



# Is there any Relation between the Type of Surgery and Radiation Induced Non-rectal Bowel Toxicity in Patients with Gynecologic Cancer Receiving Adjuvant Radiotherapy?

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## OBJECTIVE

Dosimetric and clinical comparison of the effects of surgical type on the risk of developing radiation-induced non-rectal bowel toxicity in patients with gynecologic cancer who have received adjuvant radiotherapy.

## METHODS

36 patients who meet study criteria were retrospectively evaluated and classified as laparoscopy (group 1) and open surgery (group 2). Intestinal volumes that received a 10% range of total radiotherapy dose at 10% ( $V_{10\%}$ ) to 100% ( $V_{100\%}$ ) and dosimetric data ( $V_{40-45}$  Gy,  $D_{max}$ ) were obtained from the dose-volume histogram. The toxicities were graded acute and late according to Radiation Therapy Oncology Group (RTOG) scoring.

## RESULTS

The median follow-up was 55 months in group 1 and 37 months in group 2. Grade 2 acute bowel toxicity was observed in seven patients (38.9%) in group 1 and three patients (16.7%) in group 2. One patient in group 1 was diagnosed with ileus as late toxicity requiring surgery. There was no significant difference between the groups concerning surgical type and toxicity development.

## CONCLUSION

A similar risk of developing radiation-induced non-rectal bowel toxicity in patients who underwent laparoscopic or open surgery has been demonstrated in this study. However, due to the small number of patients, prospective studies with large sample sizes are needed for the correct interpretation.

**Keywords:** Enteritis; gynecologic cancer; pelvic radiotherapy; surgery; toxicity.

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## Introduction

Radiotherapy (RT) is an effective treatment modality for gynecological malignancies, either definitive or adjuvant therapy following surgery, but most patients

experience gastrointestinal complications because of radiation-induced normal tissue toxicity.[1]

Radiation enteritis is a common complaint in acute and late periods in patients who underwent abdominal and pelvic radiotherapy. Severity can be variable, and

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even in severe cases and may cause bowel obstruction, perforation, and death.[1] According to the reports of the National Cancer Institute, the prevalence of chronic radiation enteritis among women treated pelvic radiotherapy is 5-15%.[2]

The radiation-induced enteropathy is related to several factors. One of the most important risk factors is intraperitoneal adhesions that fix bowel loops due to the prior surgery. Other risk factors are total radiation dose, hypertension, diabetes mellitus, and age.[3-6]

In the last decade, laparoscopic surgery has been more preferred rather than abdominal surgery in the field of gynecological oncology, which is the result of advances in surgical techniques. When compared with laparotomy, it is thought to reduce the risk of developing adhesions and radiation-induced bowel toxicity due to be minimally invasive.[7,8] However, there is no clear evidence in this regard.

Really, is there any difference concerning development non-rectal bowel toxicity after adjuvant radiotherapy in patients with gynecologic cancer who underwent abdominal and laparoscopic surgery? To our knowledge, there is currently no randomized clinical trial comparing both types of surgery in this respect.

In this study, we analyzed 36 patients with gynecologic malignancies who were treated adjuvant pelvic radiotherapy following surgery and evaluate the effects of surgery type (laparoscopy or laparotomy) on radiation-induced non-rectal bowel toxicity by comparing dosimetric and clinical characteristics of patients.

## Materials and Methods

### Patients

Between 2010 and 2016, a total of 134 patients referred to our clinic for adjuvant pelvic radiotherapy after type 2 radical hysterectomy and bilateral salpingo-oophorectomy±lymphadenectomy were retrospectively evaluated. We classified patients into two groups as follows: Group 1 consisted of 18 patients who underwent laparoscopic surgery. According to the patient characteristics of group 1, we selected 18 of 116 patients as a control group (Group 2). The selection of patients was made using the matching method, considering the patient's age, primary tumor site, stage, lymph node dissection status and delivered RT dose. The patients' characteristics of groups are listed in Table 1.

Before the RT, all the patients were physically and gynecologically examined. Pathology and surgical reports, complete blood count, liver and kidney function

tests, preoperative radiological images of the abdomen, pelvis and chest were evaluated and staged. None of the patients had surgery-related complications. They are also assessed for inflammatory bowel disease, irritable bowel syndrome, or autoimmune disease, and if so, were excluded from this study.

