Title

Perfusion Assessment in Left-Sided/Low Anterior Resection (PILLAR III): A Randomized, Controlled, Parallel, Multicenter Study Assessing Perfusion Outcomes With PINPOINT Near-Infrared Fluorescence Imaging in Low Anterior Resection.

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ORIGINAL CONTRIBUTION

Perfusion Assessment in Left-Sided/Low Anterior Resection (PILLAR III): A Randomized, Controlled, Parallel, Multicenter Study Assessing Perfusion Outcomes With PINPOINT Near-Infrared Fluorescence Imaging in Low Anterior Resection

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See "Editorial" on page 921.

BACKGROUND: Indocyanine green fluoroscopy has been shown to improve anastomotic leak rates in early phase trials.

OBJECTIVE: We hypothesized that the use of fluoroscopy to ensure anastomotic perfusion may decrease anastomotic leak after low anterior resection.

DESIGN: We performed a 1:1 randomized controlled parallel study. Recruitment of 450 to 1000 patients was planned over 2 years.

SETTINGS: This was a multicenter trial.

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PATIENTS: Included patients were those undergoing resection defined as anastomosis within 10 cm of the anal verge.

INTERVENTION: Patients underwent standard evaluation of tissue perfusion versus standard in conjunction with perfusion evaluation using indocyanine green fluoroscopy.

MAIN OUTCOME MEASURES: Primary outcome was anastomotic leak, with secondary outcomes of perfusion assessment and the rate of postoperative abscess requiring intervention.

RESULTS: This study was concluded early because of decreasing accrual rates. A total of 25 centers recruited 347 patients, of whom 178 were randomly assigned to perfusion and 169 to standard. The groups had comparable tumor-specific and patient-specific demographics. Neoadjuvant chemoradiation was performed in 63.5% of perfusion and 65.7% of standard ($p > 0.05$). Mean level of anastomosis was 5.2 ± 3.1 cm in perfusion compared with 5.2 ± 3.3 cm in standard ($p > 0.05$). Sufficient visualization of perfusion was reported in 95.4% of patients in the perfusion group. Postoperative abscess requiring surgical management was reported in 5.7% of perfusion and 4.2% of standard ($p = 0.75$). Anastomotic leak was reported in 9.0% of perfusion compared with 9.6% of standard ($p = 0.37$). On multivariate regression analysis, there was no difference in anastomotic leak rates between perfusion and standard (OR = 0.845 (95% CI, 0.375–1.905); $p = 0.34$).

LIMITATIONS: The predetermined sample size to adequately reduce the risk of type II error was not achieved.

CONCLUSIONS: Successful visualization of perfusion can be achieved with indocyanine green fluoroscopy. However, no difference in anastomotic leak rates was observed between patients who underwent perfusion assessment versus standard surgical technique. In experienced hands, the addition of routine indocyanine green fluoroscopy to standard practice adds no evident clinical benefit. See **Video Abstract** at http://links.lww.com/DCR/B560.

VALORACIÓN DE LA IRRIGACIÓN DE LADO IZQUIERDO/RESECCIÓN ANTERIOR BAJA *(PILAR III)*: UN ESTUDIO ALEATORIZADO, CONTROLADO, PARALELO Y MULTICÉNTRICO QUE EVALÚA LOS RESULTADOS DE LA IRRIGACIÓN CON *PINPOINT* IMÁGENES DE FLUORESCENCIA CERCANA AL INFRARROJO EN LA RESECCIÓN ANTERIOR BAJA

ANTECEDENTES: Se ha demostrado que la fluoroscopia con verde de indocianina mejora las tasas de fuga anastomótica en ensayos en fases iniciales.

OBJETIVO: Nuestra hipótesis es que la utilización de fluoroscopia para asegurar la irrigación anastomótica puede disminuir la fuga anastomótica luego de una resección anterior baja.

