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Indocyanine Green Fluorescence in Colorectal Cancer

Elvis Vargas and Cesar Ginesta

Abstract

Fluorescence vision using indocyanine green is a surgical tool with increasing applications in colorectal cancer surgery. This tool has received acceptance in several disciplines as a potential method to improve visualization of the surgical field, improve lymph node resection and decrease the incidence of anastomotic leaks (ALs). In colorectal surgery specifically, some studies have shown that intraoperative fluorescence imaging is a safe and feasible method to evaluate anastomotic perfusion, and its use could affect the incidence of anastomotic leaks. Currently, controlled trials are carried out to validate these conclusions, as well as new indications for indocyanine green such as detection and guidance in the management of hepatic colorectal metastases, visualization of ureters and even as tumor marking and improvement the lymph node harvest of early tumors. These advances could offer great value to surgeons and patients, by improving the accuracy and results of cancer resections.

Keywords: indocyanine green fluorescence, colorectal cancer surgery, anastomotic leaks, tumor marking, lymph node harvest

1. Introduction

Some basic concepts are necessary to define as Fluorescence, which is a form of luminescence, that is, it is a process of light emission, caused by an energy, in this case it is by ultraviolet rays and that said energy is absorbed in form of electromagnetic radiation to later be emitted in the form of wavelengths and thus can be captured by an image system.

And what is the Indocyanine green? (ICG). As it is a colorant that is soluble in water and has a spectral absorption of light of approximately 800 nanometers, this spectrum is capable of binding both oxygenated and reduced hemoglobin and has 5 pharmacological characteristics: one that is not metabolized by therefore it is considered almost inert by binding to plasma proteins. Two, which is eliminated by a concentration gradient, that is, passively. Three, it is eliminated by the hepatocyte into the bile canaliculi. Four, it does not suffer from enterohepatic circulation and fifth, that its use is clearly diagnostic and not curative since its approval by the FDA in 1960 when Fox IJ of Mayo Clinic [1], showed in a work the physical and metabolic properties of this substance and its use diagnosis in liver diseases, ophthalmological, cardiac, neurological, etc.

Colorectal Cancer is the 4th most frequent in the USA, more than 135,000 new cases are diagnosed per year, of which 95,500 are colon and almost 40,000 rectal, with an estimated and unfortunate mortality of more than 50,000 cases, that is,

approximately 35% [2]. In Spain, despite the fact that a little more than 41,000 cases per year of colorectal cancer are diagnosed according to the Spanish society of medical oncology (SEOM), it constitutes the first cancer in incidence in that country, logically due to the demographic density - incidence relationship and with a mortality close to 25% [3].

Another concept we must handle is anastomotic leakage because as we all know the standard care in colon and rectal cancer to date is surgery, before or after neo-adjuvant treatment. And what is an anastomotic leak?. Since a very simple concept is the one proposed in 1991 by the study group of surgical infections in the United Kingdom [4], where it comments that "it is the escape of luminal content from the surgical union between two hollow viscera". Concept that seems very simple, but that generates a lot of controversy at least in the literature where they talk about the subject, because these works are not homogeneous many times at least in the diagnosis of this entity since there may be an anastomotic leak, for example radiological, It is that detected in imaging studies performed routinely, without the patient showing signs or clinical symptoms, but does not require changes in management. To give an example, it is the typical case of the patient who has been left with an ileostomy or protective colostomy and before closing or restoring it, imaging studies are performed and a leak is detected or the patient who is performed due to postoperative leak prevention protocols blood markers such as C-reactive protein, procalcitonin or other acute phase reactants that, despite the patient being asymptomatic, can lead to imaging studies. It can also be an anastomotic leak with a minor clinic where the patient presents intestinal or purulent discharge from the wound or drainage, associated with fever, leukocytes, presence of abscess. And they do not require surgical intervention at least initially, but lengthens the hospital stay, the use of antibiotics, the need for percutaneous drainage, endoscopic procedures, etc. And the anastomotic leak that already presents with greater symptoms, that is, with more spectacular symptoms due to a degree of severe disruption of the anastomosis and that does require surgical intervention.