### Treatment

In our study, adjuvant pelvic RT was performed for endometrial cancer stage IB with high risk up to IIIC according to the International Gynecology and Obstetrics (FIGO) staging system. Adjuvant pelvic RT was also applied in patients with cervical cancer, with parametrial invasion, positive surgical margin, nodal involvement and lymphovascular invasion. Concurrent cisplatin-based chemotherapy 40 mg/m<sup>2</sup> was added for cervical cancer patients with positive surgical margins, parametrial invasion, and positive pelvic lymph nodes. Carboplatin 5AUC and Paclitaxel 175 mg/m<sup>2</sup> sequential chemotherapy regime were delivered at 21-day intervals before RT for endometrial cancer patients with high grade, such as serous papillary or clear cell carcinoma, grade 3 adenocarcinoma and advanced stage with adnexal or serosal involvement.

### Simulation

All patients were informed about RT before the treatment. We also described our bowel and bladder preparation protocol. According to our protocol, the patients were asked to avoid gas-producing food, to use a low-fiber diet before simulation and during treatment. Additionally, 30 minutes before the planning computed tomography (CT) scan and treatment, patients were asked to urinate and after that to drink 500 cc water. The bladder volumes were checked before simulation and during treatment using ultrasonography (USG) and it was requested that the bladder should be around 150-200 cc full. In short, patients were asked to come to treatment with an empty rectum and half-filled bladder.

All patients were immobilized on the belly-board in the prone position during simulation and treatment. Planning CT was obtained with a 2.5 mm slice thickness from the level of the third lumbar vertebrae to the middle of the femurs on a GE Lightspeed 16 CT scanner. Then, all structures (normal tissues and target volumes) were contoured based on the Radiation Therapy Oncology Group (RTOG) guidelines. In all CT sections, the intestinal cavity was contoured as a bowel bag and separated from the planning target volume.

**Table 1** Comparison of patient and treatment characteristics in both groups

	Laparoscopy group		Laparotomy group		p
	(n=18)	(%)	(n=18)	(%)	
Age (mean±SD)	53.4±11.6		53.3±9.6		0.988
Primary tumor location					
Cervical cancer	7	(38.9)	8	(44.4)	0.735
Endometrial cancer	11	(61.1)	10	(55.6)	
Stage					
Cervical cancer					
Stage IB1-IIA	3	(16.7)	3	(16.7)	0.982
Stage IIB-IVA	4	(22.2)	5	(27.8)	
Endometrial cancer					
Stage I	2	(11.1)	2	(11.1)	
Stage II-III	9	(50)	8	(44.4)	
Lymph node dissection					
Yes	14	(77.8)	14	(77.8)	1.0
No	4	(22.2)	4	(22.2)	
Comorbidity (DM and HT)					
No	14	(77.8)	13	(72.2)	1.0
Yes	4	(22.2)	5	(27.8)	
Treatment					
Adjuvant RT+KT	2	(11.1)	2	(11.1)	0.738
Concurrent RT+KT	6	(33.3)	7	(38.9)	
RT alone	10	(55.6)	9	(50)	
RT dose (Gy)					
≤45	16	(88.9)	15	(83.3)	1.0
>45	2	(11.1)	3	(16.7)	
Intravaginal brachytherapy					
No	3	(16.7)	3	(16.7)	1.0
Yes	15	(83.3)	15	(83.3)	
Interval between operation-RT (median)	47.5 days		54 days		0.462

### Treatment Planning

The treatment plans were performed in the Precise planning system with forward IMRT technique using 6 MV photon beams. The radiation field was limited from the L4-L5 interspace cranially and to the trochanter major caudally. The total prescription dose was 45-54 Gy in 25-30 fractions. In the plans, the prescribed dose was normalized to cover 100% of the clinical target volume, 95% of the planning target volume. The rectum, bladder and bowel doses were defined according to tolerance doses reported in the literature.

Pelvic irradiation was performed in a linear accelerator with 80 MLC, which is capable of delivery step and shoot IMRT (Elekta Precise). Field verification was done with portal imaging every day for the first week and then weekly.

