



# Transvaginal natural orifice transluminal endoscopic surgery (VNOTES) retroperitoneal sentinel lymph node BIOPSY compared with conventional laparoscopy in patients with endometrial cancer

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## ABSTRACT

**Introduction:** To explore the possibility of treatment with VNOTES sentinel lymph node dissection concept in patients with endometrial cancer.

**Methods:** Patients who underwent VNOTES sentinel lymph node biopsy with the Comba modification were compared to patients who underwent conventional laparoscopic sentinel lymph node biopsy performed by the same surgical team. A total of 38 patients who underwent sentinel lymph node biopsy + total laparoscopic hysterectomy and bilateral salpingo-oophorectomy (BSO) were compared with 19 patients who underwent VNOTES retroperitoneal sentinel lymph node biopsy + hysterectomy and BSO. Surgical steps were described.

**Results:** The average operation time, perioperative blood loss, the number of sentinel lymph nodes, presence of complications, and preoperative-postoperative hemoglobin-hematocrit differences, tumor stages, grades, largest tumor diameter, depths of invasion, and histological subtypes were similar in both the VNOTES and conventional laparoscopy groups. The postoperative pain scores were lower and the hospital stay was shorter in the VNOTES group than in the conventional laparoscopy group. No disease recurrence had been detected in either group at the time of writing.

**Conclusion:** Compared to conventional laparoscopy, sentinel lymph node biopsy with the VNOTES technique provides similar surgical results and is more advantageous in terms of postoperative pain and hospital length of stay.

## 1. Introduction

Endometrial cancer (EC) is the most common gynecological cancer around the world. The sentinel lymph node biopsy concept has become more widely used and has been featured in recently published guidelines for EC [1]. Sentinel lymph node biopsy (SLNB) has been shown to minimize the complications associated with comprehensive staging lymphadenectomy. Surgical staging of early-stage endometrial cancer

can be accomplished using this technique in an accurate and feasible manner. Compared to complete lymphadenectomy, SLNB appears to improve surgical outcomes while maintaining reliable surgical staging results [2].

The Transvaginal Natural Orifice Transluminal Endoscopic Surgery (VNOTES) technique has been widely used in gynecological surgery in recent years. However, its use in gynecologic oncology has not yet become widespread. Studies on VNOTES in gynecologic oncology

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include few cases or are in the form of case reports [3,4]. In the literature, VNOTES surgery, especially the sentinel lymph node concept has generally been performed for endometrial cancer surgery [5,6].

The purpose of this study was to compare the surgical results of patients who underwent retroperitoneal VNOTES sentinel lymph node biopsy with the Comba modification technique with patients who underwent conventional laparoscopic sentinel lymph node biopsy.

2. Material and methods

This retrospective cohort study compared patients who underwent VNOTES retroperitoneal sentinel lymph node biopsy with the Comba modification with patients who underwent conventional laparoscopic sentinel lymph node biopsy performed by the same surgical team, between February 2021 and June 2023. The patient group numbers were in the ratio of one to two. Approval for the study was obtained from Istanbul Aydin University Non-Interventional Clinical Research Ethics Committee (decision no: 2023/29).

The study inclusion criteria were defined as age between 30 and 85 years, a diagnosis of endometrial cancer, no distant organ metastases detected on preoperative imaging, no medical problems which would contra-indicate surgery, and surgical management with sentinel lymph node biopsy. The most important criteria of the chosen type of surgery was adequate vaginal width for VNOTES surgery. A total of 38 patients who underwent sentinel lymph node biopsy + total laparoscopic hysterectomy and bilateral salpingo-oophorectomy (BSO) were compared with 19 patients who underwent VNOTES sentinel lymph node biopsy + hysterectomy and BSO. The study exclusion criteria were defined as systemic lymph adenectomy performed for endometrial cancer, or the presence of distant organ metastases.

