Table 1) were defined according to the European Academy of Allergy and Clinical Immunology 2021 guidelines[26] and the Sampson criteria 2006.[27] We identified any potential allergic and other adverse reactions that occurred within the first 7 days after surgery. Then a specialist in allergic diseases carefully reviewed the electronic medical record to determine the likelihood that the reaction was triggered by indocyanine green.

RESULTS

A total of 923 patients with endometrial cancer who underwent surgical staging and received intracervical indocyanine green stromal injection for sentinel lymph node mapping were

Table 1 Definitions of allergic reaction severity

Severity grade	Features
Mild	Heat/cold feeling, nausea, vomiting, flushing, mild urticaria or other anatomically limited skin disease, itching
Moderate	Angioedema, generalized urticaria or other skin disease (eg, maculopapular exanthema), bronchospasm, dyspnea, stridor, wheeze, moderate hypotension, tachycardia, chest or throat tightness, dizziness
Severe	Prolonged hypotension, ventricular fibrillation, angina, myocardial infarction, cardiac arrest, severe bronchospasm, pulmonary edema, respiratory arrest

retrospectively reviewed. Patient characteristics are shown in Table 2. The mean age was 64.6 years (range 29.3–93.5), and the mean body mass index was 34.7 kg/m^2 (range 15.6–67.7). More than half of our population (565, 61.2%) had a history of hypersensitivity to drugs and/or other agents, of whom 51 (5.5%) had at least one documented episode of a severe hypersensitivity reaction. Hypersensitivity categories included antibiotics (n=301, 32.6%), non-steroidal anti-inflammatory drugs (NSAIDs) (n=49, 5.3%), and other agents (pollen, dust, animal hair, food, and other medications) (n=415, 45.0%). Twenty-five patients among those who had previously received contrast media (25/490, 5.1%) had a documented reaction to contrast media, of whom six had a history of a severe reaction. A history of asthma was present in 82 (8.9%) patients. No patients reported a history of allergy to indocyanine green. Thirty (3.3%) patients had a history of chronic moderate/severe renal disease, none had chronic moderate/severe liver disease, and 209 (22.6%) were on β-blocker therapy for medical reasons (hypertension). Among the 676 patients with a reported injected indocyanine green volume, median volume was 3 mL (dose of indocyanine green 3.75 mg; concentration 1.25 mg/mL) (IQR 2–4). The volume of indocyanine green injected was >4 mL (dose of indocyanine green 5 mg; concentration 1.25 mg/mL) in 80 (11.8%) patients, likely due to re-injection in the event of mapping failure.

Table 2 Characteristics of the study population

Characteristic	N=923
Age at surgery (years), mean (SD)	64.6 (10.1)
BMI (kg/m^2), mean (SD)	34.7 (8.8)
Volume of indocyanine green injected (mL)	
N	676
Median (IQR)	3*(2, 4)
Allergy history†	
Asthma	82 (8.9)
History of severe hypersensitivity reaction	51 (5.5)
Antibiotic allergy	301 (32.6)
NSAID allergy	49 (5.3)
Other agents	415 (45.0)
None	347 (37.6)
Previous ICM application	
No	264 (28.6)
Yes	490 (53.1)
Unknown	169 (18.3)
Previous reaction to ICM	25/490 (5.1)
β-blockers co-medication	209 (22.6)
Chronic moderate/severe liver disease	0 (0.0)
Chronic moderate/severe kidney disease	30 (3.3)

Results presented as N (%) unless otherwise specified.
*Corresponding to 3.75 mg indocyanine green (concentration 1.25 mg/mL).
†Several patients had more than one allergy.
BMI, body mass index; ICM, iodinate contrast media; NSAID, non-steroidal anti-inflammatory drug.

There were no anaphylactic or other adverse reactions intra-operatively or peri-operatively recorded after indocyanine green injection. During the first 7 days after surgery, 10 (1.1%) patients contacted their healthcare providers with a new-onset skin reaction (Table 3). Most (nine out of 10) skin reactions were reported after the second post-operative day. All 10 reactions resolved after discontinuation of the triggering cause and administration of steroids and/or antihistamines. Seven of 10 were attributed to antiseptic skin cleansing solution, surgical tape, or other contact dermatitis. The remaining three occurred with the initiation of new medications. No emergency department presentations were reported. From this review we concluded that the skin reactions were extremely unlikely to be caused by indocyanine green. Definitive allergic testing was not pursued for these 10 patients.

