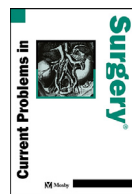


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# Determination of parathyroid function after total thyroidectomy by objective analysis of its fluorescence intensity with indocyanine green using purpose developed computer software

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*Abbreviations:* AF, Autofluorescence; ASA, American Society of Anaesthesiologists; AUC, Area under the curve; BMI, Body mass index; FI, Fluorescence intensity; ICG, Indocyanine green; LND, Lymph node dissection; NIFTP, Neoplasm with papillary-like nuclear features; NIR, Near-infrared (light); NPV, Negative predictive value; OR, Odds Ratio; PG, Parathyroid glands; PPV, Positive predictive value; PTH, Parathyroid hormone; ROC, Receiver Operating Characteristic; SE, sensibility; SP, Specificity; TBR, Target-to-background ratio; TPH, Transient postoperative hypoparathyroidism; TT, Total thyroidectomy; UIB-DMI, Department of Mathematics and Computer Science of the University of the Balearic Islands.

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## Introduction

Thyroid surgery is considered a standardized and safe surgery, with a very low mortality rate (0,065%) most often associated with a combination of factors including advanced age, the presence of giant goiters, and upper airway complications.<sup>1</sup> Transient postoperative hypoparathyroidism (TPH), and the consequent hypocalcaemia, is the most common complication after performing a total thyroidectomy (TT), and represents an incidence of up to 30–50% of patients undergoing this surgery.<sup>2,3</sup> The incidence varies depending on whether routine calcium and/or vitamin D supplementation is administered, which differs according to the standard practice of each center.<sup>4,5</sup> Risk factors for post-thyroidectomy TPH include the performance of bilateral thyroid surgery and/or central neck dissection, the presence of autoimmune thyroid disease, substernal goiter, malabsorption conditions and surgeon inexperience.<sup>4,6–8</sup>

As early as 1907 Halsted and Evans<sup>9</sup> described the importance of preserving the parathyroid glands (PGs) to avoid the risk of TPH, something that can be challenging since normal postoperative parathyroid function is not guaranteed, even when the PG appear to be well preserved during surgery. The occurrence of TPH may be due to interruption of the parathyroid arterial supply or its venous drainage, mechanical, thermal or electrical injury to the gland, or its partial or complete exeresis.<sup>4</sup> Thus, in addition to glandular preservation, the maintenance of proper parathyroid vascularization is essential to avoid TPH since adequate blood perfusion correlates with proper postoperative glandular function.<sup>10,11</sup> In this regard, several authors have studied the use of fluorescence-guided surgery to determine postoperative PG function.<sup>12</sup> Specifically, the use of indocyanine green (ICG) for the measurement of its fluorescence intensity when illuminated with near-infrared (NIR) light has been correlated with the rate of development of hypocalcemia after TT.<sup>13,14</sup> In any case, the vast majority of works describe a subjective measurement of fluorescence using analog scales,<sup>15–17</sup> based on the subjective ICG fluorescence measurement scale (ICG-2 score) devised by Vidal-Fortuny et al.<sup>11</sup> That score classifies each PG with the values 2 (hyperfluorescent, well vascularized gland), 1 (slightly fluorescent or heterogeneously shaped, partially vascularized gland) or 0 (nonfluorescent, nonvascularized PG). The authors proposed a strong correlation between parathyroid perfusion and function, suggesting that a single well-vascularized parathyroid gland (scored as 2 on the ICG-2 scale) could be sufficient to prevent TPH. However, the main limitation of these measurement scales is precisely their subjective nature, since it is the surgeon who determines the fluorescence intensity of each PG with the values 0, 1 or 2.

Some authors approach this analysis of PG fluorescence objectively by means of computer programs but postoperatively with the analysis of previously recorded surgical images, which does not provide any advantage in the operative or postoperative management of patients.<sup>18</sup> Recently,<sup>19</sup> has been described an objective, intraoperative determination of parathyroid fluorescence intensity but does so in terms of relative intensity only and with a fluorescence intensity measurement system totally dependent on the fluorescence acquisition device.

To our knowledge, there is no evidence published to date that analyzes the correlation between ICG-PG fluorescence after TT and parathyroid glandular function through an objective, automated, and real-time intraoperative assessment using software independent of the imaging device. The main objective of our study is to enhance surgical outcomes by providing a reliable method for identifying cases that will not present TPH. This entails verifying if high fluorescence intensity in at least 1 PG reliably predicts the absence of TPH.

## Materials and methods

### *Trial design and patients*

A prospective, observational, and single-center study involving low-intervention drugs was conducted. The study included consecutive patients who underwent TT, with or without cervical

lymph node dissection (LND) based on oncologic criteria, between November 2016 and June 2021.