The demographic data of the patients such as age, obstetric history and body mass index, operative and surgical characteristics, pathological data and postoperative pain scores and follow-up periods were extracted from the hospital records. The postoperative pain score was obtained on the first morning postoperatively using a linear visual analog scale (VAS) marked by the patients to represent the severity of pain felt. Surgical steps for Comba modification are described below.

2.1. Surgical steps for VNOTES

VNOTES was performed with the following steps, based on the surgical technique previously published by the current authors as a video article [7].

1. Incision of lateral fornix vaginal walls at 3–5 o'clock and 7–9 o'clock and expansion of the retroperitoneal space
2. Placement of the vaginal access platform and control of the retroperitoneal area
3. Injection of ICG into the side where sentinel lymph node biopsy will be performed (3 or 9 o'clock; 1.25 mg deep and 1.25 mg superficially)
4. Performing unilateral sentinel lymph node biopsy and removal of the vaginal access platform
5. Application of steps 2-3-4 for the other side
6. Making a circular incision to the vaginal mucosa above the cervix and entering the abdominal cavity anteriorly or posteriorly
7. Replacement of the vaginal access platform to the abdominal cavity to take peritoneal irrigation fluid, hysterectomy and BSO
8. Closing the three incisions on the vaginal mucosa (video)

2.2. Surgical steps for laparoscopy

Laparoscopy was performed with the following steps, based on the surgical technique previously published by the current authors as a video article [8].

1. Entering the abdomen with a Veress needle and providing pneumoperitoneum
2. Insertion of trocars
3. Taking peritoneal irrigation fluid
4. Injection of ICG into the cervix (deep and superficial at 3 and 9 o'clock)
5. Removal of sentinel lymph nodes
6. Performing hysterectomy and BSO without uterine manipulator
7. Closing vaginal mucosa

2.3. Statistical analysis

SPSS 20 program designed for Windows was used for the statistical analysis. All continuous variables were stated as mean and standard deviation (SD) values, and categorical variables as number (n) and percentage (%) of the total group. All statistical tests were performed by comparing the two groups. The Mann Whitney U test was used for the comparative analysis of independent variables, and the Chi-square test for categorical variables. A value of  $p < 0.05$  was accepted as statistically significant.

3. Results

Evaluation was made of a total of 57 patients who met the specified criteria, comprising 38 patients who underwent conventional laparoscopic sentinel lymph node biopsy and 19 who underwent VNOTES retroperitoneal sentinel lymph node biopsy.

In terms of age, body mass index, and waist circumference, there was no statistically significant difference between the groups ( $p > 0.05$ ). The comparative analysis of patient demographic characteristics between the groups is shown in Table 1.

The average operation time was 192.5 min in the conventional laparoscopic sentinel lymph node biopsy group, and 208.4 min in the VNOTES group ( $p > 0.05$ ). Perioperative blood loss was calculated as 97.9 ml in the conventional laparoscopic sentinel lymph node biopsy group and 76.3 ml in the VNOTES sentinel lymph node biopsy group ( $p > 0.05$ ). No statistically significant difference was detected between the groups in respect of the number of sentinel lymph nodes, presence of complications, and preoperative-postoperative Hemoglobin-Hematocrit differences ( $p > 0.05$ ). Comparative analysis of the groups in terms of laboratory values and operational characteristics is shown in Table 2. Three patients in the laparoscopy group stayed in intensive care unit. The first patient of these suffered from chronic lung disease and obesity; The other patient stayed there due to uncontrolled hypertension and diabetes, and the last patient remained in intensive care due to uncontrolled hypertension and obesity. Two patients in the VNOTES group stayed in the intensive care unit. The first patient's stay in the intensive care unit was due to obesity and uncontrolled hypertension. The second patient's stay in the intensive care unit was due to diabetes and obesity.

