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A quantitative assessment of perfusion of the gastric conduit after oesophagectomy using near-infrared fluorescence with indocyanine green

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ABSTRACT

Introduction: Anastomotic leakage is a severe complication after oesophageal resection with gastric conduit reconstruction. Poor perfusion of the gastric conduit plays an important role in the development of anastomotic leakage. Quantitative near-infrared (NIR) fluorescence angiography with indocyanine green (ICG-FA) is an objective technique that can be used for perfusion assessment. This study aims to assess perfusion patterns of the gastric conduit with quantitative ICG-FA.
Methods: In this exploratory study, 20 patients undergoing oesophagectomy with gastric conduit reconstruction were included. A standardized NIR ICG-FA video of the gastric conduit was recorded. Postoperatively, the videos were quantified. Primary outcomes were the time-intensity curves and nine perfusion parameters from contiguous regions of interest on the gastric conduit. A secondary outcome was the inter-observer agreement of subjective interpretation of the ICG-FA videos between six surgeons. The inter-observer agreement was tested with an intraclass correlation coefficient (ICC).
Results: In a total of 427 curves, three distinct perfusion patterns were recognized: pattern 1 (steep inflow, steep outflow); pattern 2 (steep inflow, minor outflow); and pattern 3 (slow inflow, no outflow). All perfusion parameters were significantly different between the perfusion patterns. The inter-observer agreement was poor − moderate (ICC:0.345,95%CI:0.164−0.584).
Discussion: This was the first study to describe perfusion patterns of the complete gastric conduit after oesophagectomy. Three distinct perfusion patterns were observed. The poor inter-observer agreement of the subjective assessment underlines the need for quantification of ICG-FA of the gastric conduit. Further studies should evaluate the predictive value of perfusion patterns and parameters on anastomotic leakage.

1. Introduction

Annually, around 600.000 patients are diagnosed with oesophageal or junctional cancer worldwide [1]. For most patients with curable disease, neoadjuvant therapy followed by oesophagectomy with gastric conduit reconstruction is the treatment of choice. Major complications related to the gastric conduit or the anastomosis, such as anastomotic leakage, abscesses, gastric conduit necrosis, or fistulas are reported in 4−30% of the cases [2,3]. Occurrence of major complications increases postoperative mortality significantly and decreases long term survival [4−6]. Poor perfusion of the gastric conduit is thought to play a significant role in the development of these complications. Therefore, interest in intraoperative perfusion assessment of the gastric conduit using optical imaging techniques is growing. The most commonly used

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technique is near-infrared fluorescence angiography with indocyanine green (ICG-FA) [7].

ICG-Fluorescence Angiography (ICG-FA) is being used extensively for perfusion assessment of tissue such as colorectal anastomoses. However, no high-quality evidence has been published yet proving the additional value of ICG-FA to prevent these anastomotic complications [8,9]. Evidence that ICG-FA reduces the risk of anastomotic leakage of the gastric conduit is also scarce [10,11]. This might be due to the subjective interpretation of the fluorescence signal, which depends on the 'real-time' interpretation of the surgeon. With this subjective approach, it can be challenging to distinguish well-perfused from poorly-perfused parts of the gastric conduit [12]. We hypothesized that quantification of the NIR fluorescence signal could be used to objectively assess various perfusion patterns [13].

Few studies have performed quantitative ICG-FA of the gastric conduit [14–17]. Time-intensity curves of proximal parts of the gastric conduit generally showed a steep inflow, with a peak immediately followed by a steep outflow. Distal parts showed a gradual increase of fluorescence intensity without reaching a peak intensity. However, in these studies, the location of the ROIs were pre-selected based on parts of the gastric conduit that were subjectively assumed by surgeons to be well perfused or poorly perfused. In addition, none of these studies plotted curves on the exact location of the anastomosis. This study aimed to identify perfusion patterns within the entire gastric conduit to differentiate between well and poorly perfused areas and to identify transition areas that could be of clinical relevance.

2. Methods

This study was reviewed and approved by the medical ethical committee 'Leiden-Den Haag-Delft' (MEC-2021-0876) and was performed according to the declaration of Helsinki (10th version, Fortaleza, 2013). Informed consent was obtained from all patients. The study was conducted in the Leiden University Medical Centre (LUMC) and the Erasmus MC Cancer Institute (EMC).