To calculate the sample size needed for statistically significant results, an anticipated TPH rate of approximately 40% was used, along with a set alpha risk of 0,05 and a beta risk of 0,2 for a 2-tailed test. Based on these parameters, 60 subjects were required to detect a difference of 0,1 or greater in fluorescence intensity units. A common standard deviation of 0,1 was assumed, and a 10% estimated loss rate was factored in.

The inclusion criteria were age  $\geq$  18 years old, normal liver and kidney function, no allergies to ICG or iodine, ability to understand and follow study procedures and having provided signed consent. The exclusion criteria were age  $<$  18 years old, liver or kidney dysfunction, known history of hyperparathyroidism, allergy to ICG or iodine, pregnancy or breast-feeding and inability to understand and follow study procedures. The patient withdrawal criteria were withdrawal of informed consent or lost to follow-up. Patient data were collected at enrolment, during surgery, immediately after surgery and up to 90 days postoperatively. Preoperative blood tests were collected prior to the preanesthetic assessment.

All patients signed the informed consent form prior to recruitment for the study. The study was approved by the Research Committee of the University Hospital Son Espases, by the Research Ethics Committee of the Balearic Islands and by the Spanish Agency of Medicines and Medical Devices. Additionally, it was registered in the ClinicalTrials.gov and EudraCT registries.

### *Surgical and fluorescence techniques*

In all surgeries, the same vascular sealing device was utilized (LigaSure™ Exact), and the integrity of the recurrent laryngeal nerves was monitored through intermittent intraoperative neuromonitoring. Once the TT was completed, the PGs detected were viewed under NIR light using the Karl Storz Image 1 HD® device for laparoscopic surgery with Spectra A spectral filter, in an attempt to improve their determination thanks to their autofluorescence (AF) property and to differentiate them from other tissues with which there may have been doubts as to their nature.<sup>12,20,21</sup>

A single dose of 5 mg (2 ml of a 25 mg dilution in 10 ml of distilled water) of ICG was then administered intravenously for subsequent determination of the fluorescence intensity of the PGs 1 minute after ICG administration. Parathyroid fluorescence intensity was initially assessed using the subjective analog scale (ICG-2 score),<sup>11</sup> with values of 0, 1, or 2 as previously detailed, by 3 expert surgeons members of the Endocrine Surgery Unit of the hospital. (Real examples of these measures can be seen in the previous published article).<sup>12</sup> Concurrently, images of parathyroid fluorescence with ICG taken during the intervention were collected, with the camera held approximately 3 cm from the objective and with the operating room lights completely off. These images are intended for further processing to develop specialized computer software by the Department of Mathematics and Computer Science of the University of the Balearic Islands (UIB-DMI). This software aims for the objective determination of parathyroid fluorescence intensity.

### *Development of the computer software*

Parathyroid fluorescence images with ICG taken during the intervention were analyzed by UIB-DMI for the determination of the mean fluorescence intensity (FI) of each PG. For this purpose, the set of pixels corresponding to PGs were previously demarcated by the surgery team. This analysis revealed the frequent presence of specular spots in the surgical images, the result of brightness created by NIR light on different tissues or surgical materials. The presence of these specular spots on the PG would create an important bias in the measurement of the FI since they appear as very bright areas. The computer software created by the UIB-DMI cal-

culated the FI of each gland by automatically discarding those pixels corresponding to specular images (Fig. 1).

In parallel, to account for potential interindividual variability in fluorescence among patients, efforts were made to minimize bias by adjusting the FI of each PG to the mean fluorescence intensity of the surrounding periglandular tissue, known as the target-to-background ratio (TBR). To calculate the TBR, different percentages of the most hyperfluorescent pixels of the periglandular tissue or background were considered. In this way, the UIB-DMI software was able to determine both the FI and the TBR for each PG visualized in the surgical procedure (Fig. 1).

