Original article

Bowel function and quality of life after superior mesenteric nerve plexus transection in right colectomy with extended D3-mesenterectomy

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Abstract

Background The aim of this study was to ascertain the impact of injury to the superior mesenteric nerve plexus caused by right colectomy with extended D3 mesenterectomy as performed in the prospective multicenter trial: “Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multi-detector Computed Tomography”in which all soft tissue surrounding the superior mesenteric vessels from the level of the middle colic artery to that of the ileocolic artery was removed. **Methods** Bowel function and

gastrointestinal quality of life in two consecutive cohorts that underwent right colectomy with and without extended D3 mesenterectomy were compared. Main outcome measures were the Diarrhea Assessment Scale (DAS) and Gastrointestinal Quality of Life Index (GIQLI). The data was collected prospectively through telephone interviews. **Results** Forty-nine patients per group, comparable for age, sex, length of bowel resected but with significantly shorter follow-up time in the experimental group, were included. There was no difference in total DAS scores, subscores or additional questions except for higher bowel frequency scores in the D3 group (p=0.02). Comparison of total GIQLI scores and subscales showed no difference between groups. Regression analysis with correction for confounding factors showed 0.48 lower bowel frequency scores in the D2 group (p=0.022). Within the D3 group presence of jejunal arteries cranial to the D3 dissection area showed 1.78 lower DAS scores and 0.7 lower bowel frequency scores. **Conclusions** Small bowel denervation after right colectomy with D3 extended mesenterectomy leads to increased bowel frequency but does not impact gastrointestinal quality of life. Individual anatomical variants can affect postoperative bowel function differently despite standardized surgery

Key words: Right hemicolectomy; Colorectal cancer; Mesenterectomy; Superior mesenteric plexus; Bowel motility

Introduction

Data in the literature imply that the frequency of D3 resection for right-sided colon cancer is on the rise, and is performed in up to 75% of patients operated on for stage III disease in Japan [1]. The procedure is performed in the belief that a more complete lymphadenectomy can increase survival rates. A recent publication has mapped the lymph nodes of the right colonic D3- volume, demonstrating nodes that lie both anterior and posterior to the superior

mesenteric vessels [2]. In Western countries, the traditional surgical procedure does not include the central lymph nodes surrounding the superior mesenteric vessels. In an ongoing trial ("Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multi-detector Computed Tomography"), a complete resection of these lymph nodes from the level of the middle colic artery (MCA) to that of the ileocolic artery (ICA) origin is performed. All soft tissue surrounding the superior mesenteric vessels at this level is removed. This procedure includes the whole D3 volume including the vascular sheaths and is, therefore, a more complete dissection than the procedures usually referred to as D3-right colectomy or right colectomy with complete mesocolic excision. Anatomy books describe how individual nerves of the superior mesenteric plexus (SMP) follow arteries [3] . There is, therefore, substantial reason to believe the resection described above includes a significant segment of the SMP (Fig.1). The consequences of this denervation are not yet fully understood [4]. Intractable diarrhea is described after pancreatic surgery [5, 6], surgery for mesenteric neuroblastoma [7] and small bowel transplantation [8, 9]. A hypothesis to explain the diarrhea is that extrinsic sympathetic denervation (division of the SMP) results in stable and high-level peristaltic activity. An imbalance in the gut autonomic innervation occurs; a parasympathetic overactivity due to loss of the dampening effect of the sympathetic nerves [10]. Concerns related to bowel motility disorders after right colectomy with such an extended mesenterectomy around the superior mesenteric vessels still remain.

The aim of the study was not to evaluate cancer outcomes but rather to identify the consequences of small bowel denervation caused by extended D3 mesenterectomy on bowel function and quality of life. A secondary aim was to determine if individual anatomical variants affect postoperative bowel function differently.

