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Use of fluorescence imaging and indocyanine green during thyroid and parathyroid surgery: Results of an intercontinental, multidisciplinary Delphi survey

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ABSTRACT

Background: In recent years, fluorescence imaging—relying both on parathyroid gland autofluorescence under near-infrared light and angiography using the fluorescent dye indocyanine green—has been used to reduce risk of iatrogenic parathyroid injury during thyroid and parathyroid resections, but no published guidelines exist regarding its use. In this study, orchestrated by the International Society for Fluorescence Guided Surgery, areas of consensus and nonconsensus were examined among international experts to facilitate future drafting of such guidelines.

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Methods: A 2-round, online Delphi survey was conducted of 10 international experts in fluorescence imaging use during endocrine surgery, asking them to vote on 75 statements divided into 5 modules: 1 = patient preparation and contraindications to fluorescence imaging (n = 11 statements); 2 = technical logistics (n = 16); 3 = indications (n = 21); 4 = potential advantages and disadvantages of fluorescence imaging (n = 20); and 5 = training and research (n = 7). Several methodological steps were taken to minimize voter bias.
Results: Overall, parathyroid autofluorescence was considered better than indocyanine green angiography for localizing parathyroid glands, whereas indocyanine green angiography was deemed superior assessing parathyroid perfusion. Additional surgical scenarios where indocyanine green angiography was thought to facilitate surgery are (1) when >1 parathyroid gland requires resection; (2) during redo surgeries, (3) facilitating parathyroid autoimplantation; and (4) for the predissection visualization of abnormal glands. Both parathyroid autofluorescence and indocyanine green angiography can be used during the same procedure and employing the same imaging equipment. However, further research is needed to optimize the dose and timing of indocyanine green administration.
Conclusion: Though further research remains necessary, using fluorescence imaging appears to have uses during thyroid and parathyroid surgery.

Introduction

Thyroid and parathyroid gland (PG) surgeries comprise the bulk of endocrine surgeries,[1,2] with >150,000 thyroidectomies performed annually in the United States alone,[1] and postoperative hypocalcemia and hypercalcemia are frequent complications of these 2 procedures, respectively.

After total thyroidectomy, the incidence of hypocalcemia has been estimated between 18% and 59%,[3–7] the most common reason being unintentional injury to PG blood supply. Such injury typically occurs while the thyroid capsule is being dissected[8,9] and is a challenge to avoid, even among experienced surgeons, given the small size, soft texture, and variable number and locations of PGs.[8,10] Preventing it relies on surgeons being able to accurately count the number of glands and localize where each is before they commence resection.

Another surgical scenario in which PG localization is crucial is when resecting ≥1 PGs to treat hyperparathyroidism, because not removing all the hyperactive glands generally results in persistent hypercalcemia.[10] The long-term rate of failed parathyroidectomy ranges from 5% and 10%,[11] to between 20% and 30%.[12,13] However, as with the hypocalcemia complicating many thyroidectomies, failure to correct the hypercalcemia of hyperparathyroidism usually results from a surgeon's inability to identify all the PGs.

Various approaches have been proposed to assist with PG localization during endocrine surgery.[14–16] Among the most recently developed approaches is using a PG's own autofluorescence under near-infrared (NIR) light, a phenomenon first described in 2011.[17–20] Since then, others have documented that a statistically greater number of PGs are identified when NIR light is employed than under standard white light.[17–19] This includes one recently published randomized controlled trial, in which the number of PGs identified predissection increased from 2.6 to 3.5 per patient toggling from white to NIR light.[20]

Another approach adopted to facilitate PG perfusion assessments, called indocyanine green (ICG) angiography, involves viewing PGs under NIR light within seconds after the systemic injection of ICG,[21] a fluorophore in widespread use since the 1950s that has a well-documented, extremely favorable safety profile.[10] As with parathyroid autofluorescence under NIR light, studies have been published demonstrating the ability of ICG angiography to localize PGs[21] and predict postoperative hypocalcemia, including one study in which 0 of 146 patients with ≥1 PG clearly visible with ICG angiography exhibited postoperative hypocalcemia versus 11 of 50 (22.0%) in whom no well-perfused gland was identified (P = .007).[22]

Despite all this, no guidelines have yet been published on when or how these 2 approaches should be used. It was with this in mind that the International Society for Fluorescence Guided Surgery (ISFGS) decided to survey international experts in fluorescence-guided thyroid and parathyroid surgery (TPS) to identify areas of consensus and nonconsensus.