One week after completion of external beam radiotherapy (EBRT), 30 patients were treated with intra-

vaginal high dose rate brachytherapy using an Ir-192 remote afterloading technique. The prescribed dose to the vaginal surface was defined as 15-21 Gy in three fractions with a cylinder or ovoid applicators.

### Follow-Up

During radiotherapy, all patients were interviewed once a week, the number of daily stools and density, and complaints of abdominal pain and gas were questioned and reported. After the RT completed, patients were followed up every three months for the first two years, every six months between the two and five years and annually after five years. All patients were examined at each visit and assessed for late toxicity.

### Data Collection

For the purposes of our study, we performed a retrospective analysis with appropriate Local Ethics Com-

**Table 2** RTOG acute and late radiation morbidity for Lower GI/Pelvis

<b>Type of acute complication</b>	
Grade 1	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics
Grade 2	Diarrhea requiring parasympatholytic drugs (e.g. Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics
Grade 3	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)
Grade 4	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
<b>Type of late complication</b>	
Grade 1	Mild diarrhea; mild cramping; bowel movement <5 times daily; slight rectal bleeding
Grade 2	Moderate diarrhea and colic; bowel movement >5 times daily; intermittent rectal bleeding
Grade 3	Obstruction or bleeding requiring surgery
Grade 4	Necrosis/perforation/fistula

RTOG: Radiation Therapy Oncology Group

mittee approval. Informed consent was taken from all patients before treatment in order to their archived data to be used for research purposes. All details of the patients about the preoperative examination and risk factors, surgical procedure, pathology reports, adjuvant therapy and follow up evaluations were documented in each patient's file. Acute and late bowel toxicities were graded according to the RTOG gastrointestinal morbidity criteria (Table 2). Bowel complications that occurred three months after the initiation of radiation treatment were accepted as acute toxicity. The others were considered as late toxicity.

The doses received by the bowels from external radiotherapy were obtained from the dose-volume histogram as Dmax, V40 Gy, V45 Gy.

We calculated the intestinal volumes that received a 10% range of total radiotherapy dose of 10% ( $V_{10\%}$ ) to 100% ( $V_{100\%}$ ) from the treatment planning system.

### Statistical Analysis

All statistical analyses were performed using SPSS version 20 for Windows (IBM Corp., Armonk, NY). Comparison of parametric and non-parametric variables was calculated by the t-test and Mann-Whitney U test. Fisher's exact test was performed to analyze proportions. Univariate analysis was used to determine variables that potentially affect the risk of developing acute or chronic bowel toxicity. Thus, patients were classified into two groups based on primary tumor localization, tumor stage (stage I endometrial cancer and stage IB1 cervical cancer patients were

considered as early-stage and stage II-III endometrial cancer and stage IB2-II-III cervical cancer patients were considered as advanced stage), type of surgery (laparoscopic or laparotomic), presence or absence of lymph node dissection, patient age, comorbidities (hypertension, diabetes), external radiation dose ( $\leq 45$  Gy vs.  $>45$  Gy) and presence or absence of KT (concurrent or sequential) and presence or absence of brachytherapy (Table 1). Also, these predictive factors entered into the Cox regression model for multivariate analysis. Additionally, the relationship between irradiated bowel volume and bowel toxicity was compared in the two groups by independent t-test.

### Results

Thirty-six of 134 patients have been evaluated after surgery and pelvic radiotherapy. Treatment was applied with external beam radiation alone (17%) or with a combination of external beam and vaginal brachytherapy (83%). Median follow up for Group 1 was 55 months (range, 11-86 months) and for group 2 was 37 months (range, 12-83 months). No locoregional recurrence or distant metastasis was detected in any of the patients' follow-ups

We observed grade 2 acute bowel toxicity in seven patients (38.9%) in group 1 and three patients (16.7%) in group 2. Grade 3-4 acute toxicity was not seen in any patient. In addition, only one patient in group 1 developed grade 3 late bowel toxicity due to ileus at 11. month. No late complication was observed in group

2. Comparing two groups for acute and late toxicity, there was no statistically significant difference found between them ( $p>0.05$ ).