### Outcome measures

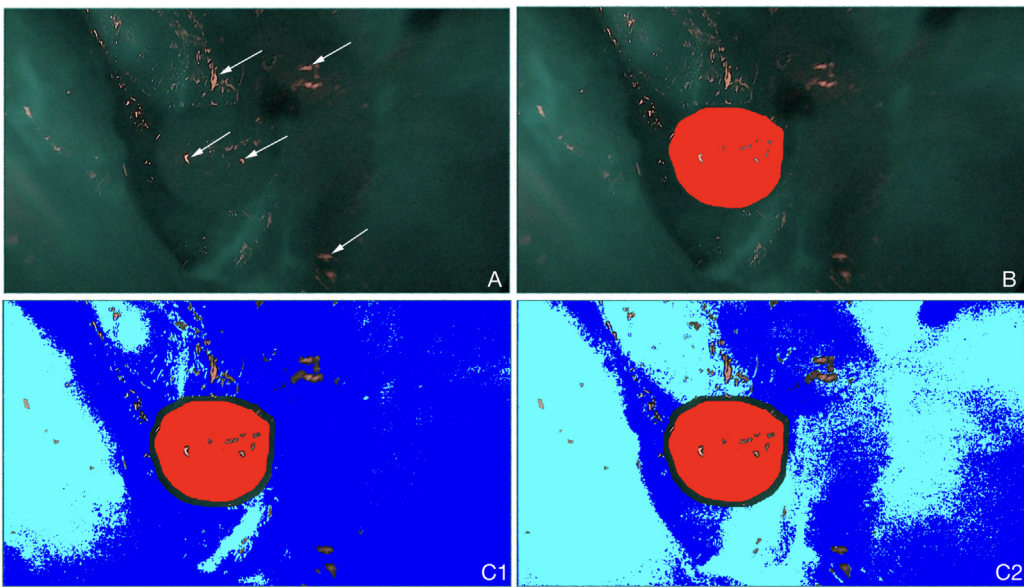
The data recorded included age, gender, body mass index (BMI), American Society of Anaesthesiologists (ASA) physical status classification, surgical indication, preoperative 25-OH-vitamin D and parathyroid hormone (PTH) levels, type of surgery performed (with or without LND), duration of surgery, number of PGs identified, subjective fluorescence intensity of PG after ICG administration (measured by ICG-2 score), serum PTH value at 10 minutes after completion of TT, intraoperative PTH gradient (preoperative PTH level minus value 10 minutes after TT), calcemia at 24h postoperatively adjusted by albumin, pathological anatomy result, thyroid weight, presence and number of PGs in the surgical specimen, postoperative stay, and postoperative complications graded according to the Clavien–Dindo classification.<sup>22</sup>

For ethical reasons, all patients who presented a drop in PTH levels below laboratory reference values (<15 pg/ml) received treatment with oral calcium and vitamin D, and were considered as cases of hypocalcemia. In addition, hypocalcemia was also considered if the level of calcemia, measured in terms of total calcium corrected by albumin, was less than 8 mg/dL at 24 hours postoperatively. According to the results of these analyses and the appearance or not of hypocalcemia symptoms, PTH treatment was established according to the center's protocol. The patients were followed up in the outpatient department of the General and Digestive Surgery Service for a minimum of 90 days after surgery to detect possible postoperative complications.

Finally, the results obtained with the 3 possible methods for predicting postoperative normocalcemia were compared: the intraoperative PTH gradient, the subjective intensity of parathyroid fluorescence measured by the ICG-2 score, and the objective intensity of glandular fluorescence determined by the UIB-DMI software.

### Statistical analysis

Normality test and graphs were used to determine whether variables followed a normal distribution. In descriptive analysis, data are presented as median values and interquartile ranges for the quantitative variables, and as frequency and percentage for qualitative variables. For the comparison of groups the Mann-Whitney U test was used for quantitative variables and the Chi-square test or Fisher's exact test for qualitative variables. The Rho Spearman coefficient was used for correlation between numerical variables. Multivariate analysis was performed by binary logistic regression (backward Wald), obtaining an Odds Ratio (OR) for each variable. The Receiver Operating Characteristic (ROC) curves to compare the indicators of normocalcemia were analyzed according to Youden and maximum negative predictive value (NPV) criteria. Given the specific design of this study, it was crucial to demonstrate that the patients identified by the diagnostic tests did not develop hypocalcemia, rather than the opposite, since not all parathyroid glands may have been visualized during surgery. To ensure this, achieving a high NPV was important. Therefore, the cut-off points for the diagnostic tests were calculated using the maximum NPV criteria. A P value of less than 0,05 was considered statistically significant. Statistical analyses were carried out with IBM-SPSS software v.26 (SPSS Inc., Chicago, IL, USA).



**Fig. 1.** Complete image analysis for the creation of the UIB-DMI software. Image A shows a PG imaged under NIR light viewing using the Karl Storz Image1 HD device in Spectra A mode. Specular spots are indicated by arrows. Image B shows in red the pixels corresponding to the PG, where the pixels identified as specular spots have been discarded. Images C show in dark blue the entire periglandular area shown in the image, and highlighted in cyan blue is the background area corresponding to the percentage of pixels with the highest fluorescence intensity (20% in C1 and 60% in C2). In all processed areas the pixels corresponding to the specular spots are automatically removed.

## Results

### *Patient characteristics and complications*

A total of 65 patients underwent consecutive TT, with or without LND, based on oncologic criteria. Four patients were excluded from the study: 2 received an indocyanine green (ICG) dose different from the protocol-specified 5 mg, one had concomitant primary hyperparathyroidism, and one was mistakenly classified in the hypocalcemia group due to an analytical error. Consequently, all were excluded from the analysis. Finally, 61 patients, 53 female (86,9%) and 8 male (13,1%), were included (Table 1).