Methods

Expert recruitment

A survey adhering to published guidelines on Delphi survey methodology[23] was completed in the months of February through May 2021, coordinated by an MD-PhD level expert in survey design (K.P.W.). Delphi surveys are a broadly accepted means of identifying areas of consensus and nonconsensus among experts spanning a broad spectrum of health- and nonhealth-related fields.[23] They consist of multiple rounds (usually 2 or 3) of anonymous voting on various statements pertinent to the topic at hand. Anonymous voting is a critical component that distinguishes the Delphi approach from other consensus-assessment formats, included in survey design to minimize any risk of bias that might be caused by peer pressure.

The experts in the current survey were identified both by word of mouth and using a list of corresponding authors that we generated reviewing all currently published studies on fluorescence-guided endocrine surgery. Further eligibility criteria were the following: (1) coauthorship of ≥1 clinical study examining the use of fluorescence imaging (FI) during thyroid/parathyroid surgery published in a peer-reviewed scientific journal; or (2) ≥10 years in surgical practice and 5 years performing fluorescence-guided TPS. They also had to (3) be acknowledged as an expert in fluorescence-guided TPS by the ISFGS advisory board, (4) be fluent in written English, (5) agree to participate, and (6) express willingness to review the manuscript before submission. Although the survey was developed by ISFGS advisory board members, the expert panel consisted of nonmembers.

Out of an initial list of 76 endocrine surgeons, 27 met the first 4 criteria listed above, all of whom were sent email invitations to participate. Of these, 10 experts (37%)—spanning 4 continents (Asia, Europe, and Latin and North America) and 3 surgical fields (endocrine, cancer, and head and neck surgery)—agreed to participate.

Survey development

After several iterations reviewed independently by 2 experts in fluorescence-guided TPS (M.B., F.D.), a final survey was generated consisting of 5 questions on the nature of each expert's surgical

Table I
Practice characteristics of the sample

Practice characteristic	No. of	%
Region of practice ($N = 10$)		
Asia-Pacific	1	10.0
Europe	4	40.0
North America	3	30.0
Latin America	2	20.0
Surgical specialty ($N = 10$)		
Cancer surgery	3	30.0
Endocrine surgery	6	60.0
Head and neck surgery	1	10.0
Nature of practice ($N = 9$)*		
Primarily university based	6	66.7
Some university affiliation	3	33.3
Nonacademic	0	0.0
Years performing thyroid/parathyroid surgery ($N = 10$)		
10–20	5	50.0
>20	5	50.0
Years performing fluorescence-guided surgery ($N = 10$)		
<5	4	40.0
5–10	5	50.0
>10	1	10.0

* One respondent did not answer this question.

practice, followed by 75 statements for participating experts to vote on, divided into 5 modules: module 1: patient preparation and contraindications ($n = 11$ statements); module 2: technical logistics ($n = 16$); module 3: indications ($n = 21$); module 4: potential advantages/benefits and disadvantages/limitations ($n = 20$); module 5: training and research ($n = 7$). Among these 75 statements, 58 had the binary response options agree/disagree, whereas 17 had >2 response options, such as never/selectively/routinely or different ICG doses.

While designing the survey, attempts were made to minimize the risk that the survey tool itself might influence voter responses via the wording and/or order of its statements and/or response options (acquiescence bias). Such attempts included roughly balancing the number of statements potentially perceived by voters as favorable, unfavorable, and neither favorable nor unfavorable to FI and varying the order of the available response options, sometimes listing the most fluorescence-supporting option first, sometimes last, and sometimes in between. Whether statements were considered favorable, unfavorable, or nonjudgmental was determined by a panel of 4 judges who rated the statements independently, with further discussion or altering of statements performed, as necessary, to achieve unanimous agreement.

