

# Effect of a uterine manipulator on the incidence of lymphovascular propagation (LVSI) in treatment of endometrial cancer

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## Research Article

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# Abstract

## Background

Endometrial cancers are among the epithelial malignancies of the lining in the uterine cavity. The invasion of carcinoma into the lymphovascular space (LVSI – lymphovascular space invasion) is considered a risk factor for the course of the disease. In our study, we investigated the potential effect of an intrauterine manipulator on the presence of LVSI in a definitive preparation.

## Methods

Based on the inclusion and exclusion criteria, we were retrospectively evaluating 170 female patients. During endoscopic procedures we use a uterine manipulator. As the primary objectives were determined to be the finding of the difference in the incidence of LVSI in female patients with and without an intrauterine manipulator. As the secondary objective was set to determine the effect of a type of an intrauterine manipulator on the incidence of LVSI. Tertiary we analysed grading of tumor, myometrial invasion and method of obtaining primary histology in connection to the incidence of LVSI.

## Results

We used logistic regression to identify the risk factors for LVSI. Using a manipulator during a surgery was not associated with the occurrence of LVSI (with a manipulator vs. without, 11.5% vs. 21.7%; OR 1.8; 95% CI 0.73–4.39;  $p = 0.199$ ). The type of method used to obtain the primary histology had a statistically significant effect on the incidence of LVSI in our set (hysteroscopy vs. curettage; OR 4.27; 95% CI 1.39–13.07;  $p$  value = 0.011); grading and TNM (especially the grading G2 and G3 and TNM 1b).

## Conclusions

In our study we have not confirmed the effect of a uterine manipulator on the possible increase of LVSI positive cases. Similar results have been published in other studies.

The secondary analysis indicated a higher incidence of LVSI in the female patients diagnosed with curettage than in those who underwent hysteroscopy. Further studies will be needed to confirm this phenomenon.

## Background

Endometrial cancers are among the epithelial malignancies of the lining in the uterine cavity [1]. Based on the currently available data from the National Health Information Center, according to the Register of Malignant Diseases of 2012 endometrial cancer ranks in the 4th place of the most common malignancies in women in Slovakia. Altogether, 914 cases were newly diagnosed [2]. In 2020, according to the European Cancer Information System - ECIS, the estimated number of new cases in Slovakia was 1081, which corresponds to 8.0%. The estimated world standardised incidence ratio – (WSR) of 19.9 per

100,000 population, which ranks in the third place in the most common malignancies in women, right after breast and colorectal cancer [3].

The invasion of carcinoma into the lymphovascular space (LVSI – lymphovascular space invasion) is considered a risk factor for the course of the disease [4,5,6,7]. In the histological view, LVSI is characterized by the presence of tumor cells in the tumor periphery of the lymphatic space and the adjacent non-invaded myometrium with the identified epithelial tumor cells [8].

Based on the recommended procedures of ESGO-ESTRO-ESP (2020) in the management of endometrial cancer, in the event of significant LVSI positivity, the female patients are included in the upper-medium risk group [9]. A confirmation of LVSI in the preparation is of diagnostic, therapeutic and theoretical importance [10,11,12,13]. The incidence of LVSI in first-stage tumors is around between 16,0-25,1% [5,14]. The LVSI intercepted in the preparation of low-risk groups of female patients changes the strategy of oncological therapy. In the case of LVSI positivity, adjuvant radiotherapy is indicated [15]. Therefore, it is important to correctly describe and evaluate this [16,17].

In 1988, Dr. Charles Koh in his work published his experience with a patented uterine manipulator, which he used during total laparoscopic hysterectomy (TLH) and which bears his name [18].

A combination of a Hegar dilator with a McCartney tube (LiNA Medical), with their joint fixation similar to laparoscopically assisted vaginal hysterectomies (LAVH), is also used to perform TLH and robotically assisted hysterectomies [19,20].

In several papers, the possibility of manipulating the histo-pathological characteristics of the preparation and the impact on the subsequent treatment, and on the overall survival of female patients, are considered [21,22]. In our study, we investigated the potential effect of an intrauterine manipulator on the presence of LVSI in a definitive preparation.

## Methods

Female patients with a planned endometrial cancer treatment were included in the surgical program. At our workplace, we perform hysterectomy using abdominal, vaginal, laparoscopic assisted vaginal (LAVH), total laparoscopic (TLH), or laparoscopic robotic assisted (RH). During the laparoscopic approach (LAVH, TLH, RH) we use an intrauterine manipulator. We use two types of uterine manipulators, namely the Koh-RUMI manipulator (Cooper Surgical) and the Hegar dilator in combination with the McCartney tube (LiNA Medical).