Materials and methods

Patients

Experimental group: Consecutive patients included in the multicenter trial "Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multi-detector Computed Tomography" from 2012-14 at Akershus University Hospital, Oslo, Norway and Haukeland University Hospital, Bergen, Norway. These are two of the largest university hospitals in Norway providing healthcare to 838.000 people (17% of the population). *Control group:* The control group was drawn from the electronic patient journal (DIPS version 7.1) at the Department of Digestive Surgery, Akershus University Hospital, Oslo. The software has the search option for both diagnosis and procedure codes in predefined time intervals. A search for the (NOMESCO Classification of Surgical Procedures NSCP) code [11] for open right colectomy (JFB30) from 2007 to 2014 was performed. Patients operated on for benign conditions were manually excluded. .

Inclusion criteria (criteria used in the multicenter trial): Patients diagnosed with primary right-sided colon cancer (cecum, ascending colon, hepatic flexure and proximal transverse colon) under the age of 75 years, planned surgery:resection with intent to cure planned operated with intent to cure; cleared for general anesthesia; signed informed consent form.

Exclusion criteria: To maximize the external validity of the groups, all patients with conditions that can cause motility disorders were excluded: inflammatory bowel disease, celiac disease, extended bowel resection, ileostomy, incurable recurrence and those receiving adjuvant chemotherapy within the last 6 months. Patients with shorter follow-up than 6 months (the minimal interval needed for bowel adaptation after surgery [12]) were excluded. Additional exclusion criteria were: death, refusal to participate, and dementia.*Matching:* After exclusions were made an equal number of control patients were matched to the experimental group for sex and age.

1. *Anatomy:*

A 3D anatomical map of the central mesentery derived from the preoperative CT scan using open source Osirix software was used as a roadmap during the surgical procedure in the experimental group [2]. The preoperative mapping included all branches of the superior mesenteric artery (SMA) and superior mesenteric vein (SMV). This also allowed division of the experimental group into two subgroups for comparison, namely patients with one or more jejunal arteries (JA) arising cranial to the origin of the MCA and those without such JA. The basis for this grouping was that nerves follow arteries, and a JA origin proximal to the dissection area had the potential to preserve innervation; since this artery would not be divided the nerves that followed it would be preserved. No such artery would imply a more complete denervation (Fig. 2.).

Surgical procedure:

The surgical technique has been previously described [2]. Briefly, it includes the removal of all tissue anterior and posterior to the SMA and SMV including the vascular sheaths from a level 5 mm cranial to the origin of the MCA (level of the pancreatic notch) to 1 cm distal to the origin of the ICA. The medial border follows a line running along the left border of SMA. The procedure is medial to lateral and *en bloc*.

Histopathology:

The surgical specimen was removed *en bloc* at surgery. The predefined D3 area was then severed from the specimen and underwent histopathological analysis separately. After routine 48-hour fixation, tissue blocks were cut into 3-4 µm sections and stained with hematoxylin, eosin and saffron (HES), and evaluated by an experienced pathologist for the presence of nerves. Data on lengths of resected bowel were drawn from the histopathology report.

Data collection:

A single senior staff surgeon (YT) reviewed patient files and interviewed all patients in both groups by telephone regarding their bowel habits. The patients were informed that a quality of life (QoL) questionnaire would be sent to them on the same occasion.

The instruments used:

- *Diarrhea Assessment Scale (DAS):* a validated instrument for determining four aspects of diarrhea (frequency, consistency, urgency and abdominal discomfort) in the setting of oncologic treatment [13]. Results are presented on a scale of 0-12, where 0 is best, and 12 represents severe diarrhea. (The DAS is presented under table 1)
- Additional questions (3 questions were added to the scale):

-Can you postpone stools for 15 minutes? (always: 0, usually: 1, occasionally: 2, never: 3)

-Do you pass stools at night? (never: 0, occasionally: 1, usually: 2, always: 3)

-Do your bowel habits bother you? (no: 0, a little:1, much:2, very much: 3)

- *Gastrointestinal Quality of Life Index (GIQLI):* QoL was assessed through the validated GIQLI questionnaire, including subscales: physical role, large bowel function, emotional role, upper gastrointestinal tract function and meteorism [14].

The only retrospective data collected at interview was data on bowel frequency and urgency at least 6 months prior to the diagnosis of cancer. These two subscales isolated from the DAS were intended to define patients with a significant deviation in bowel habits from normal values.