31 patients (50,1%) were submitted to surgery for multinodular goiter, followed in number by those affected by papillary thyroid carcinoma (31,1%). The total number of patients who presented TPH was 26 (42,6%). There were no statistically significant differences between the groups of patients who did or did not develop hypocalcemia according to the variables age, gender, BMI, ASA, surgical indication and preoperative vitamin D and PTH levels. Type of surgery performed was TT in 45 patients (73,8%), TT associated with central LND in 13 patients (21,3%), and with central and lateral LND in 3 (4,9%). No statistically significant differences were found for variables type of surgery, duration and number of PGs located during surgery.

At least 1 hyperfluorescent PG was identified in 23 patients (value 2 in the ICG-2 score), of which only 2 presented TPH. As for the intraoperative PTH decrease gradient, among the patients who did present hypocalcemia, this was 78.9% of median, while in those who did not develop hypocalcemia it was 44.8% of median. Both variables showed statistically significant differences according to the hypocalcemia variable. The same occurs with the PTH gradient with a cut-off point of 71,5%: of the 40 patients who presented a PTH gradient <71,5%, only 9 (22,5%) presented hypocalcemia and 31 (77,5%) did not develop it, with statistically significant results.

As for the postoperative pathologic result, 31 cases (50,8%) were differentiated thyroid carcinomas, followed by 24 patients with benign nodular hyperplasia (39,3%), 5 cases of lymphocytic thyroiditis (8,2%) and 1 case of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). No significant differences were found between the groups with and without hypocalcemia in pathological anatomy and number of PGs identified in the surgical specimen variables. The mean postoperative hospital stay was 2 days, while in the subgroup with hypocalcemia it was 3,5 days, with statistically significant differences. Eleven patients (18%) presented complications classified as Clavien-Dindo grades I-II (9 transient dysphonias, 1 wound infection and 1 cardiac arrhythmia). There was only 1 case of Clavien-Dindo grade III complication. This was a case of asphyxial hematoma that required urgent surgical drainage. There were no differences in the rate of other complications in relation to the development of TPH. All the patients who presented hypocalcemia normalized their calcium and PTH values during the following 6 postoperative months.

All other patient characteristics, intraoperative data and postoperative outcomes, and their relationship to the development of hypocalcemia, are shown in Table 1.

### *Objective measurement of fluorescence intensity*

For the development of the software for the objective determination of the fluorescence intensity of PGs, the results obtained by measuring FI and TBR in a single measurement were studied, as shown in Table 2. To calculate the TBR, percentages of 20, 60 and 90% of the most hyperfluorescent pixels of the periglandular tissue or background were considered. When considering 60% of the most hyperfluorescent periglandular tissue (TBR60), the highest NPV value (85,7%) was obtained for the calculation of TBR, although lower than that obtained with FI alone (91,7%). Anyway, the best results in terms of sensibility (SE), specificity (SP), negative predictive value (NPV), positive predictive value (PPV) and area under the curve (AUC) were obtained by combining both parameters: the determination of FI with a cut-off point of 0,22 combined with

**Table 1**

Patient characteristics, intraoperative data and postoperative results, and their distribution according to the variable hypocalcemia.