Once the final round 1 survey was finalized, an email was sent to all 10 experts who had agreed to participate, providing them with a link to the online survey platform SurveyMonkey. After the analysis of the round 1 results, all statements on which <8 of the 10 experts had expressed consensus were voted on again. Still adhering to published Delphi survey guidelines,[23] before voting on each statement in the round 2 survey, the participants were provided the number of voters who had selected each response option in round 1.

Data analysis

Percentage consensus—defined as agreement between responders, not agreement with any given statement—was calculated as the number of voters choosing the most commonly selected response option divided by the total number of experts voting on that particular statement, with 70% to 79% consensus considered “borderline consensus” and ≥80% consensus “clear consensus.” Percentage participation also was calculated for each

Table II
Overall summary of results

Summary of statements (75 statements)	No. of	%
Consensus (≥80.0%) reached	63	84.0
Borderline consensus (70.0%–79.9%) reached	5	6.7
No consensus (<70.0%) reached	7	9.3
Number of agree/disagree statements	58	77.3
Statements agreed with, *n* (% out of 58)	36	62.1
Statements disagreed with, *n* (% out of 58)	20	34.5
Statements evenly split, *n* (% out of 58)	2	3.4
Statements worded favorably to FI/ICG	34	45.3
Statements worded unfavorably to FI/ICG	18	24.0
Nonjudgmental statements	23	30.7
Mean consensus reached Module 1		88.0
Mean consensus reached Module 2		86.0
Mean consensus reached Module 3		86.2
Mean consensus reached Module 4		84.1
Mean consensus reached Module 5		78.6
Mean overall consensus		85.1
Minimum consensus		50.0
Maximum consensus		100.0
When consensus reached (68 statements)		
100% consensus reached	14	20.6
90%–99% consensus reached	30	44.1
80%–89% consensus reached	19	27.9
70%–79% consensus reached	5	7.4

FI, fluorescence imaging; *ICG*, indocyanine green.

statement, with ≥80% participation considered necessary for consensus/nonconsensus to be considered valid.

Results

Voter characteristics

Practice characteristics of the expert panel are summarized in Table I.

Consensus results

Clear consensus was achieved on 63 of the 75 statements, whereas borderline and no consensus were reached on 5 and 7 statements, respectively (Table II). Clear consensus was achieved 43 times in the first round and 20 times in the second. Among these 20 statements achieving consensus in the second round were 9 for which only borderline consensus was apparent in the first round. All 9 statements with borderline consensus in the first round achieved clear (≥80%) consensus in the second.

Among the 63 statements on which clear consensus was reached, unanimous consensus was reached on 14, strong consensus (90%–99%) on 30, and clear consensus (80%–89%) on 19. Among the 34 statements deemed favorable to FI by the review panel a priori, agreement with the statement occurred 28 times (82%), whereas among statements considered unfavorable, the experts agreed 5 times (28%). The percentage of consensus was fairly consistent throughout the first 4 modules, ranging from 84.1% to 88.0%, but slightly lower for the fifth module on training and research (78.6%). The mean level of consensus achieved over the 5 modules was 85.1%.

Consensus results for modules 1 through 5 are summarized in Tables III to VII, respectively. In no instance did <9 of the 10 participating voters cast a vote on a given statement, meaning that

Table III
Module 1: Patient preparation and contraindications

Statement	No. of votes	% Voting	Response	No. of rounds	% Consensus
Consensus reached					
Allergic reactions to ICG are extremely rare	10	100.0	Agree	1	100.0
Prior to undergoing FI, patients should be informed that its use is still experimental.	10	100.0	Disagree	2	100.0
Prior to receiving ICG, patients must provide informed written consent specific to its use.	10	100.0	Disagree	2	100.0
All patients should be asked about possible allergies to iodine, shellfish or ICG before having ICG administered.	10	100.0	Agree	1	90.0
Prior to receiving ICG, patients should be provided with written information specifically addressing its use.	10	100.0	Disagree	2	90.0
Prior to undergoing FI, patients must provide informed written consent specific to its use.	10	100.0	Disagree	2	90.0
Known or suspected allergy to iodine or shellfish is an absolute contraindication to FI with ICG.	10	100.0	Agree	2	80.0
Prior to undergoing FI patients should be provided with written information specifically addressing its use.	10	100.0	Disagree	2	80.0
Inability to provide informed written consent is an absolute contraindication to using FI.	10	100.0	Disagree	1	80.0
Inability to provide written informed consent is an absolute contraindication to using ICG.	10	100.0	Disagree	1	80.0
Pregnancy is an absolute contraindication to FI with ICG	9	90.0	Disagree	2	77.8*

FI, fluorescence imaging; *ICG*, indocyanine green.
* Borderline (70.0%–79.9%) significance.