And how frequent is an anastomotic leak in colorectal surgery? This will depend on the anastomosed segment. And according to this multicenter and prospective study carried out in Europe [5], the leak rate of an ileocolic anastomosis varies between 1 to 18%, of the colo-colonic between 2 to 13%, ileo-rectal between 3 to 11% and colorectal or coloanal between 5 to 21%, although on average the Spanish Rectal Cancer Project carried out in the main colorectal surgery units in Europe showed an average leakage rate for rectal anastomosis of 10% [6]. And well, the anastomotic leak is associated with a large increase in morbidity and mortality, therefore it is the most feared complication by every surgeon and any health system in the world due to expenses that generates that are calculated that they are approximately between 1.6 to 5 million Euros per year or 40,000 € approximately per patient [7].

And what are the risk factors for an anastomotic leak to occur? They are preoperative risk factors that generally depend on the patient and that are many but the most important seem to be obesity, age, sex, tobacco, alcohol, steroids, non-steroidal anti-inflammatory drugs, nutritional status, type of ASA, tumor size, the performance of chemo or radiotherapy previously and intraoperative factors that depend a lot on the surgeon and that perhaps are the ones that we can intervene or modify with some exceptions such as the distance from the anal margin, since the closer the greater the risk, but if we could modify, for example, the duration of the intervention, perioperative sepsis or need for transfusion, the performance of protective stomas that are known not to reduce the incidence of anastomotic leaks, but if the severity of their presence, the intestinal preparation that some studies say that there are no differences with their use, but others who speak that if especially when using them with antibiotics and especially orally, this for a reason perhaps

from the gut microbiota. And another very important factor is the quality of the anastomosis that we perform, because as we all know it must be tension-free and adequately vascularized, regardless of whether it is handsewn or mechanical. In addition to predicting the risk of anastomotic leak, there are many scales in the literature, some that predict morbidity and mortality and indirectly the risk of leak, such as the ASA, APACHE, POSSUM and others more specific such as the Dekker Score or Colorectal Leak Score (CLS) [8], which is perhaps the most used that it consists of 11 items that score the patient between 0 and 41, with a high risk of AL being a score greater than 11; this with a sensitivity of 67% and Specificity of 89%; However, on the internet, very practical and easy scales and calculators are available, such as the www.anastomoticleak.com [9] and the real-score that is specific for rectal cancer [10].

Now, how do we evaluate intraoperatively that our anastomosis is fine and that it will not leak? Well, there is a subjective assessment such as the visualization of the anastomosis, with the fingers we evaluate the caliber, the color of the serosa and the mucosa, which bleeds when cutting the intestine, palpating the pulses of the Riolo arch, etc. But unfortunately demonstrated by many works and corroborated by Karliczek in 2009 [11], the prediction of AL with these methods is very low and he recommends in his work to carry out some other tests to make a more objective assessment and here they enter by for example, the verification of donuts when we use mechanical suture, air leak test or with methylene blue as sometimes used by some bariatric surgeons and or the performance of intraoperative endoscopy. Regarding air leakage, in a systematic review and meta-analysis published in 2016 by a Chinese group [12], they showed that ALs are lower in patients who undergo the test vs. those who do not, but that it is not statistically significant and that when the air test is positive that this occurred according to the review of the multiple works on the subject between 1.5 to 24.7%, the AL is higher 11.4% vs. 4.2% in those that is negative. And this is the reason why it continues to be used because in the cases that are positive, some measure must be taken, be it reinforcement of the anastomosis, performance of protective ostomies or replacement thereof.