Variables	Total = 61	Hypocalcemia		P value
		No = 35 (57,4%)	Yes = 26 (42,6%)	
Gender				0.063
Male	8 (13.1%)	2 (25%)	6 (75%)	
Female	53 (86.9%)	33 (62.3%)	20 (37.7%)	
Age (years)	53 (43 - 61)	53 (43-64)	51 (43-61)	0.688
BMI (kg/m <sup>2</sup> )	26,5 (23 - 30)	26 (22-32)	26,8 (24-30)	0.554
ASA score				0.080
I	13 (21.3%)	5 (38.4%)	8 (61.5%)	
II	43 (70.5%)	26 (60.5%)	17 (39.5%)	
III	5 (8.2%)	4 (80%)	1 (20%)	
Preoperative diagnosis				NA*
Multinodular goiter	31 (50.8%)	21 (67.7%)	10 (32.3%)	
Lymphocytic thyroiditis	2 (3.3%)	0 (0%)	2 (100%)	
Bethesda III nodule	9 (14.8%)	6 (66.7%)	3 (33.3%)	
PTC	19 (31.1%)	8 (42.1%)	11 (57.9%)	
Preoperative vitamin D (ng/ml)	22,5 (12-34)	24 (14-37)	22 (10-29)	0.523
Preoperative PTH (pg/ml)	66 (46.8-94.7)	75 (48-97.9)	55,4 (36-78.4)	0.129
Surgery performed				NA*
TT	45 (73.8%)	29 (64.4%)	16 (35.6%)	0.061
TT + central LND	13 (21.3%)	5 (38.5%)	8 (61.5%)	0.120
TT + central + lateral LND	3 (4.9%)	1 (33.3%)	2 (66.7%)	0.570
Duration of surgery (minutes)				
Total of surgeries	88 (77-117)	85 (77-124)	93 (76-115)	0.810
TT	85 (77-106)			
TT + central LND	93 (78-115)			
TT + central + lateral LND	188 (187-230.5)			
Number of PGs identified				0.660
2	25 (41%)	16 (64%)	9 (36%)	
3	22 (36.1%)	12 (54.5%)	10 (45.5%)	
4	14 (22.9%)	7 (50%)	7 (50%)	
Subjective fluor. (ICG-2 score)				<0.001
+ (score =2 in any PG)	23 (37.7%)	21 (91.3%)	2 (8.7%)	
- (score <2 in all PGs)	38 (62.3%)	14 (36.8%)	24 (63.2%)	
Intraop. PTH gradient (%)	56.4 (39.9-77.6)	44.8 (34.4-65)	78.9 (50.2-86.8)	<0.001
Intraoperative PTH gradient				<0.001
<71.5%	40 (65.6%)	31 (77.5%)	9 (22.5%)	
>71.5%	21 (34.4%)	4 (19%)	17 (81%)	
Postoperative calcemia (mg/dl) (n = 43) <sup>†</sup>	8.7 (8.2-9)			
Thyroid weight	33.5 (19.7-68)	30 (18-95)	35 (25-48)	0.776
Pathological anatomy result				NA*
Nodular hyperplasia	24 (39.3%)	17 (70.8%)	7 (29.2%)	0.703
Lymphocytic thyroiditis	5 (8.2%)	0 (0%)	5 (100%)	0.029
NIFTP	1 (1.6%)	1 (100%)	0 (0%)	0.852
PTC	31 (50.8%)	17 (54.8%)	14 (45.2%)	
PTC T1	19 (31.2%)			
PTC T2	9 (14.8%)			
PTC T3	3 (4.9%)			
Number of PGs in specimen				NA*
0	45 (73.8%)	27 (60%)	18 (40%)	0.487
1	14 (23%)	8 (57.1%)	6 (42.9%)	
2	2 (3.3%)	0 (0%)	2 (100%)	
Postoperative stay (days)	2 (2-4)	2 (2-2)	3.5 (3-4)	<0.001
Postoperative stay				<0.001
1 - 2 days	33 (54.1%)	27 (81.8%)	6 (18.2%)	
>2 days	28 (45.9%)	8 (28.6%)	20 (71.4%)	

(continued on next page)

**Table 1** (continued)

Variables	Total = 61	Hypocalcemia		P value
		No = 35 (57,4%)	Yes = 26 (42,6%)	
Complications (Clavien–Dindo)				0,731
No	49 (80,3%)	30 (61,2%)	19 (38,8%)	
I-II	11 (18%)	5 (45,5%)	6 (54,5%)	
III	1 (1,6%)	0 (0%)	1 (100%)	

Qualitative variables are expressed as frequencies and percentages and quantitative variables as median and interquartile range.

BMI, body mass index; ASA, American Society of Anaesthesiologists; PTC, papillary thyroid carcinoma; PTH, parathyroid hormone; TT, total thyroidectomy; LND, lymph node dissection; PGs, parathyroid glands; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

\* NA, not applicable. When more than 1 P value appears in the categorical variables, the comparison was performed for each category separately with respect to the rest.

† Patients with postoperative PTH levels <15 pg/ml were considered cases of hypocalcemia and were treated with oral calcium and vitamin D, so their 24-hour calcemia values were not used for numerical analysis.

**Table 2**

Results of the objective determination of parathyroid fluorescence intensity according to the different measurement parameters of the computer software for the prediction of postoperative normocalcemia.

Valuation method	AUC*	P value	Cut-off point	SE (%)	SP (%)	NPV (%)	PPV (%)
FI	0.729 (0.602-0.856)	0.002	0.329	96.2	31.4	91.7	51
TBR (20%)	0.71 (0.575-0.847)	0.005	1.141	88.5	48.6	85	56.1
TBR (60%)	0.67 (0.532-0.813)	0.022	1.422	88.5	51.4	85.7	57.5
TBR (90%)	0.66 (0.522-0.806)	0.030	2.137	88.5	37.1	78.6	48.9
FI + TBR (60%)	0.784 (0.665-0.902)	<0.001	FI: 0,22 TBR: 0,96	96.2	65.7	95.8	67.6

FI, parathyroid gland mean fluorescence intensity; TBR, fluorescence intensity target-to-background ratio (in parentheses, the percentage of the most hyperfluorescent pixels of background used for calculation); AUC, area under the curve; SE, sensibility; SP, specificity; NPV, negative predictive value; PPV, positive predictive value.

\* Area under the ROC curve is expressed with interquartile range.

**Table 3**

Comparison of postoperative normocalcemia indicators.