Table IV
Module 2: Logistics of performing fluorescence imaging during thyroid and parathyroid surgery

Statement	No. of votes	% Voting	Response	No. of rounds	% Consensus
Consensus reached					
Research is necessary to determine the optimum dose and concentration of ICG and timing of ICG administration for parathyroid or thyroid surgery.	10	100.0	Agree	1	100.0
FI with ICG is better at assessing PT perfusion than performing FI without ICG.	10	100.0	Agree	1	100.0
Parathyroid autofluorescence under NIRL is useful for the identification and localization of PGs during thyroidectomy procedures.	10	100.0	Agree	1	90.0
Parathyroid autofluorescence under NIRL is useful for the identification and localization of PGS during parathyroidectomy procedures.	10	100.0	Agree	1	90.0
Parathyroid perfusion can be effectively assessed using the gland's autofluorescence alone.	10	100.0	Disagree	2	90.0
For FI with ICG, the concentration of ICG administered is very important.	10	100.0	Agree	2	90.0
When using ICG to detect normal PGs, the optimum dose to administer is… (<5 mg, 5 mg, >5 mg).	10	100.0	<5 mg	1	90.0
When using ICG to detect abnormal PGs, the optimum dose to administer is… (<5 mg, 5 mg, >5 mg).	10	100.0	<5 mg	1	90.0
When using ICG, the optimum timing for ICG administration before PT gland localization is… (<60 s before, 1–2 min before, >2 min before).	10	100.0	<60 s Before	2	90.0
During thyroid or parathyroid surgery, FI can be performed both with and without ICG during the same surgical procedure.	10	100.0	Agree	1	90.0
The best time to look for parathyroid autofluorescence during a thyroidectomy is...	10	100.0	Post-TLM, predissection*	2	80.0
For FI with ICG, the dose of ICG administered is very important.	10	100.0	Agree	1	80.0
For FI with ICG, the timing of ICG administration (how long before the surgery) is very important.	10	100.0	Agree	1	80.0
A second IV dose of ICG can be given intraoperatively to better visualize the PGs.	10	100.0	Agree	1	80.0
Different imaging equipment should be used when using ICG than when looking for parathyroid autofluorescence.	10	100.0	Disagree	1	80.0
No consensus reached					
The dose of ICG to administer for FI should be determined on a milligram per kilogram basis or as an absolute dose.	9	90.0	mg/kg	2	55.6

AF, autofluorescence; *FI*, fluorescence imaging; *ICG*, indocyanine green; *NIRL*, near-infrared light; *PG*, parathyroid gland; *PT*, parathyroid; *TLM*, transoral laser microsurgery.
* Post-TLM, predissection = after thyroid lobe medialization, before any dissection.

the results for all 75 statements are considered valid (≥80% voter participation).

The 14 statements for which unanimous consensus was reached were the following: in terms of patient preparation (module 1, Table III) (1) agreement that allergic reactions to ICG are extremely rare; (2) disagreement that patients need to be told that FI is still experimental; and (3) disagreement that patients need to provide informed written consent specific to ICG. Regarding the technical logistics of performing FI during TPS (module 2, Table IV), unanimous consensus was reached that (4) research remains necessary to determine the optimum dose, concentration, and timing of ICG administration during TPS and that (5) ICG angiography is better than relying on the PGs' autofluorescence for assessing parathyroid perfusion. Pertaining to indications for FI during TPS (module 3, Table V), unanimous consensus was reached (6) disagreeing with the routine use of ICG during thyroidectomies, (7) that ≥50% of PGs are detectable without using ICG, and yet (8) that ICG is especially helpful when it is necessary to resect >1 PG. Unanimous perceptions regarding advantages and disadvantages of ICG (module 4, Table VII) all related to advantages, specifically (9) that its use enhances the assessment of PG perfusion over white light alone; (10) that its use enhances the assessment of PG perfusion over FI without ICG; and (11) that its use facilitates PG autoimplantation. Finally, pertaining to training and research (module 5, Table VII),