DISCUSSION

Summary of Main Results

We demonstrated that, in a large population of patients undergoing sentinel lymph node mapping for surgical staging of endometrial cancer, cervical injection of indocyanine green did not cause any anaphylactic or other immediate allergic reactions, and likely did not contribute to delayed skin reactions. This was true even in patients with a history of allergies to other substances.

Results in the Context of the Literature

Our data confirm the findings of Zammarrelli et al,[24] who published the only other study specifically investigating the likelihood of adverse events related to indocyanine green intracervical stromal injection. They also observed no patients with signs or symptoms of allergic reaction, and determined that the cause of other adverse

Table 3 Characteristics of patients who experienced a postoperative allergic-like skin rash

Age	History of (one or more): chronic urticaria; allergic rhinitis; use of β-blockers; asthma	History of allergy	Allergen	Grade of the allergic reaction	Previous ICM injection	Allergic reaction to ICM	Intra-operative complications	Number of days from surgery to reaction	Immediate vs delayed	Hypotension during surgery	Grade of the allergic reaction	Description of the allergic reaction	Plausible cause of the allergic reaction
44	No	Yes	Morphine	Mild	No	na	No	2	Delayed	No	Mild	Itchy rash and hives of bilateral legs. Resolved with diphenhydramine (Benadryl) by day 4	Unknown, suspect contact agent
51	No	Yes	Amoxicillin	Mild	No	na	No	5	Delayed	No	Mild	Itchy rash around umbilical incision then spread all over the abdomen and back. Resolved by day 10 with cetirizine (Zyrtec)	Unknown, suspect antiseptic solution
59	Asthma	Yes	Sulfamethoxazole, oatmeal nuts (pistachios)	Moderate	No	na	No	2	Delayed	No	Mild	Non-itching pustular rash on abdomen, extremities and back. Improvement after discontinuing ibuprofen and acetaminophen. In the meantime, the patient has also been taking amoxicillin for sinusitis	Unknown, suspect analgesic, oral antibiotic
53	No	No	na	na	No	na	No	7	Delayed	No	Mild	Rash across the entire abdomen improved after discontinuing topical chlorhexidine	Unknown, suspect antiseptic solution
58	Allergic rhinitis	Yes	Seasonal (pollen)	Mild	No	na	No	<1	Delayed	No	Mild	Skin rash soon after surgery after administration of oxycodone, resolved with diphenhydramine (Benadryl)	Unknown, suspect oxycodone
67	Asthma, allergic rhinitis, use of β-blockers	Yes	Penicillins, cefuroxime, levofloxacin	Severe	Yes	No	No	5	Delayed	No	Mild	Itchy rash with onset at the left groin area, with spread to the abdomen	Unknown, suspect antiseptic solution
54	Asthma, use of β-blockers	Yes	Cerufoxime	Mild	Yes	No	No	5	Delayed	No	Mild	Itchy rash across the chest that turned into welts, located right where the tape was. Diarrhea for 1–2 days	Unknown, suspect contact agent

Continued

Table 3 Continued

Age	History of (one or more): chronic urticaria; allergic rhinitis; use of β-blockers; asthma	History of allergy	Allergen	Grade of the allergic reaction	Previous ICM injection	Allergic reaction to ICM	Intra-operative complications	Number of days from surgery to reaction	Immediate vs delayed	Hypotension during surgery	Grade of the allergic reaction	Description of the allergic reaction	Plausible cause of the allergic reaction
55	No	Yes	Sulfonamide, erythromycin, kiwi	Moderate	Yes	No	No	2	Delayed	No	Mild	Itchy rash with red bumps on the entire abdomen, resolved with steroids and discontinuation of newly prescribed oxycodone and chlorhexidine topical solution	Unknown, suspect antiseptic solution
49	No	Yes	Sulfamethoxazole, tramadol, clonazepam	Mild	No	na	No	3	Delayed	No	Mild	Itchy rash on the abdomen with raised nodules	Unknown, suspect ciprofloxacin
66	No	Yes	Penicillins	Mild	Yes	No	No	3	Delayed	No	Mild	Red bumpy rash on trunk, back, and neck	Unknown, suspect antiseptic solution

ICM, iodinate contrast media; na, not applicable.

reactions were likely unrelated to indocyanine green administration. Table 4 reviews nine studies, with a total of 3787 patients, investigating sentinel lymph node mapping; only one severe reaction was found to be attributable to indocyanine green. Papadia et al[28] reported one case (out of 234) of anaphylaxis after an 8 mL (total dose 40 mg; concentration 5 mg/mL) intracervical indocyanine green injection. The authors attributed the anaphylaxis to indocyanine green, but specific indocyanine green allergy testing was indeterminate. To our knowledge, this case represents the only available evidence of a severe adverse event associated with intracervical indocyanine green administration.