2.1. Study design and imaging protocol

This was a prospective cohort study. Twenty patients undergoing oesophageal resection with gastric conduit reconstruction with cervical anastomosis were included.

After creating the gastric conduit, it was placed on a flat surface. The Quest V2 Fluorescence imaging platform (Quest Medical Imaging, Middenmeer, The Netherlands) was positioned at a distance of 30 cm above the gastric conduit, at a 90° angle. The gastric conduit was positioned in such a way that it could be imaged completely. All ambient light was switched off and the windows were blinded. Camera settings were as follows: the gain was set on 3.5 (colour) and 20 (ICG) decibels, exposure was set on 11 (colour) and 100 (ICG) milliseconds. Five mg (2 ml of 2.5 mg/ml) ICG solution was then rapidly injected in a peripheral intravenous catheter, followed by a flush of saline. After administration of ICG, a standardized ICG-FA video was recorded for 5 min.

2.2. Outcomes

The primary outcome measure was the time-intensity curve and its derived parameters. Secondary outcomes were the inter-observer agreement of subjective interpretation of the ICG-FA videos by every upper-GI surgeon separately (HH, WS, MH, PS, SL, BW). For the subjective interpretation, surgeons were asked to mark the most distal location of the gastric conduit where perfusion was still deemed sufficient based on the ICG-FA video (i.e. the location where they would create the anastomosis in order to save as much length as possible). Finally, anastomotic complications (defined as: anastomotic leakage, fistulas originating from the gastric conduit, gastric conduit necrosis, or abscesses near the anastomosis) within 30 days from surgery were recorded.

2.3. Quantification

Postoperatively, continuous ROIs of approximately 1 cm width were drawn from proximal to distal across the gastric conduit using the Quest Research Framework (Fig. 1). Overexposed videos were excluded. From each ROI, an absolute- and normalised time intensity curve was plotted from which nine perfusion parameters were derived [18]. The following five inflow and four outflow parameters were determined: time to maximum fluorescence intensity (time to max); maximum fluorescence intensity (Imax); mean slope of the inflow (ingress rate); maximum slope of the inflow (max ingress slope); normalised maximum slope of the inflow (normalised ingress slope); maximum slope of the outflow (maximum egress slope); and the area under the curve (AUC) after 30, 60, 120 s (auc30, auc60, auc120) starting from the Imax.

2.4. Statistics

Statistical analyses were performed with R-studio software (version 4.1.0, R Foundation for statistical computing, Vienna Austria). Descriptive statistics were used to describe numerical data (mean with standard deviation (SD), median with interquartile range (IQR), or median with range). To calculate statistical differences in parameters between perfusion pattern groups (>2 groups, normal distribution), a one-way ANOVA was used. To test statistical difference in perfusion parameters between anastomotic leakage and non-leakage groups (2 groups, non-normal distribution), a Mann-Whitney *U* test was conducted. To assess inter-observer agreement, an intraclass correlation coefficient (ICC) with 95% confidence interval (CI) was calculated according to a two-way mixed modal, absolute agreement type, single measurement method. An ICC of <0.5 was defined as 'poor agreement'; ≥0.5 to 0.75 was defined as 'moderate agreement'; >0.75 to 0.90 was defined as 'good agreement'; and >0.90 was defined as 'excellent agreement' [19]. The distance between the chosen locations was measured with ImageJ (version 1.53 k, National Institutes of Health, USA) according to a previously published method [12]. The most proximal selected location (i.e. the closest to the base of the gastric conduit) was used as the baseline measurement. Figures were created in Graphpad (version 9.3.1., Graphpad software Inc. San Diego, California, USA).

3. Results

3.1. Patient characteristics

The study comprised of 20 patients, 17 (85%) males and 3 (15%) females. The median age was 63 years (IQR: 62–70.5). All patient characteristics are shown in Table 1. In total, 427 curves were plotted. The median number of curves per gastric conduit was 22 (range 18–25).

3.2. Perfusion patterns

Based on qualitative and quantitative assessment of the time-intensity curves and the corresponding perfusion parameters, three distinctive perfusion patterns of the gastric conduits were observed. These patterns were present on every gastric conduit. Pattern 1: a steep inflow with a short peak and steep outflow.