Table 1  
Comparative analysis of patients' demographic data between groups.

|                                     | Laparoscopic sentinel lymph node biopsy group n = 38 | V-NOTES sentinel lymph node biopsy group n = 19 | p      |
|-------------------------------------|------------------------------------------------------|-------------------------------------------------|--------|
| Age                                 | 59,8 ± 9,9 (44–78)                                   | 59,4 ± 11,6 (43–80)                             | 0,892' |
| Body Mass Index                     | 32 (19–54)                                           | 29 (24–38)                                      | 0,514' |
| Waist circumference                 | 99,2 ± 15,1 (75–140)                                 | 93,5 ± 6,3 (84–106)                             | 0,129' |
| Gravida                             | 4 (0–8)                                              | 3 (1–6)                                         | 0,012' |
| Parity                              | 3 (0–7)                                              | 2 (1–6)                                         | 0,077' |
| Number of normal spontaneous births | 3 (0–7)                                              | 2 (0–5)                                         | 0,086' |
| Number of cesarean births           | 0 (0–2)                                              | 0 (0–1)                                         | 0,513' |

**Table 2**

Comparative analysis of groups in terms of laboratory values and operational characteristics.

|                                                                                                    | Laparoscopic<br>sentinel lymph node<br>biopsy group n = 38     | V-NOTES<br>sentinel lymph<br>node biopsy<br>group n = 19 | p      |
|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------|--------|
| <b>Operation time (minutes)</b>                                                                    | 192,5 ± 59,2<br>(120–366)                                      | 208,4 ± 56,5.                                            | 0,216' |
| <b>Perioperative blood loss<br/>(ml)</b>                                                           | 97,9 ± 55,1<br>(20–240)                                        | 76,3 ± 43,9<br>(20–150)                                  | 0,153' |
| <b>Number of sentinel<br/>lymph nodes</b>                                                          | 3 (2–6)                                                        | 3 (2–5)                                                  | 0,449' |
| <b>Number of positive<br/>sentinel lymph nodes</b>                                                 | 0 (0–3)                                                        | 0 (0–2)                                                  | 0,633' |
| <b>Presence of<br/>complications</b>                                                               | 3 (% 7,9) subileus<br>subileus + covid<br>trocar site hematoma | 1 (% 5,3) vaginal<br>cuff hematoma                       | 0,544* |
| <b>Intensive care unit<br/>requirement</b>                                                         | 3 (% 7,9)                                                      | 2 (% 10,5)                                               | 0,741* |
| <b>Preoperative hemoglobin<br/>amount (g/dl)</b>                                                   | 11,9 ± 1,9<br>(7,8–16,3)                                       | 12,5 ± 1,3<br>(10,1–15)                                  | 0,294' |
| <b>Preoperative hematocrit<br/>amount (%)</b>                                                      | 36,1 ± 5,1 (26–48,6)                                           | 38,2 ± 3,8<br>(32,3–44)                                  | 0,104' |
| <b>Preoperative leukocyte<br/>amount (10<sup>3</sup>/μl)</b>                                       | 7,9 ± 1,9 (4,5–13,3)                                           | 6,6 ± 1,4<br>(3,7–9,9)                                   | 0,007' |
| <b>Preoperative platelet<br/>amount (10<sup>3</sup>/μl)</b>                                        | 216,7 ± 66,4<br>(83–349)                                       | 264,7 ± 64,4<br>(147–391)                                | 0,017' |
| <b>Postoperative<br/>hemoglobin amount<br/>(g/dl)</b>                                              | 10,6 ± 1,7<br>(6,9–14,8)                                       | 11 ± 1,3<br>(9,4–13,8)                                   | 0,414' |
| <b>Postoperative hematocrit<br/>amount (%)</b>                                                     | 32,8 ± 4,4 (25–43)                                             | 33,7 ± 3,9<br>(29–42,4)                                  | 0,411' |
| <b>Postoperative leukocyte<br/>amount (10<sup>3</sup>/μl)</b>                                      | 10,6 ± 2,6 (3,9 -<br>15,8)                                     | 10,7 ± 3,7<br>(3,5–19,8)                                 | 0,548' |
| <b>Postoperative platelet<br/>amount (10<sup>3</sup>/μl)</b>                                       | 187,9 ± 56,8<br>(109–319)                                      | 231,8 ± 52,6<br>(148–340)                                | 0,017' |
| <b>Difference between<br/>preoperative and<br/>postoperative<br/>hemoglobin values (g/<br/>dl)</b> | 1,3 ± 1,4<br>(–1,6–7,57)                                       | 1,5 ± 1,1 (0–3,6)                                        | 0,582' |
| <b>Difference between<br/>preoperative and<br/>postoperative<br/>hematocrit values (%)</b>         | 3,3 ± 2,7.<br>(–5,1–10,4)                                      | 4,5 ± 3,5 (–1 -<br>11,6)                                 | 0,294' |