Statistical analysis:

A statistician at the Helse Sør-Øst Health Services Research Center, Akershus University Hospital, Lorenskog, Norway performed the data analysis (JCL). The impact of the D3 procedure versus the D2 procedure on DAS score, bowel frequency, and the five GIQLI subscales were analyzed using linear regression. The frequency score in the DAS is truncated at the lower and upper end, but was used as if it has a one-to-one correspondence to

frequency. This applies under the assumption that few patients have stools less than once or more than four times daily. To control for possible confounding in the two groups the regression models were corrected for sex, age at time of the interview and time interval between surgery and interview. The regression equations where then in the form:

$$Y_i = \beta_0 + \beta_1 GENDER_i + \beta_2 AGE_i + \beta_3 OBSTIME_i + \beta_4 D2_i + \varepsilon_i$$

where Y is either one DAS score, bowel frequency score or a score on the GIQLI subscales. The D2 variable was coded as 1 for patients receiving the D2 procedure and 0 for those receiving the D3 procedure. All estimated differences should be read as the effect of receiving D2 instead of D3 surgery. The analysis of bowel frequency also contained a term for bowel frequency prior to surgery.

The answers to the three additional questions were given on a 0-3 scale, but recoded into a dichotomous scale and analyzed with logistic regression, controlling for patient sex, age and time from surgery to interview. A similar regression analysis was modeled to investigate the impact of previously identified anatomical variants on bowel function within the experimental group.

Sample size calculation:

Considering the fact that bowel frequency data does not demonstrate normal distribution a computer simulation based on simplified data distribution was performed. This simulation indicated that a sample size of 49 patients per group provides a study power of 80% to detect a 60% higher bowel frequency in the D3 extended mesenterectomy group. The level of significance was $p < 0.05$.

Ethics committee approval:

"Safe Radical D3 Right Hemicolectomy for Cancer through Preoperative Biphasic Multi-detector Computed Tomography" has ethical committee approval from the regional ethical committee (REK Sør-Øst no. 2010/3354), and is registered at *ClinicalTrials.gov* on May 9th,

2011 (NCT01351714). Written informed consent was obtained from patients prior to inclusion. Comparison of bowel function after D3 to conventional (D2) right colectomy was also approved (REK Sør-Øst no. 2013/206 and 2015/403-3).

Results

Patients:

a) *The experimental group:* A total of 68 patients underwent D3 right colectomy at Akershus University Hospital and Haukeland University Hospital within the period 2012-14. Forty-nine patients were included in the experimental group: 20 men (40.8%) with a median age of 67years (range 27-75 years).

The control group consisted of 49 patients operated from 2007-14, with a median age of 65 (28-75), 19 men (38.8%). The groups were comparable for age (p=0.58 Mann-Whitney), sex (p=1, X^2 test of independence) and length of bowel resected (p=0.15 student t-test). There was a significant difference in time from surgery to interview (p<0.001 Mann-Whitney test) namely 14.9 (D3) and 34.4 months (D2).

Exclusions for both groups are shown in Fig. 3.

Histopathology

All D3-volume specimens underwent a histopathological examination (34 at Akershus University Hospital and 15 at Haukeland University Hospital). All specimens had nerves around the superior mesenteric vessels, except for 2, examined at Haukeland University Hospital. In these two cases there were only slides containing lymph nodes preserved from the D3 resection which were not excluded from the analysis.

The lengths of small bowel resected are presented in table 3. (Missing data for 1 D3 (woman) and 2 D2 patients (2 women)).

Retrospective data on bowel frequency and urgency:

Preoperative stool frequency scores were 0.40 (standard deviation (SD): 0.65) in the D3 and 0.20 (SD: 0.50) in the D2 group (p=0.07, Mann-Whitney test). (Missing data: 2 men in the D3 and 4 (1 man) in the D2 group). Preoperative stool frequency was correlated to postoperative values using Pearson's test and showed a moderate (r=0.46) but significant correlation (p<0.01).