In univariate analysis, age ( $p=0.043$ ), primary tumor site (endometrial cancer) ( $p=0.011$ ) and only RT treatment without chemotherapy ( $p=0.031$ ) were found to be significant on the development of grade 2 acute bowel toxicity. Whereas, in multivariate analysis, none of the potential predictive factors were significant (Table 3). Additionally, there was no significant difference between the two groups concerning the dosimetric data (Table 4).

When comparing the intestinal volumes that received 10% range of total radiotherapy dose of 10% ( $V_{10\%}$ ) to 100% ( $V_{100\%}$ ) and treatment field size (X, Y, Z-axis) no statistically significant difference was found between two groups ( $p>0.05$ ) (Table 4).

In each group, the relationship between clinically moderate to severe acute bowel toxicity and irradiated bowel volumes ( $V_{10\%}$ - $V_{100\%}$ ) were also investigated and compared separately (Table 5). However, there was no significant difference determined for acute toxicity ( $p>0.05$ ). Because of the nonsignificant differences, ROC (Receiver operating characteristic curves) analysis was not performed. Only one patient developed late bowel toxicity (grade 3). Thus, patients' irradiated bowel volumes and late bowel toxicities were not compared.

## Discussion

Postoperatively, for cervical cancer with major risk factors and stage 2-3 endometrial cancer, the standard therapy consists of adjuvant RT±chemotherapy.

**Table 3** Univariate and multivariate analysis of the effect of various potential predictive factors on the development of grade 2 acute bowel toxicity

Variable	No. of patients	No. of patients with grade 2 acute toxicity	p		RR (95%CI)
			Univariate	Multivariate	
Age					
<60 years	25	6	0.043	0.485	0.5 (0.71-3.5)
≥60 years	11	4			
Comorbidity*					
No	27	7	0.548	0.375	0.375 (0.043-3.272)
Yes	9	3			
Primary tumor site					
Cervix	15	1	0.011	0.225	0.107 (0.003-3.977)
Corpus uteri	21	9			
Disease stage					
Early	10	2	0.378	0.223	5.296 (0.362-77.413)
Advanced	26	8			
Type of surgery					
Laparoscopy	18	7	0.180	0.934	-
Open	18	3			
Lymphadenectomy					
No	8	2	0.844	0.280	3.173 (0.391-25.732)
Yes	28	8			
Adjuvant chemotherapy					
No	19	8	0.031	0.343	0.236 (0.012-4.674)
Concurrent	13	1			
Sequential	4	1			
EBRT dose					
≤45 Gy	31	10	0.143	0.976	3369055.355(0.00--)
>45Gy	5	0			
Brachytherapy					
No	6	3	0.132	0.218	-
Yes	30	7			

Comorbidity\* (hypertension and diabetes); EBRT: External beam radiation therapy; RR: Relative risk; CI: Confidence interval

**Table 4** Comparison of doses, bowel volumes, treatment fields and volumes of bowel (10%-100) between Group 1 and 2

	Group 1 (Laparoscopy)	Group 2 (Laparotomy)	p
Dmax (Gy)			
Mean	48.8	49.1	0.913
Median (range)	48.5 (46.6-53.9)	48.2 (45.94-54.49)	
V40 (%)			
Mean	12.1	13.5	0.372
Median(range)	9 (2-45)	12.2 (3-31)	
V45 (%)			
Mean	9.5	10.3	0.563
Median (range)	6 (1-40)	8 (2-28)	
Bowel volume (cc)			
Mean	2038.82	1892.28	0.719
Median (range)	2137.75 (557.4-3417)	1867.35 (659.5-3860)	
Field size			
X axis (cm)	18.5±0.6	18.9±0.4	0.54
Y axis (cm)	18.9±0.6	20.4±0.5	0.10
Z axis (cm)	15.2±0.6	15.8±0.5	0.46
Volumes of bowel (10%-100)			
*V <sub>10%</sub>	1335.9±176.4	1316.5±127.8	0.92
V <sub>20%</sub>	1124.8±149	1157.9±116.9	0.86
V <sub>30%</sub>	951.1±128.5	1010.7±120.2	0.73
V <sub>40%</sub>	811.7±120.3	880.7±119.4	0.68
V <sub>50%</sub>	679.2±114.7	717.5±103.6	0.80
V <sub>60%</sub>	428.6±68.3	506.1±77.8	0.46
V <sub>70%</sub>	324.5±56.6	362.3±63.2	0.65
V <sub>80%</sub>	268.4±48.4	296.8±52.6	0.69
V <sub>90%</sub>	229.5±46.0	248.2±47.2	0.77
V <sub>100%</sub>	173.0±39.0	191.3±42.7	0.75