No statistically significant difference was detected between the two groups in terms of tumour stage, grade, largest tumor diameter, depths of invasion, and histological subtypes ( $p > 0.05$ ). Postoperative pain scores were lower and the length of hospital stay was shorter for the patients operated on with VNOTES sentinel lymph node biopsy compared to the patients operated on with conventional laparoscopic sentinel lymph node biopsy (pain score: median 4 vs 6; hospital stay: 23.6 vs. 32.7 h) ( $p < 0.05$ ).

Postoperative follow-up periods of the patients were similar in both groups with no statistically significant difference detected ( $p > 0.05$ ). The pathological data of the patient tumors, postoperative pain scores and follow-up periods are shown in Table 3.

The sentinel lymph node could not be detected in one patient in the VNOTES group despite access to the right retroperitoneal area. In the same patient, the left retroperitoneal area could not be accessed. The patient then underwent conventional laparoscopy. The sentinel lymph nodes could not be detected in the laparoscopy, and a hysterectomy, BSO, and pelvic lymphadenectomy were performed (detection of ICG rate 94.8 % for the VNOTES sentinel lymph node biopsy group).

No recurrence was detected in either group at the time of writing the manuscript.

**Table 3**

Comparative analysis of pathology data, pain scores and follow-up periods of the groups.