One woman in the D3 group and 4 patients (1 man) in the D2 group could not postpone bowel movements before surgery (Missing data: 3 men in the D3 and 6 (3 men) in the D2 group).

The DAS

All patients answered all DAS questions. The results of the comparison between groups (including additional questions) are presented in Table 1. The only significant difference between the groups was the stool frequency score (p=0.022).

1) *Bowel frequency.* The regression model revealed that the D2 procedure was associated with 0.48 lower bowel frequency score than the D3 procedure (p=0.022).
2) *Vascular anatomy and postoperative bowel function in patients operated with D3 resection.* The 3D anatomy reconstruction demonstrated that 39 (79.6%) of the patients had one or more JA (1-5) originating cranial to the origin of the middle colic artery (proximal to the D3 area). Regression analysis demonstrates that patients with one or more arteries cranial to the D3 area had a 1.78 lower DAS score than patients without these arteries (p=0.02, CI=3.285, 0.269), and 0.73 lower bowel frequency score (p=0.013, CI=1.300, 0.163).

Additional questions

All patients answered all additional questions at interview.

a. Question 1. Can you postpone stools for 15 minutes? Always: 17 (34.7%) vs. 25 (51.0%); usually: 19 (38.8%) vs. 12 (24.5%); sometimes: 9 (18.4%) vs. 7 (14.3%) and never: 4 (8.2%) vs. 5 (10.2%) patients for D3 and D2 patients, respectively.

b. Question 2. Do you pass stools at night? Never: 40 (81.6%) vs. 41 (83.7%); occasionally: 8 (16.3%) vs. 8 (16.3%); usually: 0 (0.0%) vs. 0 (0.0%) and always: 1 (2.0%) vs. 0 (0.0%) patients for D3 and D2 patients, respectively.

c. Question 3. Do your bowel habits bother you? No: 24 (49.0%) vs. 31 (63.3%); little: 22 (44.9%) vs. 16 (32.7%); much: 2 (4.1%) vs. 1 (2.0%) and very much: 1 (2.0%) vs. 1 (2.0%) patients for D3 and D2 patients, respectively.

No significant differences were found between groups. Scores and estimated differences between groups are presented in table 1.

Gastrointestinal Quality of Life Index (GIQLI)

A total of 88 (89.8%) patients filled out and returned the GIQLI forms. Three patients (2 men) in the D3 and 7 (4 men) in the D2 group failed to return the forms. There were no significant differences in overall or subscale GIQLI scores between D3 and D2 patients (Tab. 2).

Discussion

This article documents changes in bowel habits occurring after right colectomy for cancer with and without division of the SMP at the level of the pancreatic notch. An increased bowel frequency and urgency are found in both right colectomy groups with only a significantly higher stool frequency in the experimental group. None of the patients had more than 4 stools daily. According to our results, the increase of frequency does not manifest itself on gastrointestinal QoL.

There is little information in the literature on bowel habits after right colectomy for cancer [12, 15, 16]. These studies reveal a tendency towards higher stool frequency and softer stools

after right colectomy and are very much in accordance with our data. Ohigashi et al. [16] reported significant differences between right and left colectomies concerning stool consistency and night defecation frequency, revealing softer stool and a higher night defecation frequency in the right colectomy group when compared to the left. Ho et al. [12] found that 89 % of the patients have ≤ 2 bowel movements per day after right colectomy. The corresponding data in our study was 67.3 % vs. 87.7% for D3 and D2 patients, respectively. All patients in the D2 group reported ≤3 bowel movements daily whereas 6 of the patients (12%) in the D3 group reported 4 stools daily. Theodoropoulos et al [15] reported only on the 3 months global GIQLI score for the right colectomy group, leaving the 6 and 12 months scores out, apparently there were no differences in scores. The reported postoperative GIQLI score of 109.3 is comparable to that of our patient groups of 112.2 vs. 110.3 for D3 and D2 patients, respectively.