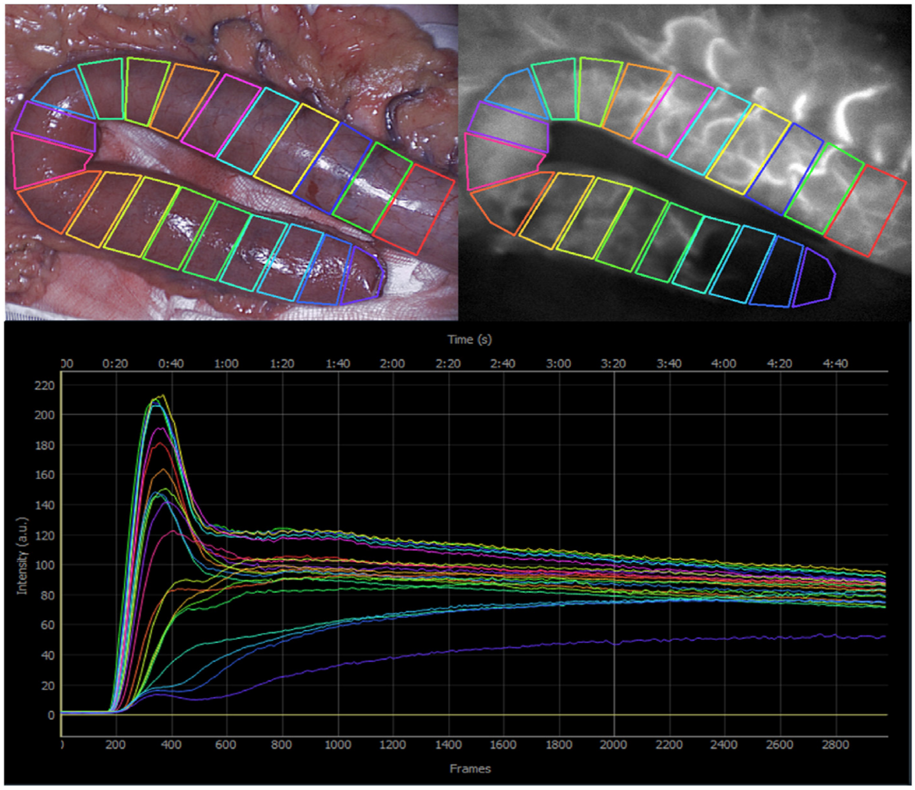

Fig. 1. Output of the Quest research framework with time-intensity curves of the corresponding ROIs.

Table 1
Patient characteristics.

Characteristic	N (%)
Sex	
Male	17 (85)
Female	3 [15]
Age (median [IQR])	63.00 [62.00, 70.50]
Hospital	
LUMC	12 (60)
EMC	8 (40)
T stage	
c1	1 [5]
c2	3 [15]
c3	13 (65)
c4	3 [15]
Surgical approach	
Transthoracic	9 (45)
Transhiatal	11 (55)
Minimal invasive	
Yes	12 (60)
No	8 (40)
Days of admission (median [IQR])	8.00 [7.00, 23.50]

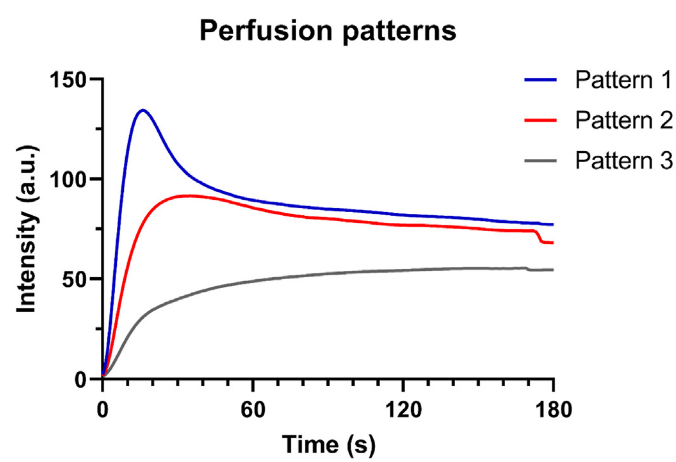

Fig. 2. Average curves of the three perfusion patterns.