|                                                          | Laparoscopic sentinel<br>lymph node biopsy<br>group n = 38                                | V-NOTES<br>sentinel lymph<br>node biopsy<br>group<br>n = 19 | p      |
|----------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------|--------|
| <b>Stage</b>                                             | 1A - 27 (% 71,1)<br>1B - 8 (% 21,1)<br>1C - 1 (% 2,6)<br>3A - 1 (% 2,6)<br>3C - 1 (% 2,6) | 1A - 11 (% 57,9)<br>1B - 7 (% 36,8)<br>3C - 1 (% 5,3)       | 0,595* |
| <b>Grade</b>                                             | 2 (1–4)                                                                                   | 2 (1–3)                                                     | 0,588' |
| <b>Presence of invasion</b>                              | 36 (% 94,7)                                                                               | 19 (% 100)                                                  | 0,548* |
| <b>Largest tumor diameter</b>                            | 30,2 ± 17,2 (4–90)                                                                        | 24 ± 9,9 (6–40)                                             | 0,253' |
| <b>Depth of Myometrial<br/>Invasion (%)</b>              |                                                                                           |                                                             | 0,744* |
| <%50                                                     | 25 (% 65,8)                                                                               | 13 (% 68,4)                                                 |        |
| %50                                                      | 1 (% 2,6)                                                                                 |                                                             |        |
| >%50                                                     | 10 (% 26,3)                                                                               | 6 (% 31,6)                                                  |        |
| <b>Depth of Invasion<br/>(mm)</b>                        | 7,4 ± 8,8 (1,5–55)                                                                        | 5,9 ± 3,5 (1–12)                                            | 0,893' |
| <b>Presence of perineural<br/>invasion</b>               | 2 (% 5,3)                                                                                 | 1 (% 5,3)                                                   | 1*     |
| <b>Presence of<br/>lymphovascular<br/>space invasion</b> | 7 (% 18,4)                                                                                | 1 (% 5,3)                                                   | 0,247* |
| <b>Histological subtype</b>                              |                                                                                           |                                                             | 0,486* |
| <b>Endometrioid</b>                                      | 26 (% 68,4)                                                                               | 14 (% 73,7)                                                 |        |
| <b>Serous</b>                                            | 8 (% 21,1)                                                                                | 2 (% 10,5)                                                  |        |
| <b>Mucinous</b>                                          | 2 (% 5,3)                                                                                 | 3 (% 15,8)                                                  |        |
| <b>differentiated</b>                                    |                                                                                           |                                                             |        |
| <b>Squamous</b>                                          | 1 (% 2,6)                                                                                 |                                                             |        |
| <b>differentiated</b>                                    |                                                                                           |                                                             |        |
| <b>Clear cell</b>                                        | 1 (% 2,6)                                                                                 |                                                             |        |
| <b>Length of hospital stay<br/>(hour)</b>                | 32,7 ± 11,6 (16–70)                                                                       | 23,6 ± 6,8<br>(12–36)                                       | 0,003' |
| <b>Postoperative pain<br/>score</b>                      | 6 (5–9)                                                                                   | 4 (3–5)                                                     | 0,000' |
| <b>Adjuvant therapy</b>                                  |                                                                                           |                                                             | 0,633* |
| <b>None</b>                                              | 16 (% 42,1)                                                                               | 11 (% 57,9)                                                 |        |
| <b>Radiotherapy</b>                                      | 11 (% 28,9)                                                                               | 4 (% 21,1)                                                  |        |
| <b>Radiotherapy +<br/>Chemotherapy</b>                   | 6 (% 15,8)                                                                                | 3 (% 15,8)                                                  |        |
| <b>Chemotherapy</b>                                      | 5 (% 13,2)                                                                                | 1 (% 5,3)                                                   |        |
| <b>Follow up time<br/>(month)</b>                        | 20,8 ± 8,2 (5–33)                                                                         | 22,4 ± 8,4<br>(6–30)                                        | 0,382' |

## 4. Discussion

### 4.1. Summary of main results

According to the results of this study, VNOTES retroperitoneal sentinel lymph node biopsy with the Comba modification was more advantageous than a completely conventional laparoscopic procedure in terms of postoperative pain and hospital stay.

### 4.2. Results in the context of published literature

VNOTES has recently become widely used in gynecological surgery. Especially in almost all cases where hysterectomy will be performed, VNOTES hysterectomy can be performed if the vaginal opening or the patient's medical condition can tolerate surgery. This technique may be used in adnexal surgeries such as salpingectomy, oophorectomy, cystectomy, and tubal ligation, and urogynecological surgeries such as high uterosacral ligamentopexy, lateral suspension, and sacrospinous ligament suspension. To date, the use of VNOTES in gynecological oncology has been limited despite several small studies and case reports depicting outcomes from VNOTES in sentinel lymph node biopsy, pelvic lymphadenectomy, and omentectomy. Even a history of cesarean section or endometriosis does not prevent VNOTES [7,9]. However, in a review

article published in 2023, it was stated that lymph node sampling is not performed routinely using VNOTES [9]. A study analyzed that it was calculated the learning curve for VNOTES hysterectomies at 30 cases for masterclass level [10]. But there is no data for gynecologic oncologic surgery. We believe 10 cases of vnotes sentinel lymph node biopsy after a masterclass in gynecology seems enough.

Researchers from China described their method via VNOTES sentinel lymphadenectomy intraperitoneal access in patients with endometrial cancer after hysterectomy and BSO [11]. As it is possible that the time lost due to hysterectomy may reduce the likelihood of detecting true sentinel lymph nodes, it was attempted to prevent this time loss with the method developed and described in this study.