The performance of intraoperative endoscopy, this allows us to evaluate the air leak, the staple line, presence of bleeding or areas of ischemia. In fact, there is a classification in degrees proposed by Alessio Pigazzi et al. [13] of the University of Irving, California. Grade I is an anastomosis with the pink mucosa, well perfused through the entire staple line. Grade II there is ischemia or congestion in less than 30% on one side of the anastomosis and Grade III there is ischemia or congestion in more than 30% on one side of the anastomosis or any degree on both sides. In this work with 110 patients with rectal anastomosis who underwent endoscopic evaluation, 96 being Grade I, that is, normal, 10 were Grade II and 4 patients were Grade III. Of these 4, all were taken to Grade I, that is, the anastomosis was redone. And the percentage of leakage was 9.78% for the normal ones, that is grade I, that is 9 patients out of 96. Of 40% in Grade II, that is 4 patients out of 10 and 0% in grades III that they took to GI. What this study showed despite being with few patients is that Grade III patients have to have the anastomosis re-done, Grade II have a very high risk of AL, so some other measure would have to be taken and Grade I despite being normal they escape up to almost 10%; therefore, is it possible to have another method that reduces this risk of AL?

And the answer seems to be yes, and already in 2010, 50 years after the FDA approval of Indocyanine Green, a German group made the first publication on the use of green to prevent anastomotic leaks in colorectal surgery. In this work they included 402 patients divided into two groups. A group who underwent perfusion of the anastomosis with green between 2005 and 2008 and whose leak rate was 3.5% and a retrospective group between 1998 and 2003 who did not evaluate perfusion

with green and whose rate of AL was 7.5%, that is, 4% more than the group with green. This work carried out by the disciples of Dr. Christian Tons was a dedication for him who died in 2008 before its publication, this because he is considered the pioneer of the use of this technology in colorectal surgery and inventor of the first system for this, the IC View® from Pulsion Medical Systems [14].

In these almost 10 years, interesting scientific publications on the subject have begun to appear and also private companies have improved the technology, for example a Canadian commercial company called Novadaq® appears, which is leading, already financed and supported several works in this regard with its system called PINPOINT™ for laparoscopic surgery or the SPY Elite™ for open surgery [15]. In fact, this company began to be part of Stryker in 2017. And thus also intuitive since 2016 its latest generation Da Vinci Robot Xi, the Firefly system™ for fluorescence use [16]. Companies like Medtronic®, Storz® among others have also entered the market with this technology.

2. Evolution of ICG in colorectal cancer and literature experience

The first prospective, multicenter study with the use of ICG in prospective colorectal surgery was called Pillar II published in 2015 [17]. Here the utility and feasibility of the use of indocyanine green in left colectomy and anterior laparoscopic rectal resections were evaluated using the PINPOINT™ technology from Novadaq®. Among 11 hospitals in the USA, 139 patients were included, 44% operated for diverticulitis, 25% for rectal cancer and 21% for colon cancer. The feasibility of using green was 99% with 1.4% AL and the interesting thing about the work is that the use of this technology allowed 11 patients, that is, 8% to change the area where the colon was cut due to poor perfusion in the site previously chosen by the surgeon before the placement of green, and specify that of these 11 patients when doing this, none had AL.

In 2017, the first systematic summary and metanalysis with what was published up to that date on the use of green to prevent AL in colorectal surgery was published by Espin et al. [18] in this publication after the exclusion of many methodologically weak studies, they include 5 non-randomized studies with 1302 patients of which 555 were operated using ICG and 747 without ICG. The overall rate of AL in this review was 7.4%, demonstrating that ICG reduces the risk of AL in colorectal cancer with a $p = 0.06$. And specifically, it was seen that in rectal cancer the leak rate in the group with ICG was 1.1% vs. 6.1% in the group without ICG. This with a $p = 0.02$. But it also shows that when analyzing the use of green in both malignant and benign diseases, there are no significant differences in the prevention of leakage with its use. The authors in this review conclude that the literature up to that point is very heterogeneous and that new randomized, randomized and multicenter studies should be carried out for what they propose the ICEBerg Trial [19], a study carried out to evaluate the use of ICG vs. not in colorectal surgery.