Table V
Module 3: Indications for fluorescence imaging during thyroid or parathyroid surgery

Statement	No. of votes	% Voting	Response	No. of rounds	% Consensus
Consensus reached					
ICG should be used routinely to localize normal PGs during a thyroidectomy.	10	100.0	Disagree	2	100.0
The expected rate of detection of the PGs by FI, not using ICG, is… (<50%, ≥50%)	10	100.0	≥50%	1	100.0
One surgical scenario in which performing FA with ICG is particularly helpful is during surgeries when the resection of >1 PG is required.	10	100.0	Agree	1	100.0
Parathyroid AF should be used to localize normal PGs during thyroidectomy.	10	100.0	Agree	1	90.0
Other roles exist for near-infrared imaging beyond the in situ localization of PGs during thyroid or parathyroid surgery.	10	100.0	Agree	1	90.0
The expected rate of detection of the PGs by FI using ICG is… (<50%, ≥50%)	10	100.0	≥50%	1	90.0
ICG can be used to assess parathyroid perfusion after a thyroidectomy.	10	100.0	Agree	1	90.0
For parathyroidectomy performed to treat primary hyperparathyroidism, ICG should be used… (never, selectively, routinely).	10	100.0	Selectively	1	90.0
ICG should be used... (routinely, selectively, never)... for parathyroidectomy performed to treat primary hyperparathyroidism.	10	100.0	Selectively	1	90.0
One surgical scenario in which performing FA with ICG is particularly helpful during thyroid or parathyroid procedures is during redo surgeries.	10	100.0	Agree	1	90.0
Thyroid cancer is at least a relative contraindication against using ICG.	10	100.0	Disagree	1	90.0
Using ICG during a thyroidectomy or parathyroidectomy is helpful for less experienced surgeons but has no real advantage among thyroid/parathyroid surgeons with more experience.	10	100.0	Disagree	1	90.0
ICG should be used routinely to assess parathyroid perfusion after a thyroidectomy.	10	100.0	Disagree	2	80.0
AF should be used to localize parathyroid tumors.	10	100.0	Agree	1	80.0
FI with ICG should be used to localize parathyroid tumors	10	100.0	Disagree	2	80.0
FI is helpful when surgically treating thyroid cancer limited to the thyroid.	10	100.0	Agree	1	80.0
FI is helpful when performing radical neck dissections for thyroid cancer.	10	100.0	Agree	2	80.0
FI significantly impacts the way that thyroidectomies are performed.	10	100.0	Agree	1	80.0
FI significantly impacts the way that parathyroidectomies are performed.	10	100.0	Agree	2	80.0
ICG significantly impacts the way that thyroidectomies are performed.	10	100.0	Agree	2	70.0*
ICG significantly impacts the way that parathyroidectomies are performed.	10	100.0	Disagree	2	70.0*

AF, autofluorescence; *FA*, fluorescence angiography; *FI*, fluorescence imaging; *ICG*, indocyanine green; *NIRL*, near-infrared light.
* Borderline (70.0%–79.9%) significance.

unanimous consensus was reached that (12) FI is useful for training surgical residents in TPS, and that its use will likely increase over the next decade, both in (13) surgical practice and (14) research.

The 7 statements on which no consensus was reached pertained to (1) whether ICG should be dosed on a milligram per kilogram or absolute dose basis (5/9 voted for mg/kg) (Table IV); (2) the impact of using ICG on the time required to complete TPS (6/10 voted that it increases the time required); (3) its impact on the cost of performing TPS (6/10 voted increases); and (4) whether or not its use adds a degree of awkwardness to TPS (6/10 disagreed) (all Table VI); (5) whether physician trainees should initially be exposed to FI during medical school or residency (6/10 voted residency); and the number of cases required to overcome the learning curve for FI use during both (6) thyroidectomies and (7) parathyroidectomies (5/10 voted that 20–30 cases were required for both procedures) (all Table VII).