DISEÑO: Realizamos un estudio paralelo, controlado, aleatorizado 1:1. Se planificó el reclutamiento de 450-1000 pacientes durante 2 años.

AMBITO: Multicéntrico.

PACIENTES: Pacientes sometidos a resección definida como una anastomosis dentro de los 10cm del margen anal.

INTERVENCIÓN: Pacientes que se sometieron a la evaluación estándar de la irrigación tisular contra la estándar en conjunto con la valoración de la irrigación mediante fluoroscopia con verde indocianina.

PRINCIPALES VARIABLES EVALUADAS: El principal resultado fue la fuga anastomótica, y los resultados secundarios fueron la evaluación de la perfusión y la tasa de absceso posoperatorio que requirió intervención.

RESULTADOS: Este estudio se cerró anticipadamente debido a la disminución de las tasas de acumulación. Un total de 25 centros reclutaron a 347 pacientes, de los cuales 178 fueron, de manera aleatoria, asignados a perfusión y 169 a estándar. Los grupos tenían datos demográficos específicos del tumor y del paciente similares. Recibieron quimio-radioterapia neoadyuvante el 63,5% de la perfusión y el 65,7% del estándar ($p>$ 0,05). La anastomosis estuvo en un nivel promedio de 5,2 + 3,1 cm en perfusión en comparación con 5,2 + 3,3 cm en estándar ($p>$ 0,05). Se reportó una visualización suficiente de la perfusión en el 95,4% de los pacientes del grupo de perfusión. El absceso posoperatorio que requirió tratamiento quirúrgico fue de 5,7% de los perfusion y en el 4,2% del estándar ($p = 0,75$). Se informó fuga anastomótica en el 9,0% de la perfusión en comparación con el 9,6% del estándar ($p = 0,37$). En el análisis de regresión multivariante, no hubo diferencias en las tasas de fuga anastomótica entre la perfusión y el estándar (OR 0,845; IC del 95% (0,375; 1,905); $p = 0,34$).

LIMITACIONES: No se logró el tamaño de muestra predeterminado para reducir satisfactoriamente el riesgo de error tipo II.

CONCLUSIÓN: Se puede obtener una visualización adecuada de la perfusión con ICG-F. Sin embargo, no se observaron diferencias en las tasas de fuga anastomótica entre los pacientes que se sometieron a evaluación de la perfusión versus la técnica quirúrgica estándar. En manos expertas, agregar ICG-F a la rutina de la práctica estándar no agrega ningún beneficio clínico evidente. Consulte **Video Resumen** en http://links.lww.com/DCR/B560. *(Traducción—Dr Juan Antonio Villanueva-Herrero)*

KEY WORDS: Anastomotic leak; Angiography; Colorectal anastomosis; Fluoroscopy; Indocyanine green; Perfusion.

Over the last 3 decades, great technical strides have been made to increase the restoration of bowel continuity after rectal surgery. However, anastomotic leaks (ALs) after low pelvic anastomosis continue to plague surgeons at a rate of 11% to 15%,[1–3] despite the use of multiple adjuncts and diversions. Leaks have far greater implications than increased length of stay, cost, and morbidity. AL has long-term complications, including poor oncologic and quality-of-life outcomes.[4]

Risk factors for AL include patient-related and modifiable factors. Patient-related factors include male sex, level of anastomosis, malnutrition, tobacco use, preoperative radiation and obesity. Although most of these factors are not modifiable, technical considerations can be modified to decrease the risks of AL.[5–8] Technical considerations include inadequate tissue approximation, poor tissue perfusion, and anastomotic tension.[6,7,9] These modifiable technical factors can have significant impact on the healing of the anastomosis. Although tension and tissue approximation can easily be assessed, assessment of malperfusion is often difficult and mostly subjective. This is even more so during laparoscopic cases, in which visualization depends on the available endoscopic technology.