Morales Conde et al. published in 2019 a prospective, monocentric study [20], that included 192 patients who were divided into 4 groups. Group A consisted of 67 patients undergoing right hemicolectomy, group B 9 patients undergoing segmental resection of the splenic angle, Group C with 81 patients undergoing left hemicolectomy, and group D with 35 patients undergoing anterior rectal resection. There was a change in the area of colon section in 35 patients, that is, 18.2%, and these were distributed in 4 (6%) of Group A of right hemicolectomy 1 (11%) of group B of segmental resection of the splenic angle, 21 (25.9%) from group C for left hemicolectomy and 9 (25.7%) from group D for anterior resection. The leak rate was 2.6% (5 patients), but none of the AL have been those that were able to change the cut site with the evaluation of the ICG.

In January 2019, another systematic review and meta-analysis on anastomotic tests in colorectal surgery in the new millennium was published that included a total of 11 articles with 3844 patients and where direct analyzes were compared between the control group, that is, the one that was not did no intraoperative leak test (No IOLT) with which it was verified with ICG or with ALT (Air Leak Test) and with IOC (Intraoperative Colonoscopy). This meta-analysis concluded that AL are higher in the No IOLT group, that is, no test compared to green with a $p = 0.0004$ and also that they are higher when compared with ALT (Air Leak Test) and IOC (Intraoperative Colonoscopy), but these data were not statistically significant [21]. In September Wexner et al. [22] recommend the quadruple evaluation of colorectal anastomoses to achieve the greatest possible safety, doing it in the following way: First ICG to decide the level of the proximal colon cut, second air test to the rectal stump, that is, before doing the anastomosis, third confirmation of the donuts from the self-suturing machine when performing the anastomosis and fourth the intraoperative colonoscopy with white light and again with green to evaluate the perfusion of the mucosa. In this reading it is recommended that what should never be lacking is the green test, but that one test does not discriminate against another.

In 2020 the FLAG randomized trial [23], with 377 cases, 187 had ICG and 190 were in the non-ICG group and they demonstrated ICG did not decrease the rate of AL of high anastomoses (9–15 cm from the anal verge), at 1.3% vs. 4.6% in the non-ICG group ($P = 0.37$). In contrast, a decrease in AL rate was found for low (4–8 cm) colorectal anastomoses (14.4% in ICG vs. 25.7% in the non-ICG group; $P = 0.04$).

Currently, some large randomized studies are being carried out such as the PILLAR III [24] and two more which are in the recruitment phase [25, 26], that is expected to have soon any results about this. And on the other hand, they are trying to investigate and elucidate a question that many colorectal surgeons ask themselves. How green should green be? so that we can say that the evaluated tissue is well perfused. And this question is the one that many of the detractors of this technique ask themselves that perhaps creates uncertainty when they face a real-time image with green. And for this the experts in conjunction with the companies are trying to find a solution and for that at least Medtronic® with its new technology called Elevisión® [27], have included a system for quantifying green in percentages, where through colors and on a percentage scale that it goes from 0 to 250% we can quantitatively know the irrigation of each area of the colon (**Figure 1**). And this has already been working and published by plastic surgeons. They have shown when performing a skin flap, that when an area of the flap has more than 33% of the most perfused point, it can be ensured that 88% of cases that area will not be necrotic. And when that value is less than 25% in 90% of the cases it will be necrotic [28, 29]. This is being tried to evaluate and agree, that is, what percentage of perfusion we should have in the colon to decide that it is well vascularized.

Now indocyanine green only serves to assess anastomotic perfusion? And well, although perhaps if it is its most important function, it may have others like the ones we show in a video published by Vargas et al. [30], in the Spanish journal of surgery of a clinical case of upper rectum cancer where we use green not only for the evaluation of the anastomotic perfusion but also for marking the tumor and as a guide at the time of lymphadenectomy, these very important points to achieve an ideal oncological or radical surgery. The important difference with the little-published marking is that we have done the marking by rectoscopy 4 hours before surgery (**Figure 2**), diluting the green ampoule in 100 cc of serum and from there we have injected 0.3 cc to 2 cm at the submucosal level distal to the tumor in order to locate the lesion intraoperatively because it is very small (only 3 cm) and to mark the lymph nodes to be resected as a kind of sentinel lymph node (**Figure 3**). What is