Pattern 2: a steep inflow but no/little egress and an immediate plateau phase. Pattern 3: a slow gradient inflow that does not or slowly reaches its peak fluorescence intensity. Pattern 1 was present at the base of the gastric conduit that was clinically selected as a vital part of the gastric conduit. Pattern 2 displayed the transition zone and pattern 3 the ischemic zone at the tip of gastric conduit.

Based on qualitative interpretation of the curves with a quantitative check afterwards, cut-off values were established for each pattern. pattern 1: time to max $\leq$50 s and max egress ≤ -1.5; pattern 2: time to max $\leq$50 s and max egress > -1.5; and pattern 3: time to max >50 s. Fig. 2 shows the mean curves per perfusion pattern and Fig. 3 shows the separate curves with the standard deviation (top row) and the normalised curves per perfusion pattern (bottom row). The mean perfusion parameters per pattern are presented in Table 2. All perfusion parameters were significantly different between the perfusion patterns.

3.3. Subjective interpretation of ICG-FA recordings

Six surgeons reviewed all ICG-FA videos and selected the location where they would place the anastomosis. Inter-observer agreement for this subjective evaluation was poor – moderate; ICC: 0.349 (95% CI: 0.164–0.584). Per gastric conduit, the median distance between the most proximal- and distal selected location was 2.79 cm (range 0.49–6.46 cm). Supplementary Fig. 1 shows the ICC

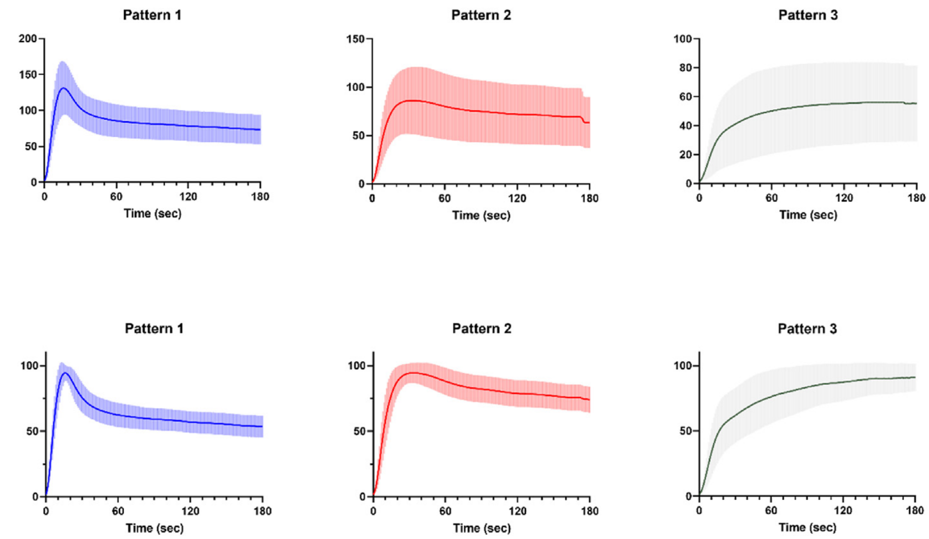

Fig. 3. The three separate perfusion patterns, with standard deviations. The top row represents the absolute curves. The bottom row represents the normalised curves.

Table 2
Quantitative perfusion parameters of all ROIs, stratified by perfusion pattern.

Perfusion parameter	Pattern 1 (mean (SD))	Pattern 2 (mean (SD))	Pattern 3 (mean (SD))	P
N (curves)	211	92	124	
Time to max (sec)	15.47 (5.22)	31.28 (11.30)	173.92 (79.68)	[a]
Imax	142.64 (33.90)	96.09 (30.99)	59.15 (27.76)	<0.001
Ingress rate (a.u./sec)	9.40 (3.44)	3.27 (1.72)	0.45 (0.39)	<0.001
Max ingress slope (a.u./sec)	16.06 (5.54)	7.67 (3.48)	3.08 (2.32)	<0.001
Max egress slope (a.u./sec)	−4.34 (1.89)	−0.96 (0.29)	−0.53 (0.61)	[a]
Normalised max slope (a.u./sec)	11.20 (2.70)	7.96 (2.63)	5.09 (2.33)	<0.001
AUC 30 (%)	78.12 (6.59)	93.19 (5.44)	96.76 (6.21)	<0.001
AUC 60 (%)	70.64 (7.16)	88.61 (7.13)	95.37 (8.38)	<0.001
AUC 120 (%)	64.85 (7.47)	83.91 (8.28)	91.59 (10.45)	<0.001

Abbreviations: sec = seconds | a.u. = arbitrary units | AUC = area under the curve.
[a] Patterns are categorized based on the time to max and the max egress slope. Therefore, these parameters are not statistically compared.

dot plot with the distance (in centimetres) between the locations selected by the surgeons.