These articles, however, often fail to describe the extent of mesenterectomy and bowel resection. In our study, the bowel segment and the extent of resection are identical within the two groups, implying that extent of mesenterectomy, i.e. injury to the SMP is the only significant additional factor influencing bowel function. The result implies that the proportion of bowel dysfunction related to small bowel denervation is significantly lower than previously assumed [4]. To our knowledge, this is the only article presenting pre- and postoperative data on bowel habits and gastrointestinal QoL after D2 and D3 right colectomy for cancer.

It seems logical that postoperative bowel function is influenced by bowel length and bowel segment removed, as well as the extent of SMP injury. An important role of the ileocecal valve is controlling chyme passage from small to large bowel, allowing it to stay longer in the small bowel. Since most of the absorption occurs in the proximal half of the colon [17], one would expect that removal of the right colon and ileocecal valve significantly changes bowel habits. It is not surprising to note an influence of preoperative stool frequency on

postoperative bowel function, demonstrated by the moderate significant correlation found. The predictive value of this correlation should be confirmed through further research since the reliability of our retrospective data on preoperative stool frequency can be questioned.

Possible bias can result from the clinical trial setting since it entails mandatory patient information on possible side effects. In our case, enrolled patients received detailed information on the SMP and possible postoperative persistent diarrhea [4], information not provided to the control group. The clinical trial is also the only reason for the difference in follow-up time between groups, since D2 resection was not performed after the start of the D3 trial.

The cornerstone of our study is the literature that describes individual nerves of the SMP as following arteries [18-21]. The previously described extent of dissection removes all tissue surrounding the superior mesenteric vessels from the level of the pancreatic notch to 1 cm distal to the origin of the ileocolic artery including the vascular sheaths. This implies that the SMP at this level is excised and lies within the surgical specimen. Histology verifies the presence of nerves while the anatomical location defines them as part of the SMP. Moreover, the fact that a difference in bowel habits is found when anatomical variants are compared within the D3 group further strengthens the case for denervation. A broad variation in origin and number of JA was noticed [2]. One or more artery proximal to the level of dissection preserved small bowel innervation through branches following the arcades in the bowel mesentery. Our results indicate that patients with one or more JA originating proximal to the middle colic artery tend to have lower frequencies of stools and lower DAS, indicating that individual anatomical variants can affect postoperative bowel function differently despite standardized surgery. Further verification is needed since there were too few patients in the "no jejunal artery proximal to the middle colic artery" group to draw a definite conclusion.

The process of compensation that leads to bowel function improvement after surgery is still

not well understood. Animal research indicates that reinnervation after complete extrinsic denervation is possible [9, 22]. The fact that only improvement in bowel function is observed diminishes the significance in difference in postoperative follow-up time between the groups. This is because it is not expected that D3 patients will develop more diarrhea over time, but rather that the possible reinnervation can contribute to an even smaller difference.

Conclusions

The change in stool frequency that occurs after surgery in both groups can be attributed to the bowel resection. The significant additional increase only in stool frequency observed in patients who underwent D3 extended mesenterectomy indicates that transection of the SMP does not have an impact on postoperative gastrointestinal QoL. Individual anatomical variants can affect postoperative bowel function differently despite standardized surgery. Our results show that the proportion of bowel dysfunction related to small bowel denervation is significantly lower than previously assumed.

Conflict of interest: The authors declare that they have no conflict of interest

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Table 1 Summary of the data collected at telephone interviews

Individual DAS questions and scoring: Frequency of stools per day: 0: 0-1 stools per day 1: 2 stools per day 2: 3 stools per day 3: 4 or more stools per day; consistency of stools per day: 0: All stools formed 1: Stools formed and loose 2: Stools loose 3: Water stools; Urgency of stools: 0: No urgency 1: Somewhat urgent 2: Urgent 3: Very urgent; Abdominal discomfort: 0: No discomfort 1: Mild-moderate 2: Somewhat severe 3: Very severe discomfort