Intraoperative indocyanine green (ICG) fluoroscopy is a technique that has been shown in retrospective studies to improve AL rates.[10–12] This technology allows for visualization of tissue perfusion under near-infrared light. We demonstrated in Perfusion Assessment in Laparoscopic Left-Sided/Anterior Resection (PILLAR) II, a multicentered open-labeled, prospective clinical trial, that intraoperative ICG fluoroscopy accurately assessed microperfusion of anastomosis.[6] This study further had a promising leak rate of 1.4% in patients undergoing anterior resection, with a mean level of anastomosis of 10 ± 4 cm, which is an 8- to 9-fold reduction compared with reported leaks of 11% to 15%.[1–3]

Based on our retrospective phase II trial, we hypothesized that assessment of microperfusion at the time of creation of anastomosis in patients undergoing low anterior resection for rectal neoplasms will decrease the rate of ALs. Therefore, we report a randomized phase III clinical trial to investigate the effectiveness of assessing perfusion of colon and rectal tissue using intraoperative ICG fluoroscopy.

PATIENTS AND METHODS

This is a multicenter randomized, controlled, unblinded, parallel study evaluating the effectiveness of intraoperative ICG fluoroscopy as an adjunct to standard surgical practice to assess anastomotic perfusion and reduce AL rates rate in low anterior resection (LAR) procedures when compared with standard surgical practice (clinicaltrials.gov NCT02205307). This study was given full approval by the institutional review board committee of each participating site, and all of the patients were provided informed consent in their native language before enrollment. Primary investigators were chosen based on experience with LAR and perfusion assessment. Patients scheduled for an open or minimally invasive LAR for a rectal neoplasm with curative intent with a planned anastomosis located ≤10 cm from the anal verge were enrolled. Exclusion/inclusion criteria are listed in Appendix A (see Supplemental Digital Content 1, http://links.lww.com/DCR/B559).

Subjects were randomly assigned (1:1) to either the perfusion arm or the standard arm (Fig. 1). The perfusion group received perfusion assessment with ICG fluoroscopy via PINPOINT and/or SPY Elite near infrared range fluorescence imaging (Stryker, Kalamazoo, MI) during surgery and underwent surgery according to the surgeon's standard practice. Before enrolling study subjects, participating surgeons at each center were trained to perform perfusion assessment with ICG fluoroscopy. Subjects randomly assigned to the standard arm underwent surgery according to the surgeon's standard practice.

The dose for imaging of the proximal colon was 3.0 ± 1.0 mL of a 2.5-mg/mL concentration of ICG. The dose for transanal imaging of the completed anastomosis was 3.0 ± 1.0 mL of a 2.5-mg/mL solution of ICG. ICG was administered as a tight bolus through a peripheral or central intravenous line and followed immediately by a 10-mL saline flush. The following assessments of perfusion were recorded: perfusion of proximal transection margin after inferior mesenteric artery ligation and before bowel transection and perfusion of the mucosal aspect of the completed anastomosis (with the exception of handsewn coloanal anastomoses, which involved assessment of the mucosal aspect of the proximal colon only). Subjects in the standard arm underwent an LAR according to the surgeon's standard practice only. Perfusion at the planned point of transection was characterized as follows: *inadequate*, indicating the absence of fluorescence or spotty and/or patchy areas of green fluorescence; *adequate*, indicating pale, dull, or faded green fluorescence; and *optimal*, indicating vivid, bright green fluorescence that entirely saturates the area of interest. Proximal transection was made within the area of optimal perfusion (bright fluorescence). The distal assessment was performed after the standard air leak test was completed (air leak test can be omitted in handsewn coloanal anastomoses). All of the portions of the anastomosis were imaged.

All of the subjects received the hospital/institution and surgeon's standard preoperative, postoperative, and postdischarge care with the addition of any study-specific requirements. An air leak test on all anastomoses (with the exception of handsewn coloanal anastomosis when applicable) was performed in the surgeon's standard fashion. Diversion was at the discretion of the attending surgeon.