3.4. Clinical outcome

In twelve patients (60%), quantitative analysis of the part of the gastric conduit that was used for the anastomosis showed perfusion pattern 2. In two patients (10%), pattern 1 was present at the location of the anastomosis and pattern 3 was present in six (30%) patients. Fig. 4 displays all 20 curves at the location of the anastomosis. Anastomotic leakage occurred in three patients (15%) and all complications were clinically relevant (Clavien-Dindo ≥3). In two (67%) patients with anastomotic leakage the anastomosis location showed pattern 2, and in one patient (33%) pattern 3. The median Imax was significantly lower in the anastomotic leakage group compared to the non-leakage group (97.69 vs. 46.81, p = 0.023). The ingress rate (2.13 vs. 0.85, p = 0.101) and max ingress slope (7.58 vs. 1.63, p = 0.153) did not significantly differ between the groups. Supplementary Table 1 presents all perfusion parameters stratified by anastomotic leakage.

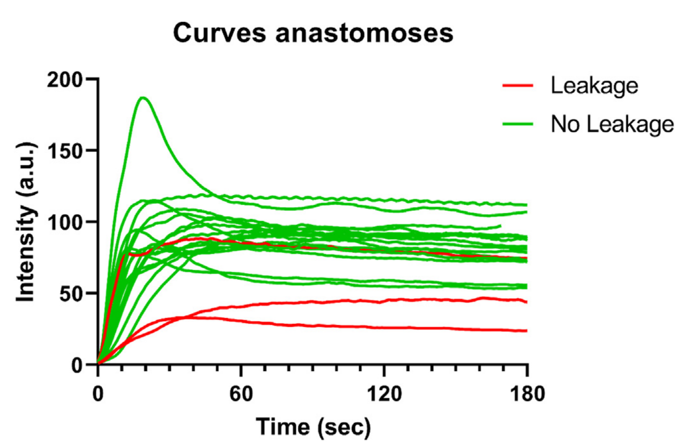

Fig. 4. All curves on locations where the anastomosis was placed. The red lines represent the patients that developed anastomotic leakage.

4. Discussion

This is the first study that used quantitative ICG fluorescence angiography to assess perfusion patterns of the complete gastric conduit after oesophageal resection. By plotting contiguous ROIs on the gastric conduit, a clear representation of perfusion of the entire gastric conduit was obtained. Based on these curves, three distinct patterns were recognized. Pattern 1 generally presented on the base of the gastric conduit, whereas pattern 3 was usually found at the distal end, corresponding with the expected area of poorest perfusion. Pattern 2 was observed in the transition zone of the gastric conduit. These three perfusion patterns were clearly distinguishable in each patient and might adequately reflect the perfusion status of the gastric conduit. Although these results suggest that quantitative ICG-FA can objectively identify differences in perfusion throughout the gastric conduit, the clinical value of these perfusion patterns should be further explored.

Another important outcome of this study was the inter-observer agreement of the surgeons' subjective assessment of the ICG-FA videos, which was considered poor − moderate (ICC = 0.349, 95% CI: 0.164−0.584). This ICC is lower than an earlier study from Hardy et al. [12], where analysis of ICG-FA videos resulted in a moderate overall ICC of 0.717 for experts and 0.641 for non-experts. Our findings underline the need for standardization and quantification of these ICG-FA assessment videos. In particular in the gastric conduit, in which a trade-off between length of the conduit and corresponding tissue perfusion is present.

This study was not powered to assess the correlation between quantitative perfusion assessment and anastomotic leakage. Although there was only a small group of patients with anastomotic leakage (n = 3), a significantly lower Imax was found in these patients, compared to patients without leakage. These findings should be interpreted with caution, as external factors such as ICG dose, administration method, and camera distance all influence Imax, even if they are standardized. Optical properties of the tissue may also influence Imax by causing scattering and absorption of the emitted photons [20]. In addition, patient-related factors, such as cardiac output and vascular status, may be of importance. Still, it remains remarkable that the two patients with the lowest Imax both developed anastomotic leakage. Other parameters, such as the ingress rate, max ingress slope, and the normalised max slope also showed a non-significant difference between the groups. Further studies should explore the clinical significance of all perfusion patterns and parameters and normalisation of the curve, and their predictive value on anastomotic leakage.