Figure 1.
Quantification of the vascularization of the colon.

published in the literature in this regard are still clinical cases or videos, but there is some experience in the literature regarding lymphadenectomy, especially in right colon tumors with the intention of performing surgery with D3 lymphadenectomy or complete excision of the mesocolon as shown by the work on a clinical case of Complete excision of the mesocolon in a right hemicolectomy using the Firefly fluorescence system of the Da Vinci® robot [31]. Now the injection of green in published cases is performed intraoperative technique of subserosal ICG injection with a fine needle for sentinel lymph node (SLN) [16]. This technique is feasible in very large tumors that can be located without problems via laparoscopy or robotics or that have been previously marked in a conventional way with ink (an important difference with our technique). The studies published to date do not show any statistically significant difference in the number of lymph nodes dissected using marked-oriented lymphadenectomy in advanced tumors but in early colon tumors, that is, T1 or T2. These findings have been demonstrated by Asian groups that have the most experience in this, as shown in a work published in 2015 but using

Figure 2.
Location of the tumor marked prior to surgery with ICG.

Figure 3.
Lymph node marking with ICG for lymphadenectomy.

conventional ink marking [32] and this other by, which is the only one published to date, used indocyanine green as a marker of the tumor [33]. In middle-low rectal cancer local recurrence greatly affects the treatment efficiency and the survival outcomes for patients with rectal cancer. Lateral pelvic lymph node (LPLN) metastasis (LPNM) is an important factor for local recurrence after surgery in patients with middle-low rectal cancer, and approximately 8.6% to 21.0% of patients with rectal cancer have associated LPNM. As one of the effective treatment methods, laparoscopic LPLN dissection (LPND) can significantly reduce the local recurrence rate compared with simple total mesorectal excision (TME) surgery. In clinical applications, LPND is limited by various complications because the ureters and hypogastric nerves might be damaged without efficient guidance, and for this using ICG improve the dissection increasing the numbers of lymph nodes harvested and decreasing complications [34].

There are also publications of its use in various situations, such as in the Japanese article of August 2019 by et al. [35] where this group devised a Kit that they called IRIS U Kit that allows them to transilluminate the urethra and prostate in transanal total mesorectal excision (TaTME) with the intention of avoiding one of the most feared complications of this technique, which is the injury of the urinary tract. As well as this, there are already published cases of its use, for example, in the transillumination of the ureters in very difficult cases from the surgical point of view, such as big tumors, complicated diverticulitis or pelvic surgery [36]. In 2017, a Belgian Group published a systematic review [37] of the use of green as a guide in the diagnosis and surgical treatment of hepatic or peritoneal metastases of colorectal origin. This work concluded that the use of green facilitates the detection and resection of hepatic and peritoneal metastases of colorectal origin.

3. Conclusions

Anastomotic leaks after colorectal surgery continue to be a serious public health problem; therefore the use of new therapies could minimize this problem.

With regard to standard tests for the prevention of ALs, they continue to be used for the structural evaluation of the anastomosis, but with the knowledge that their efficacy is often insufficient; for this reason the use of fluorescence allows us to evaluate anastomotic perfusion is becoming more and more important every day and gives us greater surgical safety for the benefit of the patient.

In addition, we must remember that the ICG is not only limited to the anastomotic perfusion, new functions begin to emerge, such as its use in tumor marking, lymphadenectomy, location of ureters, urethra, liver and peritoneal metastases, among other functions.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

ALS	Anastomotic leaks
ICG	Indocyanine green
SEOM	Spanish Society of Medical Oncology
FDA	Food Drug Administration

ASA	American Society of Anesthesiology
CLS	Colorectal Leak Score
ALT	Air Leak Test
No IOLT	No intraoperative leak test
IOC	Intraoperative Colonoscopy
SLN	sentinel lymph node
LPLN	Lateral pelvic lymph node
LPNM	Lateral pelvic lymph node metastasis
LPND	Laparoscopic lymph node dissection
TME	Total mesorectal excision
TaTME	Transanal total mesorectal excision

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