In the group of female patients without a uterine manipulator (NonManip), we included the female patients who were operated by abdominal approach without no need to use a manipulator. These female patients did not meet the predominantly anesthesiological requirements for the tolerance of the Trendelenburg position; respectively, the likelihood of adhesions in the abdominal cavity after previous laparotomy operations was there. Therefore, from a safety point of view, due to the risk of damage to the

abdominal organs and the need for extensive adhesiolysis, the primary endoscopic surgery was not performed.

The female patients suitable for endoscopic performance to laparoscopic, respectively the robotic hysterectomies, in whom the use of a uterine manipulator (Manip) was planned, were assigned random into two groups. During the surgery, in one group, we used the Hegar's dilator (ManipHe) and in another group, the Koch-Rumi manipulator (ManipKoRu). The entry criteria were defined as follows: histologised endometrioid endometrial cancer, planned primary surgical treatment - hysterectomy, medical condition enabling anesthesia and surgery, and the pre-surgical clinically-determined stage of the disease according to MRI or ultrasound to stage 1 disease. The exclusionary criteria were set as follows: non-endometrioid type of tumor in definitive histology, stage 2 of a disease and higher, previous chemo or radiotherapy, inability to adequately complete the surgery, and a uterine perforation during surgery. Prior to the commencement of the study, a meeting with the histopathology staff was performed to evaluate LVSI according to the standard procedures. The CD31 immuno-histochemical staining was used to diagnose LVSI. We monitored several parameters, namely the age, parity, BMI, history of abdominal operations, method of primary histologisation of the process (curettage or hysteroscopy), method of surgery, type of intrauterine manipulator, histological type of tumor, extent of disease (TNM), grading, presence of LVSI, length of surgery, blood loss, complications and day of discharge. The study received the approval No.29/2021 from the Ethics committee F.D.Roosevelt hospital . As the primary objectives were determined to be the finding of the difference in the incidence of LVSI in female patients with and without an intrauterine manipulator. As the secondary objective was set determine the effect of a type of an intrauterine manipulator on the incidence of LVSI. Tertiary we analysed grading of tumor, myometrial invasion and method of obtaining primary histology in connection to incidence of LVSI.

## Results

226 patients were enrolled in the overall study during the period 2015-2020. Based on the inclusion and exclusion criteria, we were evaluating 170 female patients. The drop-out rate is at 24.8%. 83 were included in the NonManip arm, 40 in ManipHe, and 47 in ManipKoRu. A statistical computer program SPSS 26.0 was used for statistical analysis.

We were comparing the inter-connected variables (the age, BMI, time of surgery and blood loss) evaluated by the Mann-Whitney U test (they were tested for normality, in all cases the normality was rejected); the table (Table No. 1) shows the median (range). The categorical or ordinal variables are reported as quantity (%) and the statistical significance was examined using  $\chi^2$  or the Fisher's exact test.

Tab. No.1

The set characteristics comparison.

<b>Comparison of characteristics</b>				
	<b>In sum (n=170)</b>	<b>Without a Manipulator (NonManip) (n=83)</b>	<b>With a Manipulator (Manip) (n=87)</b>	<b>p</b>
Inter-connected	median	median	median	
Age (years)	64 (26 – 91)	67 (40 – 91)	63 (26 – 79)	0,001
BMI	32,76 (19,5 – 58,1)	33,2 (20,1 – 58,1)	32,3 (19,5 – 45,9)	0,172
Surgery time (min.)	140 (35 - 340)	137 (35 - 340)	145 (50 - 315)	0,09
Blood loss (cc)	50 (5 - 2000)	135 (20 - 2000)	30 (5 - 300)	<0.001
Categorical	count (%)	count (%)	count (%)	
<b>Grading</b>				
G1	106 (62,4)	46 (55,4)	60 (69)	0,164
G2	45 (26,5)	25 (30,1)	20 (23)	
G3	19 (11,1)	12 (14,5)	7 (8)	
<b>TNM</b>				
1a	118 (69,4)	51 (61,4)	67 (77)	0,031
1b	52 (30,6)	32 (38,6)	20 (23)	
<b>Histologisation (n=168)</b>				
hysteroscopy	61 (36,3)	28 (34,1)	33 (38,4)	0,631
curettage	107 (63,7)	54 (65,9)	53 (61,6)	
LVSI	28 (16,5)	18 (21,7)	10 (11,5)	0,098
<b>Manipulator type</b>				
ManipHe	47			
ManipKoRu	40			

We used logistic regression to identify the risk factors for LVSI. At first, a separate logistic model was calculated for all potential variables (using a manipulator, grading, TNM, and a form of acquiring direct histology). Subsequently, a regressive method was used to determine the independently significant

variables in the final model, where the effect of the variable is expressed as an odds ratio (OR) along with a 95% confidence interval (CI). All models were adjusted for age and BMI (Table No. 2).