This study only included patients with cervical anastomoses. This was due to the difficulty of making standardized recordings when the gastric conduit is located in the thorax. Intrathoracic gastric conduits require imaging with endoscopic or robotic NIR fluorescence cameras. In the intrathoracic setting, standardization of distance and angle can be challenging. However, as there is more surgical possibility to adjust the anastomosis location on the gastric conduit in intrathoracic anastomosis, ICG-FA assessment may have more direct clinical consequences in this group of patients.

Several studies have been published regarding quantitative ICG-FA of the gastric conduit. Due to the use of varying analysis software, a clear comparison of the results is difficult. Similar to our study, Yukaya et al. reported perfusion patterns based on ICG-FA of the gastric conduit [15]. In this study, only two ROIs were drawn. Interestingly, three perfusion patterns were reported: the 'normal flow' pattern that was similar to our pattern 1, the 'inflow delayed' pattern that was similar to our pattern 3, and the 'outflow delayed' pattern that was similar to our pattern 2. A study by Jansen et al. [14] analysed quantitative ICG-FA videos of 20 patients undergoing oesophagectomy with gastric conduit reconstruction. Four preselected ROI's were analysed. Slope and maximum intensity decreased at more distal locations of the gastric conduit. Von Kroge et al. [17] measured the slope, time-to-max and Imax on 20 gastric conduits. Perfusion patterns were not reported, but a decrease in all three parameters was seen in the most proximal compared to the most distal part of gastric conduit. In general, these findings are in line with our data. However, in our study, continuous series of ROIs were drawn on the gastric conduit. Furthermore, we used an extensive set of perfusion parameters and we applied curve normalisation.

The authors recognize that there remains a subjective factor in the determination of the cut-off values for categorizing perfusion patterns. Cut-off values were chosen based on qualitative interpretation of the curves with a quantitative check afterwards. Although these cut-off values were subjective, the method of categorizing the curves is reproducible. A general limitation of ICG-FA assessment of gastric conduits is that there is often not a possibility to reduce length of the gastric conduit in a way that an anastomosis with the proximal oesophagus is still feasible. Therefore, some patients have an anastomosis on a location of high risk of anastomotic leakage. However, even when it is not possible to reduce length of the gastric conduit, clinical value of ICG-FA exists. In these high-risk patients surgeons should be more alert to anastomotic leakage by rapidly performing radiological assessment. Also other surgical options can be taken into account.

Larger datasets are needed to assess the prognostic value of the perfusion patterns and parameters that were found in this study. A follow-up study should be sufficiently powered to assess whether these patterns and parameters are correlated with anastomotic leakage. Also, quantitative measurements should be performed intraoperatively to facilitate change in surgical management.

In conclusion, this study described three perfusion patterns of the gastric conduit by performing quantified ICG fluorescence angiography. These perfusion patterns were clearly recognized in every patient. The exact clinical meaning of these perfusion patterns, and the corresponding parameters, should be evaluated further. The poor inter-observer agreement of subjective analysis of the videos underlines the need for quantification of NIR fluorescence imaging with ICG. Larger studies should assess the predictive value of the observed perfusion patterns and parameters on the occurrence of anastomotic leakage.

CRediT authorship contribution statement

Hidde A. Galema: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Roles, Writing − original draft, Writing − review & editing. **Robin A. Faber:** Conceptualization, Data curation, Investigation, Methodology, Roles, Writing − original draft. **Floris P. Tange:** Conceptualization, Data curation, Investigation, Methodology, Software, Visualization, Roles, Writing − original draft. **Denise E. Hilling:** Conceptualization, Data curation, Methodology, Supervision, Writing − review & editing. **Joost R. van der Vorst:** Conceptualization, Data curation, Funding acquisition, Methodology, Resources, Software, Supervision, Writing − review & editing, The Upper-GI ICG quantification study group.

Declaration of competing interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.02.017.

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