Valuation method	AUC*	P value	SE (%)	SP (%)	NPV (%)	PPV (%)	AC (%)
PTH gradient (cut-off: 71,5%)	0.78 (0.654-0.906)	<0.001	65.4	88.6	77.5	81	78.7
Subjective fluorescence: ICG-2 score	0.762 (0.64-0.883)	0.001	92.3	60	91.3	63.2	73.8
Objective fluorescence: FI + TBR (60%)	0.784 (0.665-0.902)	<0.001	96.2	65.7	95.8	67.6	78.7

AUC, area under the curve; SE, sensibility; SP, specificity; NPV, negative predictive value; PPV, positive predictive value; AC, accuracy; FI, parathyroid gland mean fluorescence intensity; TBR, fluorescence intensity target-to-background ratio.

\* Area under the ROC curve is expressed with 95% interquartile range.

the measurement of TBR60 with a cut-off point of 0,96, as can be seen in Table 2. Therefore, these were the parameters with which the UIB-DMI parathyroid fluorescence intensity determination software was configured.

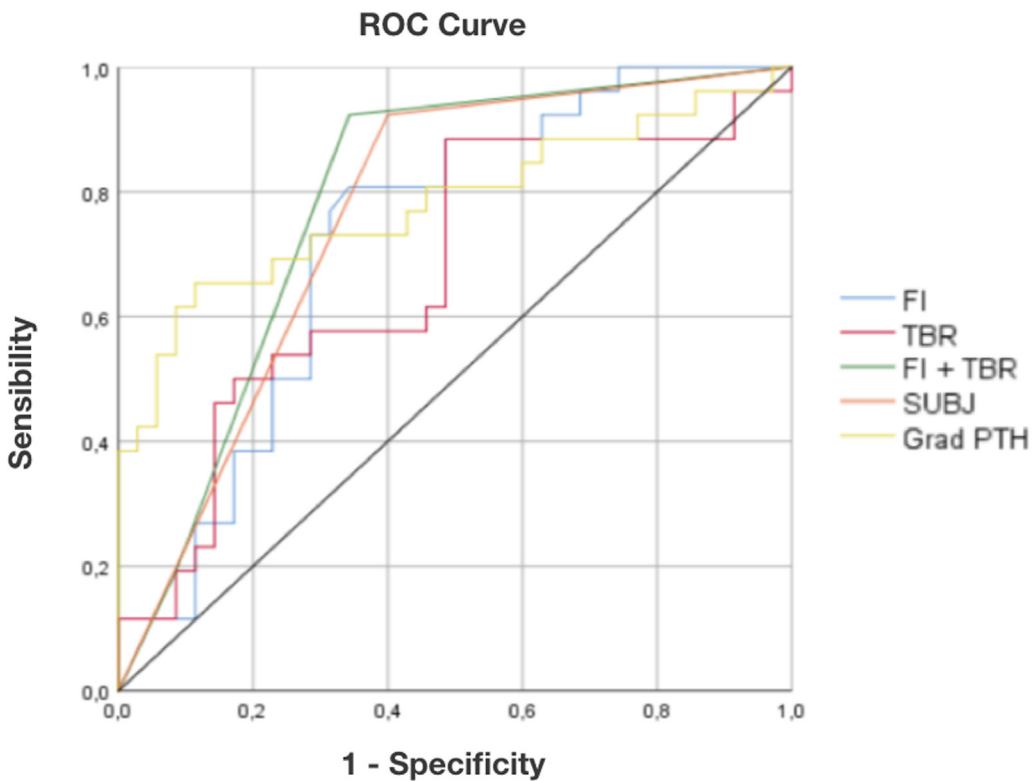
*Comparison of postoperative normocalcemia indicators*

Tables 3 and 4, and Fig. 2 show the comparative results obtained with each of the 3 methods for predicting postoperative normocalcemia. As detailed, the results obtained with the objective method of hyperfluorescence detection (UIB-DMI software, with joint determination of FI and TBR60), obtained better results than the subjective determination of fluorescence (ICG-2 score)