DAS individual questions (graded from 0-3)						DAS	Additional questions (graded 0-3)		
D3 or D2		Stool Frequency Score	Stool Consistency Score	Stool Urgency Score	Abdominal discomfort Score	Total score (0-12)	Ability to postpone stool 15 m	Need to defecate at night	My bowel habits bother me
D2	Mean	0.47	0.53	0.59	0.48	2.02	0.84	0.16	0.43
D3	Mean	1.18	0.82	0.90	0.24	3.18	1.00	0.22	0.59
Difference		-0.71	-0.29	-0.31	0.24	-1.16	-0.16	-0.06	-0.16
Regression coefficients [a]		-0.476[b]	-0.294	-0.190	0.228	-0.935	2.460[cd]	0.996[c]	0.702[c]
95% confidence		-0.881, -0.071	-0.645, 0.057	-0.603,	-0.026, 0.48	-1.998,	0.768, 8.192	0.253, 3.633	0.251, 1.927

interval			0.222		0.128			
p-value	0.022	0.100	0.361	0.078	0.084	0.133	0.995	0.492

a Controlled for age, sex and time from surgery to interview; b also controlled for preoperative stool frequency; c odds ratio estimated using logistic regression, controlled for age, sex and time from surgery to interview; d also controlled for preoperative urgency

Table 2 Results of the Gastrointestinal quality of life index (GIQLI) questionnaire, including subscales

		Subscale division of GIQLI					**Total GIQLI**
		Physical Role (0-44)	**Colon Function (0-24)**	**Emotional Role (0-32)**	**Upper GI Function (0-32)**	**Meteorism (0-12)**	**(0-144)**
D3	Mean	34.9	17.6	24.8	26.9	8.1	112,2
D2	Mean	32.7	19.1	23.5	26.6	8.3	110,3
Estimated difference (95% CI)		-1.272 (-4.98, 2.435)	0.959 (-0.789, 2.708)	-0.728 (-3.400, 1.943)	0.488 (-1.42, 2.399)	0.359 (-0.686 1.406)	0.089 (-8.67, 8.85)
p-value		0.497	0.278	0.589	0.613	0.496	0.984

GI=Gastrointestinal; CI= Confidence interval

Table 3 Comparison of variables that could affect the bowel function.

(To indicate the radicality of the mesenterectomy, numbers of lymph nodes in the D2- and the D3-area are presented)

	D2	D3	P-value
Age by the time of surgery (median)	65 (28-75)	67 (27-75)	p=0.58
Sex (number)	19 men, 30 women	20 men, 29 women	p=1
Months from surgery to interview (median)	31 (6-74)	14 (6-30)	p<0.001
Preoperative bowel frequency score (0-3)	0.20	0.40	p=0.07
Ileum resection (mean)	8,6 (SD: 10,2) cm	10,9 (SD: 6,2) cm	p=0,20
Colon resection (mean)	23,2 (SD: 7,3) cm	24,2 (SD: 7,2) cm	p=0,52
Lymph nodes total (median)	21 (10-46)	38 (22-75)	
Lymph nodes D2 area (median)	21 (10-46)	25 (13-48)	
Lymph nodes D3 area (median)	-	12 (2-54)	

SD= Standard deviation

Figure legends

Figure 1 Left - operative photograph, right - schematic. All tissue surrounding the superior mesenteric vessels is dissected free; the anterior flap of the D3 volume (AF) is rotated towards the patient's right-hand side. The middle colic artery (MCA) crosses the superior mesenteric vein anteriorly dividing into its right and left branch. The ileocolic artery (ICA) crosses the superior mesenteric vein posteriorly. A large jejunal vein (JV) crosses posteriorly to the superior mesenteric artery. ICV=ileocolic vein. The segment of the superior mesenteric nerve plexus assumed to have been excised is depicted within the dissection area, NP=nerve plexus

Figure 2 Type a: The superior mesenteric artery (SMA) with a jejunal branch proximal to the D3-area

a1: SMA with branches

a2: SMA with the nerve plexus before surgical trauma

a3: SMA with the assumed damage caused by surgery. The innervation through the arcades is in this case still preserved