Tab. No. 2

The LVSI comparison.

Logistic regression for LSVI dependent variable				
	Number	% positive LSVI	OR (95% CI)	p
Manipulator				
Yes (Manip)	87	11,5	1	
No (NonManip)	83	21,7	1,795 (0,73 – 4,39)	0,199
Grading				0,006
G1	106	8,5	0,22 (0,07 – 0,74)	0,015
G2	45	28,9	0,91 (0,28 – 2,96)	0,881
G3	19	31,6	1	
TNM				
1a	118	7,6	1	
1b	52	36,5	6,71 (2,66 – 16,97)	<0,001
Histologization (n=168)				
hysteroscopy	61	6,6	1	
curettage	107	22,4	4,27 (1,39 – 13,07)	0,011

Using a manipulator during a surgery was not associated with the occurrence of LVSI (with a manipulator vs. without, 11.5% vs. 21.7%; OR 1.8; 95% CI 0.73–4.39; p = 0.199). The type of method used to obtain the primary histology had a statistically significant effect on the incidence of LVSI in our set (hysteroscopy vs. curettage; OR 4.27; 95% CI 1.39–13.07; p value = 0.011); grading and TNM (especially the grading G2 and G3 and TNM 1b).

Tab. No. 3

The manipulators comparison.

<b>Comparison of manipulators</b>				
<b>Manipulator</b>				
	<b>ManipHe</b>	<b>ManipKoRu</b>	<b>Combined</b>	<b>p</b>
<b>LSVI</b>				0,748
<b>Yes</b>	6 (14,64%)	4 (10%)	10	
<b>No</b>	41	36	77	
<b>Combined</b>	47	40	87	

The subsequent analysis of the individual types of the manipulators used did not confirm any difference in the incidence of LVSI. In the group with the Koch-Rumi manipulator (ManipKoRu), LVSI was recorded at the level of 10%. In the group using the Hegar dilator (ManipHe) at the level of 14.64%. The difference in the groups is statistically insignificant ( $p = 0.748$ ) (Table 3).

## Discussion

The literature available discusses the influence of a uterine manipulator on the success of treatment, survival, and the possibility of recurrence. A recent multi-center retrospective analysis of 2021 compared 2661 female patients from 15 centers. Of these, 1756 patients were operated endoscopically with a uterine manipulator and 905 without it. Both groups were balanced, taking into account the histology of tumor grading, myometrial invasion, disease stage, and administration of adjuvant therapy. The recurrence rate was 11.69% in the manipulator group compared to 7.4% in patients when the manipulator was not used (HR, 2.31; 95% CI, 1.27-4.20;  $P = 0.006$ ) [23]. The authors emphasize the need to perform prospective measurements, although their results show a worse prognosis for patients where a uterine manipulator was used.

In our work, we did not evaluate the overall survival and recurrence rate, but the presence of the risk of a manipulator uses and a possible worsening prognosis by medical approach of female patients in terms of increasing the incidence of LVSI. The confirmation of the hypothesis would mean inadequate placing of female patients in the risk group and excessive treatment in terms of adjuvant therapy. However, this relationship has not been confirmed in our work. LVSI was positive 11.3% in the manipulator group versus 22.5% in the non-manipulator group (OR 1.92, 95% CI 0.77-4.77,  $P = 0.162$ ). The difference in the groups is without statistical significance.

These conclusions are also supported by the meta-analysis of 11 retrospective studies evaluating the effect of a uterine manipulator on positive abdominal cytology (RR: 1.53, 95% CI, 0.85 to 2.77), the presence of LVSI (RR: 1.18, 95% CI, 0.66 to 2.11), and the disease recurrence rate (RR: 1.25, 95% CI, 0.89 to 1.74). The authors did not observe a negative impact of a manipulator in any of the evaluated parameters [24]. In this stud there is the opposite conclusion to that of the authors in the previously mentioned study [23].