Borderline (70%–79%) consensus was achieved for 5 statements: (1) pregnancy is an absolute contraindication to performing ICG angiography (7/9, 78% disagreed) (Table III); (2) ICG significantly impacts the way that thyroidectomies are performed (7/10 agreed); and (3) ICG significantly impacts the way that parathyroidectomies are performed (7/10 disagreed) (both Table V); (4) ICG significantly enhances the predissection visualization of normal PGs, relative to white light alone (7/9, 78% agreed); and (5) inadequate empirical evidence supporting efficacy is a major limitation to performing FI, with or without ICG, during thyroidectomy or parathyroidectomy (7/9 disagreed) (both Table VI).

Discussion

Two common criticisms of opinion surveys, especially among physicians and other health care providers, are (1) that they are just that—opinions, rather than empirical evidence—and (2) that the potential for bias is great, given that such surveys inherently involve asking individuals about an issue they already are supportive of, given that they must have already integrated it into their practice to become experts at it. A third criticism that certainly could be levied against the current survey is that only 10 experts participated, largely resulting from the stringent eligibility criteria we used and there being too few surgeons with expertise performing fluorescence-guided TPS both with and without ICG. We see having restricted our expert panel to surgeons with expertise in fluorescence imaging both with and without ICG as a study strength, however, because it allowed us to compare perceptions of these 2 approaches, including the advantages and disadvantages of each. What we observed is that the experts clearly distinguished between FI of the parathyroid with versus without ICG, in terms of each approach's value and limitations.

Fluorescence imaging without ICG was strongly perceived to be an effective way to localize and identify PGs, during both thyroidectomy and parathyroidectomy procedures, but inadequate, on its own, assessing PG perfusion. Conversely, FI with ICG was considered less effective than PG auto-FI at localizing PGs, its use only indicated in selective cases, rather than routinely. Moreover, whereas FI with ICG angiography was considered impactful for thyroidectomy, it was not considered so during parathyroidectomy.

Conversely, using ICG angiography was deemed very helpful for evaluating PG perfusion, with all 10 experts agreeing that assessing gland perfusion with ICG was superior to doing so either under white light or under NIR light without ICG. There also was strong consensus that using ICG was helpful even for experienced surgeons, and that examining for PG autofluorescence and assessing PG perfusion are both feasible during the same surgical procedure and that the same NIR imaging equipment can be used for both purposes.

Table VI
Module 4: Advantages/benefits and disadvantages/limitations of using fluorescence imaging

Statement	No. of votes	% Voting	Response	No. of rounds	% Consensus
Consensus reached					
Using ICG enhances the assessment of PG perfusion over white light alone.	10	100.0	Agree	1	100.0
Using ICG enhances the assessment of PG perfusion versus using NIRL imaging without ICG.	10	100.0	Agree	1	100.0
Performing FA with ICG facilitates PG autoimplantation.	10	100.0	Agree	2	100.0
FI significantly enhances the predissection visualization of normal PGs, relative to white light alone.	10	100.0	Agree	1	90.0
Adding ICG increases the rate of identifying PGs relative to using the glands' own AF.	10	100.0	Disagree	2	90.0
FI without ICG significantly enhances the predissection visualization of abnormal PGs, relative to white light alone.	10	100.0	Agree	1	90.0
Performing fluorescence angiography with ICG helps to preserve parathyroid perfusion during thyroidectomies.	10	100.0	Agree	1	90.0
During thyroidectomy, relative to white light alone, FI… (increases, decreases, has no impact on)... the risk of postoperative hypocalcemia	10	100.0	Decreases	1	90.0
Relative to white light alone, FI... (increases, decreases, has no impact on)... the overall risks of thyroid or parathyroid surgery	10	100.0	Decreases	1	90.0
Enhanced visualization of ectopic PGs is an advantage of FI over white light alone.	10	100.0	Agree	2	90.0
Background fluorescence is a significant disadvantage of FI, with or without ICG, during thyroidectomy or parathyroidectomy.	10	100.0	Agree	1	90.0
Regulatory issues are a major limitation to performing fluorescence imaging, with or without ICG, during thyroidectomy or parathyroidectomy.	10	100.0	Disagree	2	90.0
ICG significantly enhances the predissection visualization of abnormal PGs, relative to white light alone.	10	100.0	Agree	1	80.0
Relative to white light alone, FI without ICG... (increases, decreases, has no impact on)... the overall time required to perform thyroid or parathyroid surgery.	10	100.0	Has no impact	2	80.0
Equipment unavailability is a major limitation to performing FI, with or without ICG, during thyroidectomy or parathyroidectomy.	10	100.0	Agree	1	80.0
ICG significantly enhances the predissection visualization of normal PGs, relative to white light alone.	9	90.0	Agree	2	77.8*
Inadequate empirical evidence supporting efficacy is a major limitation to performing fluorescence imaging, with or without ICG, during thyroidectomy or parathyroidectomy.	9	90.0	Disagree	2	77.8*
No consensus reached					
Using ICG during thyroid and parathyroid surgical procedures... (significantly increases or decreases, or has no impact on)... the time required to complete the surgery (eg, >2−3 min).	10	100.0	Increases	2	60.0
Relative to white light alone, fluorescence imaging... (significantly increases or decreases, or has no impact on)... the overall cost of thyroidectomy or parathyroidectomy.	10	100.0	Increases	2	60.0
Using ICG during thyroid and parathyroid surgical procedures adds a significant level of awkwardness to the procedure.	9	90.0	Disagree	2	55.6