Subject follow-up was 8 weeks postsurgery (±14 d). All of the subjects had study-specific follow-up visits on

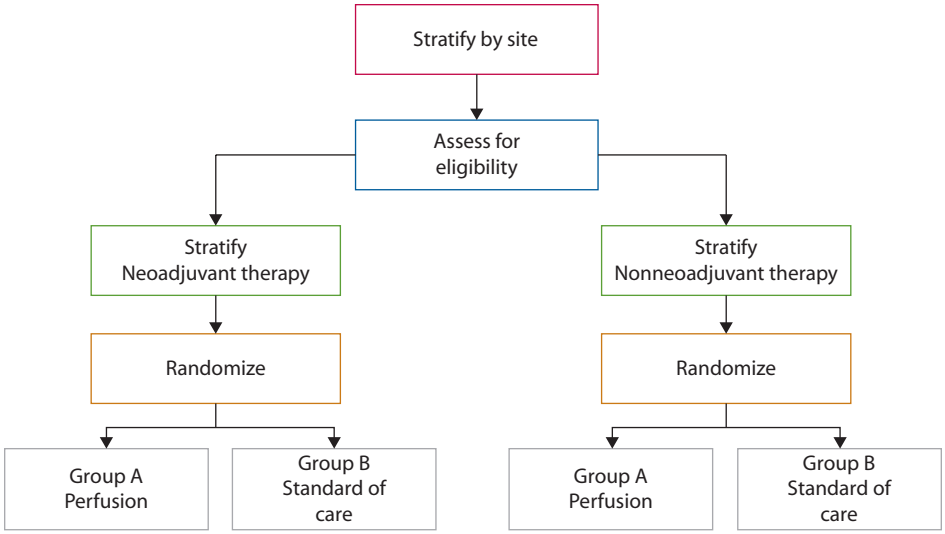

FIGURE 1. Stratification and randomization.

day 1, date of discharge, week 8, and the date of ileostomy closure (if applicable). Subjects with a discharge date later than week 8 who did not have an ileostomy were followed until the week 8 visit. All of the subjects with a diverting ileostomy had flexible sigmoidoscopy or proctoscopy and/or contrast enema to evaluate the anastomosis between 3 postoperative weeks and the week 8 visit (±14 d).

The primary end point was the rate of postoperative AL. Secondary end points were the effectiveness of assessing perfusion of colon and rectal tissue using ICG fluoroscopy and the rate of postoperative abscess requiring surgical management (including drainage performed by interventional radiology). AL was defined as any evidence of endoluminal contents (air, fluid, GI contents, or contrast material) through the anastomosis as identified by imaging, drain output or at reoperation, or by endoscopic evidence of an anastomotic defect. Subjects who presented with a clinical suspicion of AL during the study who did not require urgent reoperation had a CT scan with oral and, if diverted or if necessary, rectal contrast to confirm. All scans were reviewed by an independent radiologist for confirmation. The presence of infection or abscess thought to be related to the anastomosis was classified as an AL at the surgeon's discretion even if it could not be definitively identified as visualized during an operation or by contrast extravasation.