The impact of the Koch-Rumi manipulator on the presence of LVSI – the pseudo-invasion was evaluated by a team of authors from the United States of America. In a group of 37 female patients, 7 of whom underwent surgery for endometrial cancer and 30 for benign causes, they found that they observed a vascular pseudo-invasion. In malignant cases, in 71% and in benign cases, in 13%. [25]. They expressed a suspicion of a mechanical action of positive balloon pressure in the closed uterine cavity and its possible impact on the evaluated histological specimens. In our work, we compared the influence of a type of uterine manipulator on the presence of LVSI, both expandable (Koch-Rumi) and non-expandable (Hegar dilator). In the analysis, we did not find any difference between the individual modalities (ManipKoRu 10% vs. ManipHe 14.64%,  $p = 0.748$ ). (Tab. 3).

From the secondary analysis of our set, we evaluated the relationship between the degree of differentiation: the tumor grading, depth of myoinvasion, and the incidence of LVSI. In tumors on the grading scale 2 and 3 (OR 0.23; CI 95% 0.07 - 0.77;  $p = 0.017$ ), and in case of tumor overgrowth of more than half of the uterine wall - T1b (OR 6.24; CI 95% 2.46 - 15.8;  $p < 0.001$ ), a higher incidence of LVSI with statistical significance was observed. A similar connection to a higher incidence of LVSI positive cases at higher gradings has already been documented in the literature, 43.8% versus 17.0% [26].

In the secondary data evaluated, we observed a significant difference in the incidence of LVSI in the female patients with histology obtained by hysteroscopy versus curettage (6.6% vs 22.4%, OR 4.27; CI 95% 1.39 - 13.07;  $p = 0.011$ ). These procedures were performed in several workplaces. With the introduction of hysteroscopy as a surgical method, there has been a discussion about the safety of using a distension medium under pressure and the possible dispersal of tumor cells into the peritoneal cavity through the fallopian tubes. In their work, a group of authors observed this phenomenon in endometrial carcinomas of the second type [27]. However, a study from 2010 did not confirm the impact on prognosis of female patients [28]. A meta-analysis on the safety of hysteroscopy in the diagnosis of endometrial cancer in the first stage is currently registered [29]. Our results suggest that female patients who have undergone curettage have a higher incidence of LVSI. Hypothetically, this phenomenon could occur due to the pressure of the curette on the wall of the uterine cavity and the extrusion of tumor cells into the lymphovascular spaces. In hysteroscopic examination, samples are taken in a targeted manner, often with the help of resectoscopy, without the need for increased mechanical force. Further studies will be needed to confirm our results.

## Conclusion

This connection has not been confirmed in the previously published studies examining the effect of a uterine manipulator on the possible increase in the number of LVSI positive cases [24,30,31]. We also reached the same conclusions in our study.

The secondary analysis indicated a higher incidence of LVSI in the female patients diagnosed with curettage than in those who underwent hysteroscopy. Further studies will be needed to confirm this phenomenon.

At this time, there are no well-defined recommendations for the use of an intrauterine manipulator in the endoscopic treatment of endometrial cancer [9]. Its use or non-use often depends on the workplace habits and preferences of a surgeon. In a case of strong data confirming worsening prognosis by medical approach of female patients when using a uterine manipulator, we should give up this device.

## Abbreviations

BMI - body mass index

CI - confidence interval

ECIS - European Cancer Information System

ESGO - European Society of Gynaecological Oncology

ESP - European Society of Pathology

ESTRO- European Society for Radiotherapy and Oncology

EU - European Union

HR - hazard ratio

LAVH - laparoscopic assisted vaginal hysterectomy

LVSI - lymphovascular propagation

OR - odds ratio

TLH - total laparoscopic hysterectomy

TNM - tumor nodes metastases

RH - robotic hysterectomy

RR - relative risk

WSR - world standardised incidence ratio

## Declarations

### Declarations and ethic committee

This clinical trail was approved by the committee of our our hospital, providing approval - Ethics Committee of the F.D.Roosevelt Hospital, 21<sup>st</sup> Oct. 2021 and complies with the Good Clinical Practice and

legislation of Slovak Republic (EU). No.: 29/2021. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects.

### Competing interests

Authors declare that they have no competing interests.

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### Authors' contributions

BH and PU designed the study, analysed the data, and wrote the manuscript. KD, RŠ and contributed to study design, coordination, data analysis, and manuscript writing. KD coordinated the study, formatted data, and contributed to data analysis and manuscript editing. TK and MS analysed histology samples. All authors read and approved the final manuscript.

### Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due internal policy of *F.D.Roosevelt Teaching Hospital in Banská Bystrica*, but are available from the corresponding author on reasonable request.

### Trail registration

Trail is registered in ClinicalTrials.gov with identifier: NCT05261165.

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