Rare adverse reactions after indocyanine green administration are often compared with the non-immunologic, allergic-like or anaphylactoid reactions associated with intravenous contrast media injection. There is a misconception that non-immunologic, allergic-like contrast media reactions are caused by immunoglobulin E (IgE)-mediated responses to iodine, but the true etiology relates to the histamine release caused directly by the effect of contrast media on basophils and mast cells.[25 29 30] Physiologic reactions to contrast media (especially high-osmolality contrast media) can also mimic the cardiovascular effects seen in allergic-like or anaphylactoid reactions,[31] and are unrelated to IgE-mediated allergies. The introduction of low-osmolality contrast media has greatly reduced these reactions, further validating their non-allergic cause.[32] True IgE-mediated reactions to contrast media are extremely rare and also not related to iodine.[25]

Similar to the belief that contrast media reactions are caused by iodine, there is a myth that shellfish allergies are caused by iodine and thus patients with this allergy should not be administered indocyanine green. It is well-established that the IgE-mediated allergic reaction to shellfish is caused by the protein within the meat of the fish (tropomyosin), with iodine playing no etiologic role.[33] The information regarding reactions to contrast media and shellfish remove the possibility of iodine causing IgE-mediated allergic reactions.

Information regarding dose-intensity relationships between food allergens and anaphylaxis are well-established, but this is not true for other possible allergens.[29 34] The National Comprehensive Cancer Network recommends an injection volume of 4 mL, and also allows additional injection for non-mapping.[35] None of the 80 (11.8%) patients who received >4 mL (dose of indocyanine green 5 mg; concentration 1.25 mg/mL) in our cohort had an adverse reaction.

In this study we observed a small population of patients with delayed skin reactions, although these were deemed unlikely to be due to indocyanine green administration. Delayed allergic-like reactions in patients receiving intravenous iodinated contrast for radiologic studies are usually cutaneous and develop between 3 hours and 2 days after administration.[29] One case of delayed allergic reaction was reported in a prospective trial of patients undergoing sentinel lymph node mapping with indocyanine green and isosulfan blue, and this patient also experienced a skin reaction on post-operative day 7.[36] Although the authors attributed this reaction to indocyanine green, allergy testing was not performed. The co-administration of isosulfan blue and indocyanine green complicates this case, as isosulfan blue is known to carry a risk of IgE-mediated allergic reactions and anaphylactic shock, while the same has not been established for indocyanine green.[37]

Table 4 Review of the studies reporting allergic reaction after intracervical indocyanine green injection for endometrial cancer surgical staging

Author (year)	Type of study	Number of patients	Number of patients with ICM allergy	Indocyanine green protocol	Other tracers	Number of mild allergic reactions	Number of moderate allergic reactions	Number of severe allergic reactions (anaphylaxis)	Number of deaths	Number of adverse allergic reactions certainly related to indocyanine green
Plante *et al* (2015)[40]	R	42	Not specified	Intracervical injection (3 and 9 o'clock positions) 1 mL superficial and 1 mL deep. Total dose 10 mg (2.5 mg/mL)	No	0	0	0	0	0
How *et al* (2015)[15]	P	100	Not specified	Intracervical injection (3 and 9 o'clock positions) 1 mL superficial and 1 mL deep. Total dose 4 mL‡	BD, 99mTc‡	0	0	0	0	0
Paley *et al* (2016)[39]	P	123	Not specified	Intracervical injection (3 and 9 o'clock positions) 1 mL stromal. Total dose 2 mg (1 mg/mL)	No	0	0	0	0	0
Papadia *et al* (2017)[28]	R	234	Not specified	Intracervical injection (four cardinal points) 2 mL deep. Total dose 40 mg (5 mg/mL)	No	0	0	1	0	1
Rossi *et al* (2017)[5]	P	356	Excluded	Intracervical injection (3 and 9 o'clock positions) 1 mL deep. Total dose 1 mg (0.5 mg/mL)	No	0	0	0	0	0
Geppert *et al* (2017)	P	187	0	Cervical or fundal indocyanine green injection	No	0	0	0	0	0
Frumovitz *et al* (2018)[23]	P	169	Excluded	Intracervical injection (3 and 9 o'clock positions) 1 mL superficial and 1 mL deep. Total dose 5 mg (1.25 mg/mL)	ISB	0	0	0	0	0
Backes *et al* (2019)[36]	P	204	Excluded	Intracervical injection (3 and 9 o'clock positions) 1 mL superficial. Total dose 2 mg (1 mg/mL)	ISB	0	1	0	0	0
Cabrera *et al* (2020)[42]	P	35	Excluded	Intracervical injection (3 and 9 o'clock positions) 1 mL superficial and 1 mL deep. Total dose 20 mg (5 mg/mL)	99mTc	0	0	0	0	0
Zammarrelli *et al* (2021)[24]	R	1414	67	Intracervical injection (3 and 9 o'clock positions) 1 mL superficial and 1 mL deep. Total dose 5 mg (1.25 mg/mL)	No	0	3*	0	0	0
Current study	R	923	25	Intracervical injection (3 and 9 o'clock positions) 1 mL superficial and 1 mL deep. Total dose 5 mg (1.25 mg/mL)§	No	10†	0	0	0	0
Summary of the evidence	7 P; 4 R	3787	92	–	–	10	4	1	0	1