Statistics

The study was a 2-stage adaptive design that allows a midtrial reassessment of sample size. Available literature did not provide a precise estimate of the expected AL rate in the control group or in the treatment group. AL is reported to occur in a wide range of 3% to 20% of the time in colorectal surgery, and the risk increases for lower anastomoses.[13–17] In the limited previous experience with the PINPOINT PILLAR II study (n = 139 subjects), the AL rate was 1.4%.[6] Given the limited knowledge of control incidence and the treatment effect size, we used an adaptive design with a midtrial sample size reassessment. The planned sample size was 800, with possible early stopping for efficacy or futility at an interim analysis at 450. The planned total of 800 subjects will provide >80% power to test the 1-sided hypothesis of superiority for treatment over control in leak rate at the 0.025 significance level if the true leak rates *pc* and *pt* are 12.50% and 6.25% (a 50% relative reduction), assuming a 2-look group sequential analysis plan (with Pocock α-spending bounds and analyses at 450 and 800). If the trial did not stop at 450 patients, sample size was to be assessed at that time and possibly increased up to a maximum of 1000 subjects, using the method of Chen et al[18] and described by Mehta and Pocock.[19] Therefore, there was a plan for a minimum of 450 and a maximum of 1000 subjects to be enrolled at up to 40 centers in North America over a 2-year period. The study was stopped at 347 subjects because of low and decreasing accrual rates. All of the statistical analyses and data processing were performed using SAS Software (release 9.2; SAS Institute, Cary, NC). Analysis of hypotheses was conducted using a *z* test (ie, normal approximation to the binomial distribution, using a pooled-variance estimate and without continuity correction), using a (1-sided) significance level of 0.025. The statistical threshold for study success was sufficient visualization for assessment of blood flow and related tissue perfusion in >90% of subjects. The statistical test was a 1-sided exact binomial test of proportions. Descriptive statistics and 95% CIs were calculated. To confirm our primary efficacy interpretation, a tipping point sensitivity analysis was performed of our primary end point (AL). This analysis counted missing values for the perfusion group as no AL and counted missing values for the standard group as AL.

TABLE 1. Patient demographics

Characteristics	*Perfusion (N = 178)*	*Standard (N = 169)*
Age, mean ± SD, y	57.2 ± 11.4	57.0 ± 11.4
Men, %	61.2	58.6
BMI, mean ± SD, kg/m^2	27.8 ± 5.6	28.2 ± 5.9
Current smoker, %	27.5	18.3*
Anemia, %	14.0	14.8
Coronary artery disease %	6.2	4.1
Diabetes mellitus, %	12.4	13.6
Obesity, %	8.4	8.9
Neoadjuvant, %		
Long-course XRT	63.5	65.7
Chemotherapy	9.6	6.4
Rectal cancer site, %		
Upper	15.3	14.2
Low/mid	81.4	84.6

Chemotherapy includes only systemic treatment. Long-course XRT includes standard xeloda/5fluorouracil.
XRT = radiation therapy.
*$p < 0.05$.

RESULTS

A total of 25 centers recruited 347 eligible patients between March 2015 and February 2017, of whom 178 were randomly assigned to perfusion and 169 to the standard arm. The study was concluded at 347 patients because of low and decreasing accrual rates. A total of 343 patients were included in this population (175 in perfusion, 168 in standard). The number of patients with ileostomy who underwent endoscopy or contrast enema visit between weeks 3 and 8 was 225. Patient demographics and comorbidities including male sex, obesity (BMI >30 kg/m^2), peripheral vascular disease, and malnutrition were similar between the 2 groups. The preoperative vitals and laboratory measures were similar in both groups. Preoperative steroids were administered to 10 perfusion patients (5.8%) and 13 standard patients (7.8%; $p > 0.05$). Preoperative neoadjuvant treatment was similar in both groups, with 73.1% of perfusion compared with 72.1% of standard patients ($p > 0.05$). Low to midrectal cancer was the most common diagnosis at 82.9%, followed by upper cancer at 14.7. Table 1 lists the patient demographics.

The majority of patients underwent minimally invasive resection, 84.4% in the perfusion group compared with 86.2% in the standard group. Conversion rates were similar at 7.4% of the perfusion group compared with 4.8 of standard ($p = 0.32$). Mean level of anastomosis was 5.2 cm in both groups. Proximal diversion was similar at 73.7% of the perfusion group compared with 80.4% of the standard group ($p = 0.15$). Patients who underwent diversion had an AL in 10.7% of perfusion and 9.8% of standard. The rates of high ligation of inferior mesenteric artery, inferior mesenteric vein ligation, and splenic flexure mobilization were similar between the 2 groups (Table 2).