AF, autofluorescence; *FI*, fluorescence imaging; *ICG*, indocyanine green; *NIRL*, near-infrared light; *PG*, parathyroid gland.
* Borderline (70.0%–79.9%) significance.

Table VII
Module 5: Training and research

Statement	No. of votes	% Voting	Response	No. of rounds	% Consensus
Consensus reached					
FI is useful for training surgical residents in thyroid and PT surgery.	10	100.0	Agree	1	100.0
Over the next decade, the use of FI in surgical practice is likely to… (increase, decrease, remain the same).	10	100.0	Increase	1	100.0
Over the next decade, the use of FI in research is likely to… (increase, decrease, remain the same).	10	100.0	Increase	1	100.0
Not just surgery residents, but residents in other nonsurgical fields should learn about FI.	10	100.0	Agree	1	90.0
No consensus reached					
Exposure of physician trainees to FI should begin during… (medical school, residency training).	10	100.0	Residency	2	60.0
The number of cases using FI during thyroidectomy that need to be completed to overcome the learning curve is approximately (<20, 20–30, >30)...	10	100.0	20–30	2	50.0
The number of cases using FI during parathyroidectomy that need to be completed to overcome the learning curve is approximately (<20, 20–30, >30)...	10	100.0	20–30	2	50.0

FI, fluorescence imaging; *ICG*, indocyanine green; *PT*, parathyroid.

Such conclusions regarding the uses of FI of PGs with and without ICG are supported by the literature.[10,20,24,25] In one just-published study, among 20 patients undergoing total thyroidectomy for a variety of benign and malignant conditions, most commonly multinodular goiter ($n = 13$), 76 of 80 PGs (95%) were detected before dissection, among which 42 (55%) were detected through their own autofluorescence under NIR light, before the surgeon saw the glands under white light.[24] In the same study, with

ICG used in all patients, 2 devascularized glands were detected by ICG angiography only.[24] In another ex vivo study, the sensitivity of autofluorescence for detecting 166 PGs was 96.8%.[25] Meanwhile, in a recently published randomized controlled trial in which 170 patients were randomized to undergo thyroidectomy either exclusively under white light ($n = 85$) or combining visualization under white light and NIR FI ($n = 85$), as many PGs were identified before dissection under NIR light as with white light after dissection,[20] and the percentage of calcium levels ≤7.5 mg/dL was reduced by 90% in the combined-light group ($P = .005$). Also, in the combined-light group, toggling from white to NIR light increased the number of detected glands from 2.6 to 3.5 per patient ($P < .001$) and revealed ≥1 previously missed gland in 67.1% of patients. Patient sex, age, and primary diagnosis appeared to exert no influence on the fluorescent intensity of surrounding tissues, including thyroid,[26] suggesting that these factors should not influence decisions to use FI.