**Table 4**  
Results obtained with the different indicators of postoperative normocalcemia.

Case	Hypocalcemia	PTH Gradient (< 71,5 %)	≥ 1 Parathyroid with ICG-2 Score of 2	≥ 1 Parathyroid sufficiently fluorescent according to UIB-DMI Software (FI+TBR60)
1	+	82,07	-	-
2	+	85,24	+	-
3	+	34,28	-	-
4	-	41,46	+	+
8	+	77,14	-	-
9	-	81,81	+	+
10	-	45,83	-	-
11	+	15,15	-	-
12	+	41,44	+	+
13	+	86,78	-	-
14	-	57,72	-	-
15	-	53,47	-	-
16	+	60,23	-	-
17	+	81,43	-	-
19	+	68,94	-	-
20	-	54,4	+	-
21	-	37,93	+	+
22	+	41,03	-	-
23	+	86,38	-	-
24	-	0,13	+	-
25	+	50,23	-	-
26	-	61,25	-	-
27	-	20,13	-	-
28	-	37,98	+	+
29	+	71,63	-	-
30	-	70,55	-	+
31	-	9,49	+	+
32	-	72,4	-	+
33	+	80,08	-	-
34	+	2,76	-	-
35	-	30,7	+	+
36	+	91,2	-	-
37	-	39,87	+	+
38	-	44,78	+	+
39	-	8,37	+	+
41	+	89,38	-	-
42	+	94,71	-	-
43	-	71,12	+	+
44	-	71,37	-	-
45	-	41,28	+	+
46	-	35,73	+	+
47	+	77,63	-	-
48	+	86,02	-	-
49	+	76,15	-	-
50	-	65,02	-	-
51	-	71,27	-	+
52	-	83,67	+	+
53	-	55,06	-	-
54	-	41,97	+	+
55	-	34,41	+	+
56	+	87,76	-	-
57	-	77,3	+	-
58	-	8,39	-	+
59	+	92,87	-	-
60	-	49,21	+	+
61	-	56,44	+	+
62	-	6,06	+	+
63	+	87,64	-	-
64	-	44,7	-	-
65	-	25,02	-	+
66	+	48,88	-	-
Tota l	26/61	40/61	23/61	24/61

The cases in which each method was able to make a correct calcemia prediction are shown in green and their errors in red.



**Fig. 2.** ROC curve with the results obtained with the different indicators of postoperative normocalcemia: PTH gradient with a cut-off point of 71,5%, subjective ICG fluorescence (ICG-2 score) and objective ICG fluorescence (UIB-DMI software, FI + TBR60).

**Table 5**

Multivariate analysis. Predictor variables of calcemia.

Valuation method	OR*	P value
PTH gradient,% (as continuous variable)	0.979 (0.936-1.025)	0.364
PTH gradient (cut-off: 71.5%)	12.472 (2.275-68.38)	0.004
Subjective fluorescence: ICG-2 score	6.459 (0.632-66.027)	0.116
Objective fluorescence: FI + TBR (60%)	41.791 (4.19-416,804)	0.001

\* OR: Odds ratio, with 95% interquartile range.

and the intraoperative PTH gradient, when determining which patients were not at risk of developing TPH.

Subsequent multivariate analysis showed that both the PTH gradient as a continuous variable and the subjective assessment of fluorescence (ICG-2 score) are not independent variables of normocalcemia, as shown in Table 5. Only the PTH gradient with a cut-off point of 71,5% and the objective determination of fluorescence (UIB-DMI software) are independent variables of normocalcemia. The greatest strength of association was observed with the UIB-DMI software, which obtained an OR of 41,791 (4,190 – 416,804),  $P=0,001$ , compared to that obtained by the PTH gradient with a cut-off point of 71,5%, which was 12,472 (2,275 – 68,380),  $P=0,004$ .

## Discussion

It's known that TPH is the most common complication after performing a TT, and represents an incidence of up to 30-50% of patients undergoing this surgery.<sup>2,3</sup> In our study, the postoperative hypocalcemia rate, measured as albumin-corrected serum calcium less than 8 mg/dl 24 hours after surgery, was 42,6% (26/61). This outcome is primarily influenced by the ethical decision to treat all patients with PTH levels below the laboratory reference value (<15 pg/mL) with oral calcium and vitamin D, classifying them as hypocalcemia cases. Additionally, prophylactic preoperative calcium is not routinely administered in our center.

There is evidence in the medical literature on the usefulness of measuring parathyroid fluorescence and its correlation with postoperative glandular function.<sup>13,14,23</sup> However, the vast majority of works describe a subjective measurement of fluorescence by means of analog scales, such as the ICG-2 score.<sup>11,15,16</sup> Some authors approach this analysis of parathyroid fluorescence objectively by means of computer programs but postoperatively with the analysis of previously recorded surgical images.<sup>18</sup> Nevertheless, the use of objective intraoperative parathyroid fluorescence grading methods has been recently described in an article by Jin et al.<sup>19</sup> The authors of that study determined the intensity of parathyroid fluorescence intraoperatively after ICG administration and using the Digi-MIH-I-001® NIR light device (Beijing Precision Medicine Company, China) and obtained a relative value of each measurement with respect to surrounding tissue fluorescence (TBR), which correlated with postoperative calcium levels. Among the limitations of their study, the authors highlight the impossibility of using parathyroid AF to improve glandular identification, since their fluorescence device does not allow it to be performed, and the fact that they found no relationship between postoperative PTH levels and the fluorescence-ICG grading. In addition, it is worth noting the total dependence of the fluorescence intensity measurement system on the fluorescence acquisition device, since the software is integrated with it.