TABLE 2. Operative technique

Technique	*Perfusion (N = 178)*	*Standard (N = 169)*
Level of anastomosis, mean ± SD, cm	5.2 ± 3.1	5.2 ± 3.3
Operative approach, %		
Open	15.6	13.8
Laparoscopic	48.0	44.9
Robotic	36.4	41.3
Conversion, %	7.4	4.8
High inferior mesenteric artery ligation, %	83.7	88.8
Inferior mesenteric vein ligation, %	75.8	82.8
Splenic flexure mobilization, %	75.8	82.8
Proximal diversion, %	73.7	80.4
Successful visualization of perfusion, %	95.4	NA

All *p* values are nonsignificant at >0.05.
NA = not significant.

AL was diagnosed in 9.0% of perfusion compared with 9.6% of standard patients ($p = 0.37$). On multivariate regression analysis, there was no difference in AL rates between perfusion and standard (OR = 0.845 (95% CI, 0.375–1.905); $p = 0.34$). This was confirmed on tipping point sensitivity analysis, and the results were statistically nonsignificant (1-sided $p = 0.9190$), confirming the primary efficacy analysis interpretation. Of patients with AL, 6.9% required intervention in the perfusion group compared with 8.6% in the standard group. Postoperative complications were similar within both groups and are listed in Table 3. Postoperative abscess requiring surgical management was similar and reported in 5.7% of perfusion and 4.2% of standard patients ($p = 0.75$).

Of the 178 perfusion patients included, 167 (95.4%, 95% CI, 91.2%–98.0%) had sufficient visualization. All of the patients underwent assessment via PINPOINT technology.

DISCUSSION

To our knowledge, this is the only randomized clinical trial in the United States to report on the outcomes of ICG fluoroscopy on AL rates in low pelvic anastomosis.

TABLE 3. Surgical outcomes

Outcome	*Perfusion (N = 178), %*	*Standard (N = 169), %*
Anastomotic leak	9.0	9.6
Postoperative intervention	6.9	8.6
Abscess requiring drainage	5.7	4.2
Endoscopy	3.2	1.2
Ileus	3.5	7.7
Stoma complications	4.1	6.5
Wound dehiscence	1.2	0
Intraoperative hemorrhage	0	0.6
Multiorgan system failure	0.6	0
Mortality	0	0.6

All *p* values are nonsignificant (>0.05).

We have demonstrated that with PINPOINT technology using ICG near infrared range, perfusion was successfully assessed in 95.4% of patients. However, our primary end point did not support the alternative hypothesis that the proportion of patients with postoperative AL was lower in the perfusion group compared with the standard group. Similarly, we failed to demonstrate any difference in postoperative abscess requiring surgical management between the 2 perfusion assessment techniques.

The cause of anastomotic failure is multifactorial; however, adequate perfusion is absolutely necessary for optimizing anastomotic healing. The primary outcome measure of this study was AL based on the assumption that current standard of care evaluation of bowel perfusion may be subjective and inadequate. Current standards include macroscopic evaluation of transected bowel for color and brisk bleeding. However, we demonstrated in PILLAR II that standard visualization of the bowel wall did not correlate with actual perfusion in 6.5% of patients.[6] In addition, in an earlier report of ICG fluoroscopy, we demonstrated a 3-fold decrease in the AL rates during robotic LAR in patient who underwent ICG fluoroscopy.[10] The assumption was that this was because of a 19% change of resection margin that occurred because of direct visualization of bowel perfusion using ICG fluoroscopy. This was further validated by multiple studies that have demonstrated this change in surgical planning with ICG fluoroscopy.[20–26] We concluded that this change in surgical resection margin possibly led to lower AL rates such as the one seen in PILLAR II (1.4%). However, a direct 1:1 correlation has not been proven. Hellan et al[24] demonstrated a 40% change in resection margin; however, of these patients, 12% had ALs. Therefore, we cannot assert with certainty that the adequate perfusion as visualized by ICG fluoroscopy will ensure anastomotic healing.