\*(Mean intestinal volumes that received 10% range of total radiotherapy dose at 10% (V<sub>10%</sub>) to 100% (V<sub>100%</sub>), cc)

Postoperative radiotherapy reduces the risk of local recurrence and death rates from endometrial and cervical cancer and improves overall survival rate. The prolongation of the lifespan increases the incidence of complications due to treatment in long-term follow-ups.

Even if the delivered radiotherapy dose is limited because of the normal tissue doses, radiation enteritis is the most common complication of abdominal and pelvic radiation treatment.[9] Additionally, surgery, especially the open surgery-related adhesions may prevent mobilization of the bowel loops, these fixed bowel loops may stay in high dose area and the toxicity due to radiotherapy might increase.[10] Some reports showed that laparoscopic surgery could decrease bowel side effects compared to the open surgery in patients who underwent pelvic radiotherapy.[11,12] The underlying reason for this is thought to be that laparoscopy leads to less adhesion than open surgery. Otherwise, Weiser

et al. showed that transperitoneal selective paraaortic lymphadenectomy is associated with a higher frequency of certain postirradiation regional enteric complications.[13] In our study, eleven of 36 patients underwent the paraaortic lymphadenectomy, but when we compared two groups with or without paraaortic lymphadenectomy and also the surgery types (laparoscopic or abdominal) for the patients who had paraaortic lymphadenectomy, there were no statistically significant differences found.

In the literature, many patient and treatment-related factors have been defined for the development of radiation enteritis. One of these is the patient's age at diagnosis. There are some studies that reported the elderly patients to have a higher incidence of complications after definitive radiotherapy.[14,15] When we analyzed the results of our study, there were eleven patients over 60 years of age. Four of these patients had grade 2≤ acute bowel toxicity, and in the univariate

**Table 5** Comparison of intestinal volumes and severity of diarrhea in Group 1 and Group 2 patients

Parameters	Group 1		p
	Grade 0-1	Grade 2-3	
V <sub>10%</sub>	1356.8±242.8	1303.0±268.5	0.88
V <sub>20%</sub>	1097.7±190.7	1167.5±257.0	0.82
V <sub>30%</sub>	923.9±158.7	993.8±232.0	0.80
V <sub>40%</sub>	805.1±157.2	822.1±201.9	0.94
V <sub>50%</sub>	684.6±161.7	670.7±165.4	0.95
V <sub>60%</sub>	428.8±97.4	428.3±96.0	0.99
V <sub>70%</sub>	324.8±77.1	324.0±88.4	0.99
V <sub>80%</sub>	275.7±68.6	256.9±68.5	0.85
V <sub>90%</sub>	234.9±65.5	221.1±64.4	0.88
V <sub>100%</sub>	181.9±57.8	159.0±47.6	0.78
Parameters	Group 2		p
	Grade 0-1	Grade 2-3	
V <sub>10%</sub>	1364.1±132.2	1078.4±433.3	0.42
V <sub>20%</sub>	1197.3±119.4	960.7±417.9	0.46
V <sub>30%</sub>	1044.7±121.1	840.9±369.1	0.54
V <sub>40%</sub>	913.4±132.3	717.5±314.5	0.55
V <sub>50%</sub>	753.8±110.8	536.0±313.9	0.45
V <sub>60%</sub>	504.7±78.0	513.2±308.9	0.96
V <sub>70%</sub>	349.2±52.2	427.8±325.4	0.83
V <sub>80%</sub>	290.2±44.6	329.7±265.8	0.89
V <sub>90%</sub>	239.3±39.4	292.6±241.1	0.84
V <sub>100%</sub>	178.5±35.4	255.6±216.3	0.75

Continuous variables are presented as mean±standard error of mean

analysis, older age was found as a risk factor that increases toxicity (p=0.043).