Other commercial devices such as the SPY-PHI® (Striker®, Kalamazoo, MI, USA), together with the Pinpoint® console, are capable of quantifying the relative fluorescence intensity of a tissue in real time in percentage terms with respect to another tissue previously measured in the same surgical procedure.<sup>24</sup> However, they are not currently able to provide information on fluorescence in absolute terms or to determine whether or not this fluorescence intensity is sufficient to predict, for example, the postoperative functionality of a PG. On the other hand, such a device is also not useful in the determination of parathyroid AF.

Similar to what has been previously described by other works,<sup>18,19,24,25</sup> the software devised by UIB-DMI not only takes into account the mean fluorescence intensity of the visualized PG (FI), but also assesses the fluorescence of the surrounding tissue and the relationship between the 2 (TBR). In this way, the aim is to reduce potential bias caused by interindividual variability in parathyroid fluorescence, which may arise from factors such as differences in BMI, variations in ICG distribution volumes (as the dose was not adjusted for weight), and slight variations in the focal distance of the surgical images, etc.

The results obtained in the present study with the UIB-DMI software indicate that a cut-off point for discriminating FI of 0,22, together with a cut-off point for TBR of 0,96, provides better results, in terms of NPV and AUC, detecting those patients who will not present TPH than that obtained with the determination using FI alone (FI cut-off point: 0,329), and that obtained with the isolated determination of TBR60 (TBR60 cut-off point: 1,422).

The other 2 systems for predicting postoperative normocalcemia analyzed in the same series of patients, PTH gradient and ICG-2 score, also obtained good statistically significant results. In any case, the objective assessment of fluorescence using the UIB-DMI software obtained a higher NPV, as well as a higher AUC, followed by the subjective assessment (ICG-2 score) and finally by the intraoperative PTH gradient. Therefore, the computer system devised provides greater certainty in detecting which patients will not present TPH. In fact, when multivariate analysis was performed with the 3 methods for predicting postoperative normocalcemia, only the objective assessment using the UIB-DMI software (FI+TBR60) and the intraoperative PTH gradient with a cut-off point of 71,5% turn out to be independent variables or predictors of normocalcemia, although with a notable difference in the strength of their relationship, since the prediction by means of the computer software obtains an OR almost 4 times higher than the obtained by the PTH gradient.

In developing a future diagnostic-therapeutic algorithm, fluorescence intensity measurement using UIB-DMI software, which provides a high NPV, could be considered. The PTH gradient, with its high specificity and PPV, would then be reserved for patients in whom the software fails to identify sufficiently hyperfluorescent glands during surgery. This approach could also help avoid the unnecessary administration of preventive calcium and vitamin D therapy to patients who, based on the software results, are not at risk of developing TPH. This algorithm could encourage major outpatient surgery programs without excessive additional cost, which could not only reduce the rate of TPH, but also reduce hospital stay.

These results have encouraged the realization of further studies, currently underway, for the automatic and intraoperative determination of glandular fluorescence with a new graphic interface associated to the UIB-DMI program, for its validation.

## Study limitations

This prospective study lacked a control group to directly compare the rates of TPH and other postoperative complications with and without the use of parathyroid fluorescence. However, each patient served as their own control by comparing fluorescence-based results with those obtained from the intraoperative PTH gradient.

The findings are based on a single-center analysis of 61 patients. While the study achieved statistical significance, validation of these results in larger, multicenter studies is recommended.

Additionally, the study utilized custom-designed software to analyze parathyroid fluorescence images captured with a single surgical fluorescence device. As this software could potentially be adapted for use with other fluorescence systems, future studies should explore its performance across different devices to confirm the generalizability of the findings.

## Conclusions

The presence of a single high intensity fluorescent PG determined intraoperatively by means of the computer software devised by UIB-DMI is enough to avoid TPH after TT, with a strength

of association even greater than that provided by the intraoperative PTH gradient or by the subjective measurement of fluorescence using the ICG-2 score.

## Credit authorship contribution statement

**Jaime Bonnín-Pascual:** Conceptualization, Methodology, Validation, Formal analysis, investigation, writing, visualization; **Francisco Bonnín-Pascual:** software, conceptualization, methodology, validation, formal analysis, investigation, review, supervision, project administration; **Francesc Xavier Molina-Romero:** formal analysis, methodology, review, supervision, project administration; **Cristina Álvarez-Segurado:** data curation, resources; **Marina Jiménez-Segovia:** data curation, resources; **Aina Millan-Pons:** formal analysis; **Natalia Pujol-Cano:** data curation; **Alessandro Bianchi:** data curation; **Francesc Xavier González-Argenté:** review, supervision, project administration.

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## Declaration of competing interest

The computer software resulting from this study has been entirely designed and developed by the authors Jaime Bonnín-Pascual and Francisco Bonnín-Pascual, with the methodological support of the Department of Mathematics and Computer Science of the University of Balearic Islands (UIB) and the Health Research Institute of the Balearic Islands (IdISBa), and is in the process of obtaining intellectual property registration.

No other author has related conflicts of interest or disclosures to declare.

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