Type b: The superior mesenteric artery without any branches proximal to the D3-area

b1: SMA with its branches

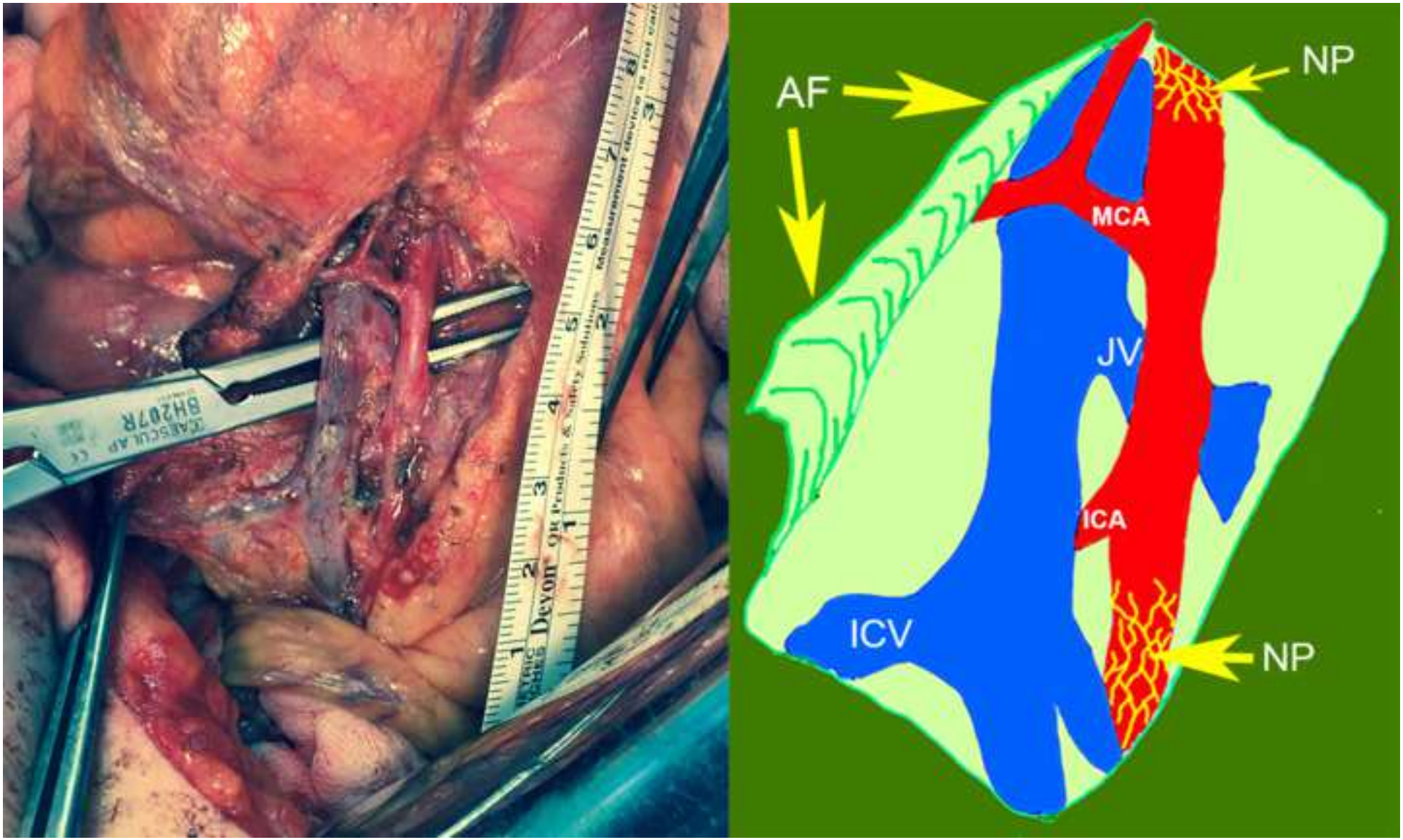
b2: SMA with the nerve plexus

b3: SMA with assumed damage done to the plexus during the D3 procedure. In this case there is no continuation of the nerves through the arcades

Figure 3 Flowchart showing patient exclusions for both patient groups. IBD=Inflammatory bowel disease.