*3 patients had laryngospasm, apnea, and a vasovagal response. After review, the likelihood these reactions were due to the indocyanine green was exceedingly low.
†Type of reaction reported in Table 3.
‡Each 1 mL syringe containing a mixture of blue dye (0.8 mL), indocyanine green (0.1 mL, 0.25 mg/mL), and 99mTc SC (0.1 mL).
§During the study period, many surgeons transitioned to solely performing a superficial injection at the 3 and 9 o'clock positions.
BD, blue dye; ICM, iodinate contrast media; ISB, isosulfan blue; 99mTc, technetium-99m; P, prospective; R, retrospective; SC, subcutaneously.

The Society of Gynecologic Oncology's consensus recommendations for sentinel lymph node mapping in endometrial cancer suggest refraining from using indocyanine green in patients with severe iodine allergies.[38] In fact, most reports on the feasibility of intracervical indocyanine green injection have also excluded patients with a history of iodine allergy. This recommendation warrants reconsideration in light of our study and other relevant research, as well as examination of the true cause of allergic-like reactions in patients receiving contrast media and allergic reactions to shellfish.[5 15 23 24 28 39–42] Perpetuating the myth that iodine causes allergic reactions to contrast media, shellfish, and indocyanine green may needlessly prevent some patients from receiving the preferred staging for endometrial cancer.

At the Mayo Clinic in Rochester, Minnesota, an internal protocol employing a combination of hydrocortisone, dexamethasone, and/or diphenhydramine is employed for patients with a history of contrast media allergic-like reactions before they undergo imaging studies which require contrast. There is a lack of scientific evidence and rationale to employ pre-injection protocols in patients who will undergo indocyanine green intracervical injection, even when they have a history of contrast media allergic-like reactions.

Strengths and Limitations

The strengths of our study include the examination of a large population of patients with endometrial cancer who all received indocyanine green for sentinel lymph node mapping. Our cohort included patients with varying histories of allergy, asthma, and other comorbidities, including allergies to contrast media. The limitations of our study include its retrospective nature with a relatively small population of patients with pre-existing allergies to contrast media and asthma. Delayed hypersensitivity reactions may occur >7 days after exposure, thus extended observation periods could be useful in the future.[43] For practical reasons, we were unable to include a comparison group of patients who received another tracer for sentinel lymph node mapping (blue dye, technetium colloid), as this cohort was not available. The determination of the cause of the 10 delayed skin reactions was subjectively assessed by a content expert and would have required formalized indocyanine green allergy testing for definitive diagnosis.

Implications for Practice and Future Research

Sentinel lymph node mapping by indocyanine green injection has become the preferred method of surgical lymphatic staging in endometrial cancer.[4] Given the extensive use of indocyanine green in gynecologic oncology, our findings contribute to the growing information on the safety of this tracer, even for patients with a history of allergies, asthma, and other comorbidities. Future prospective studies which include indocyanine green cervical injection could include a record of any allergic-type reactions and their outcomes. Based on our study, results from the Memorial Sloan Kettering group, and knowledge about the true etiology of contrast media allergic-type reactions and shellfish allergy, revising the information in the Society of Gynecologic Oncology guidelines is warranted. Updated recommendations should outline the exceedingly low risk of indocyanine green allergy and refute the myth that patients with shellfish or other contrast reactions should not receive indocyanine green. This would greatly benefit patients, allowing almost all to receive the preferred staging for endometrial cancer.

CONCLUSION

This study demonstrated that intracervical injection of indocyanine green during surgical sentinel lymph node mapping in patients with endometrial cancer is safe and that the incidence of allergic adverse events directly related to this tracer is negligible. Review of the relevant literature also illuminates a common myth which must be refuted using scientific evidence.

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