Our results also contradict recent meta-analysis that concluded that AL was significantly reduced when using ICG fluoroscopy.[27] In fact, Blanco-Colino et al[27] in systematic review of 554 patients with rectal cancer showed an 81% reduction (OR = 0.19 (95% CI, 0.05–0.75); $p = 0.02$). They reported an AL of 1.1% (in the ICG group) compared with 6.1% in the non-ICG group. Shen et al[12] in a meta-analysis of 1177 patients reported a 16.4% change in surgical planning and a decreased AL (OR = 0.27 (95% CI, 0.13–0.53); $p < 0.001$) with ICG fluoroscopy. Both studies included the same 4 studies, which were retrospective case-matched single institutional studies.[7,10,28,29] Arezzo et al[11] in an individual participant data analysis also concluded that ICG fluoroscopy is associated with a lower AL. The low leak rates discussed may be secondary to the inherent biases of retrospective reviews.

The 2 randomized trials published to date both include a higher level of anastomosis and benign disease.[30,31] De Nardi et al[31] reported a change in transection point in 11% of patients, with AL of 6% in the ICG group compared with 9% in the control group ($p > 0.05$).[31] This study recruited 240 patients and included colorectal anastomosis between 2 and 15 cm for both benign and malignant disease. Alekseev et al[30] reported a lower AL of 14.4% in the ICG group compared with 25.7% in the non-ICG group in 216 patients undergoing low anastomosis (4 to 8 cm). They failed to show any difference in 117 patients undergoing anastomosis at 8 to 15 cm. However, there was no difference in AL requiring intervention between the 2 groups.[30] Both studies had a similar definition of AL as defined by International Study Group of Rectal Cancer.[32] Our study contradicts their findings, because we found no difference in AL (9.0% perfusion compared with 9.6% standard). Our patient population had a higher risk of anastomoses (ie, closer to the anal verge) compared with these studies. They reported only a 10% to 20% rate of preoperative radiation compared with our 65%. We also report a mean level of anastomosis of 5.2 cm and 60% male patients. The FLAG study only reported a 50% male population, with a rate of 10% of preoperative radiation. Despite, a much lower rate of preoperative radiation, higher level of anastomosis, and lower percentage of male patients, the FLAG study reported an overall leak rate of 20% for low pelvic anastomosis compared with a 9.6% leak rate in our standard arm (n = 30). We also performed 85% of our procedure via minimal invasive technique compared with 43% in FLAG. This may be a surrogate for a higher level of surgical expertise in the PILLAR group.

Our study results can be explained in few ways. First, AL is multifactorial, and this study was underpowered to show the benefit of one of these factors (perfusion). Second, the current technology does not provide qualitative data despite apparently adequate perfusion seen in 95.4% of the perfusion group. It is not ethically possible to design a study in which surgeons would take the risk of not changing transection points based on available data. We know that ICG fluoroscopy will show perfused tissue.[6] However, we do not yet understand its correlation with white light subjective methods. A third possibility is that surgeons in this study had already developed, through experience with use of ICG technology, the ability to differentiate perfusion, and the benefit of the ICG fluoroscopy was less than might have been evident with novice surgeons. Last, this study was underpowered; however, no statistical difference was found on tipping point analysis.

Limitations

The interpretation of the efficacy results of this study are limited by the fact that the study was stopped early, which may have adversely affected the statistical power of the primary and secondary end points. We also did not record change in the transection point, mainly because the clinical significance of this decision is yet to be understood and is impossible to discern. This technology is limited in its ability to measure venous outflow.

CONCLUSION

In this multi-institutional, randomized clinical trial of low pelvic anastomosis, we demonstrated that ICG fluoroscopy can visualize perfusion of anastomosis adequately. However, the addition of perfusion assessment via ICG fluoroscopy does not change the rate of AL and/or postoperative abscess.

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