In a preliminary study conducted in Switzerland, where a surgical technique similar to the technique described in our video article was used [7], seven patients were included and the effectiveness of the technique was emphasized [4]. However, in our technique, ICG was given to the side where sentinel lymph node biopsy could be performed, and the passage of ICG through the sentinel lymph channels was simultaneously monitored. Therefore, biopsy of the correct sentinel lymph nodes was achieved.

Surgeons from Korea demonstrated VNOTES pelvic lymphadenectomy in a patient with endometrial

cancer in a surgical video article. Intraperitoneal pelvic lymphadenectomy after hysterectomy

resembles the conventional laparoscopic method [3]. In the current study, the retroperitoneal approach was performed. If there is failure to complete the procedure with VNOTES, these cases can be converted to laparoscopy. In the current study, one patient who did not have SLN mapped was converted to laparoscopy, but SLN could still not be identified.

In conclusion, the results of this study demonstrated that VNOTES is advantageous in terms of shorter hospital stay and less postoperative pain compared to conventional laparoscopy. No statistically significant difference was found in terms of oncological outcomes, as the sentinel lymph node detection rates were the same in both groups and there was no recurrence.

VNOTES offers some potential advantages over conventional laparoscopy in terms of postoperative pain and hospital stay. However, VNOTES requires a longer surgical time than conventional laparoscopy at the beginning of the VNOTES procedure. Further studies are needed to thoroughly evaluate the efficacy and safety of the VNOTES technique in gynecologic oncology surgery.

#### 4.3. Strengths and weaknesses

The technique we described is the first technique published in VNOTES retroperitoneal sentinel lymph node concept surgery. It is important to present the first results of surgery performed with this technique. The strengths of the study are that there was no recurrence in any of the patients during the follow-up period we specified, the sentinel lymph node detection rate was high (94,8 %), the technique had a low probability of failure, and the complications of the surgical technique were the same as those of classical laparoscopy. On the contrary, factors such as the short follow-up period, the small number of patients, the failure to adopt the use of VNOTES by gynecological oncologists, and the long learning curve of the surgical technique also constitute the weaknesses of the study.

#### 4.4. Implications for practice and future research

VNOTES use in gynecologic oncology surgery is limited. To date, only case series and case reports with a small number of patients have been published in the literature. Researcher wrote that lymph node sampling is not done routinely via the VNOTES in a review article published in 2023 [9].

Our main goal is to show the effectiveness of the technique we have

defined by sharing the first results, encourage enthusiastic gynecologic oncologists at centers that perform high number endometrial cancer surgeries to adopt this method and publish their own results, and then design prospective multicenter randomized controlled trials.

## 5. Conclusion

Briefly, in our study, VNOTES is advantageous in terms of shorter hospital stay and less postoperative pain compared to conventional laparoscopy. No statistically significant difference was found in terms of oncological outcomes such as the same sentinel lymph node detection rate and no recurrence.

## Informed consent statement

Informed consent form was obtained from the patients.

## CRedit authorship contribution statement

**Cihan Comba:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Sema Karakas:** Methodology, Investigation, Formal analysis, Data curation. **Sakir Volkan Erdogan:** Writing – review & editing, Visualization, Resources, Conceptualization. **Omer Demir:** Supervision, Project administration, Methodology, Formal analysis. **Erkan Şimşek:** Methodology, Investigation. **Fatma Karasabanoglu:** Methodology, Investigation. **Gokhan Demirayak:** Visualization, Methodology, Data curation. **Isa Aykut Ozdemir:** Writing – review & editing, Supervision, Methodology, Investigation.

## Declaration of competing interest

All authors are authors on this submission, have adhered to all editorial policies for submission as described in the Information for Authors and we declare that we have no conflict of interest in connection with this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.suronc.2024.102099>.

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