Other important risk factors for RT-related morbidity are total radiation dose and irradiated volume.[16-18] Former studies about radiation-induced bowel toxicity reported that approximately 2-9% of the patients developed radiation enterocolitis requiring surgery when total doses of 45-55 Gy pelvic radiotherapy was used with conventional fractionations.[5,19,20] Thus, it has been suggested in recent years that the dose is important concerning bowel complication and that the EBRT dose should not exceed 54 Gy.[3] In this study, the mean dose was 45 Gy, five patients received pelvic radiotherapy over 45 Gy and the maximum dose was 54 Gy. Since most of the patients received 45 Gy EBRT, a threshold dose that increased bowel toxicity was not determined as in Chen et al.'s study.[3]

When we analyzed our treatment field in X, Y, Z axis, compared the surgical types (laparoscopic surgery or laparotomy) by univariate analysis, and there was no statistically significant difference found.

Additionally, there are some studies investigated intestinal volumes that received a10% range of total radiotherapy dose at 10% (V<sub>10%</sub>) to 100% (V<sub>100%</sub>) and evaluated whether previous abdominal surgery affected the radiation-induced bowel toxicities.[21] However, to our knowledge, there is no study compared the intestinal volumes (V<sub>10%</sub> to V<sub>100%</sub>) of patients undergoing abdominal surgery or laparoscopic surgery. In our study, we evaluated whether the surgical type effects bowel complications using the intestinal volumes (V<sub>10%</sub> to V<sub>100%</sub>), and there was no statistically significant difference between the two groups (abdominal or laparoscopic surgery) in the univariate analysis. Thus, ROC analyzes used in previous studies were not performed in this study.

Several studies revealed that radiation-induced enterocolitis has mostly occurred in the ileum [9] because the ileum has a more radiosensitive structure compared to the rectum and sigmoid. In our study, only in one patient in group 1 developed grade 3 ileus as late toxicity. When we looked at this patients' medical

history, she did not develop acute bowel complications during radiotherapy. Moreover, there was no underlying factor found that cause the ileus.

Currently, as a result of improvements in radiotherapy techniques, radiation-induced toxicity is now less observed. In particular, with the widespread use of intensity-modulated radiotherapy (IMRT), both a homogeneous dose distribution is achieved in the target volume and organs at risk receive the lower dose. [1] However, when the studies that determined the risk factors for bowel toxicities were evaluated, the 3D conformal technique was used in most of them.[9,22] In this study, bowel complications were less observed because patients were treated with forward IMRT technique and between dosimetric parameters and bowel side effects were not able to determine any relation. Additionally, we performed radiation therapy in the prone position. According to some previous studies, it might significantly reduce the irradiated bowel-volumes and contribute to the decrease the radiation-induced bowel toxicity.[22] In our opinion, another factor that reduces toxicity is the intestinal and bladder preparation protocol used. During the treatment, daily control of bladder filling with USG prevented the inter-fractional change of irradiated bowel volume.

There are some limitations to our study. For example, the sample size is relatively small due to the retrospective character of this study. In addition, no radiopaque material has been used during planning tomography scans, but target volumes and OAR have been contoured by the same experienced radiation oncologist so that at least the inter-observer variability has been removed. The other limitation, some studies revealed that body mass index (BMI) was a risk of a factor for bowel complication, but in our study, we did not evaluate the BMI.

We should note that the main advantage of our study is due to CT-based planning. The dosimetric and volumetric assessment was performed besides the clinical evaluation.

## Conclusion

In our study, our hypothesis is that laparoscopic surgery is a minimally invasive surgical type, and therefore, can reduce complications during and after treatment. We compared the two surgical groups (laparoscopic or abdominal surgery) but did not find a significant difference between them. However, due to the small number of patients, it is difficult to make a correct interpretation. Further prospective studies with

large sample sizes are needed to investigate whether the surgical type plays any role in the development of radiation-induced bowel complications.

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**Conflict of Interest:** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Ethics Committee Approval:** For purposes of our study, we performed a retrospective analysis with appropriate Local Ethics Committee approval dated October 2, 2018, number of A20.

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