Among the strongest evidence supporting the use of ICG angiography for parathyroid identification during parathyroidectomy is a study by Delong et al,[27] in which ICG angiography was performed during 60 parathyroidectomies for primary hyperparathyroidism after which videos were graded by 3 independent surgeons for strength of PG enhancement. During these 60 procedures, clearly visible vascular enhancement with ICG was evident in 56 (93.3%). In addition, all 18 patients whose adenoma was not visible on a preoperative sestamibi scan had a parathyroid adenoma that fluoresced with ICG.

Other surgical scenarios in which our experts considered ICG beneficial, besides assessing PG perfusion, were when >1 PG must be resected, during redo surgeries, identifying devascularized PG that require autotransplantation, and for the predissection visualization of abnormal PGs. Using ICG also was deemed superior to using white light alone for detecting normal PG, albeit it was not as good as using the glands' own autofluorescence, an opinion that also has some empirical support in the literature.[28]

Overall, the panel of experts thought that FI is beneficial for detecting PGs, assessing their perfusion, and decreasing the risks of postoperative hypocalcemia, again consistent with published data, including a recently published meta-analysis in which 1,484 procedures spanning 13 papers were analyzed, revealing pooled short-term and intermediate-term serum hypocalcemia rates of 8% (95% CI: 5%–11%) and 1% (0–4%) with auto-FI versus 15% (9%–23%) and 5% (2%–9%) under white light, respectively.[29] Our 10 experts also reached consensus that FI decreases the overall risks of TPS and has value in surgically treating cancer procedures, whether restricted to the thyroid or requiring radical neck dissection. Interestingly, recent studies have suggested that neural tissue also autofluoresces, albeit under near-ultraviolet rather than NIR light,[30-32] suggesting another potential advantage of FI during thyroid and parathyroid resections and radical neck dissections, given the recurrent laryngeal nerve's close proximity to the thyroid and highly variable location and course[33-36] with permanent laryngeal nerve palsy documented in from 2%[37] to 8%[38] of patients undergoing thyroidectomy.

Also consistent between the views of our panel and the literature[10] is uncertainty regarding the optimum dosing and timing of ICG administration for ICG angiography, with the experts unanimously agreeing that further research is necessary to optimize both these technical components of ICG administration. Consistent with this view, there was strong consensus that background autofluorescence can be problematic, either with or without ICG. Despite this, there also was unanimous agreement that employing FI during TPS should no longer be considered experimental and strong agreement that published empirical evidence is adequate to justify such use. Similarly, there was unanimous agreement that FI is helpful training surgical residents in TPS, as already documented in a recently published study involving 10 surgical residents.[39]

Areas of nonconsensus included the approach's impact on operating time and costs, how awkward using ICG is and whether it should be dosed on a milligram per kilogram or absolute dose basis, when physician trainees should initially learn about it, and the number of cases required to overcome the learning curve, whether for thyroidectomy or parathyroidectomy.

Study limitations

Some limitations of Delphi studies have already been discussed, including the presentation of opinions, rather than empirical data, and the potential for voter bias. We attempted to minimize the impact of bias by keeping all the experts' responses anonymous; by balancing fluorescence-imaging favorable, nonfavorable, and neutral statements; and by altering the order of response options so favorable response options were first no more often than unfavorable ones.

We have already explained our rationale for the relatively small number of experts on our voting panel but admit we would have preferred more. We attempted to offset this shortage of experts somewhat by raising the percentage consensus required to satisfy our criterion for "consensus" from the much more commonly used 70% to 80%, calling percentages between 70 and 79% "borderline." We also must emphasize that, although we agree that our data are opinions, rather than empirically derived clinical data, these opinions are nonetheless those of an extremely qualified panel of experts, all of whom are highly cognizant of the published literature, most having contributed directly to it.

We also must point out the main strength of Delphi studies, which is that they permit the examination of issues that would be very difficult, if not virtually impossible, to study within the confines of any clinical trial, such as variations in ICG dosing, concentration, and timing.

In conclusion, although prospective, controlled clinical trials remain necessary to fully explore all the roles that FI, with and without ICG, has during TPS, it appears to have several empirically supported roles, most notably detecting and localizing PGs before dissection through their autofluorescence, using ICG angiography to assess PG perfusion, and reducing the risk of post-thyroidectomy hypocalcemia. Using FI for such purposes should no longer be considered experimental.

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