Figure

Click here to download Figure Fig. 1.png



Figure

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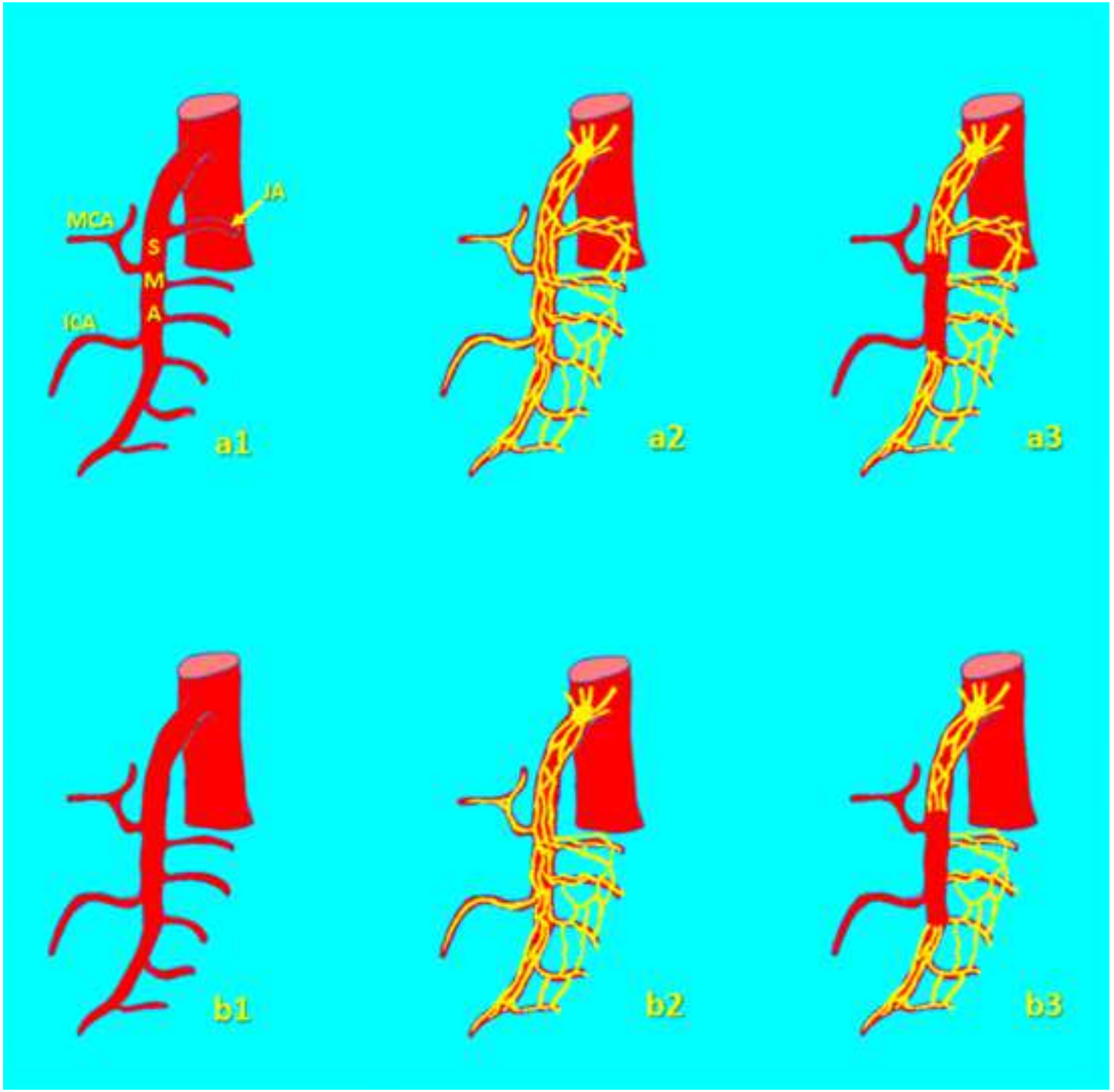

Figure

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