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Diagnostic Indices of Intraoperative Gross Assessment in the Surgical Staging of Endometrial Cancer

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ABSTRACT

Objectives: To determine the diagnostic indices of intraoperative gross assessment in the surgical staging of endometrial cancer.

Materials and Methods: We retrospectively reviewed medical records and operative notes of a total of 112 patients who were diagnosed with endometrial cancer in Prapokklao Hospital between 2014 and 2019. We aimed to determine the diagnostic indices of gross visual inspection compared with the final pathological reports. Diagnostic indices included sensitivity, specificity, negative predictive value, positive predictive value, and likelihood ratio with a 95% confidence interval. Specimen evaluation sites consisted of five parameters including cervical involvement, adnexal involvement, myometrial invasion, tumor diameter, and lymph node involvement.

Results: Intraoperative gross assessment showed good accuracy in all parameters, ranging from 71.1% to 89.9%, while tumor diameter showed the best accuracy (89.9%). Cervical involvement, adnexal involvement and myometrial invasion showed relatively poor sensitivity (46.7%, 18.8%, 56.6%) but good specificity (95.6%, 95.5%, 90.9%). For para-aortic lymph node involvement, the number of samples was too limited to assess the diagnostic performance.

Conclusion: Gross intraoperative assessment in surgical staging had good specificity and accuracy but poor sensitivity. The results implied that gross intraoperative assessment was an applicable tool. However, more modality and intervention should be combined in order to help in deciding the best surgical treatment for each individual.

Keywords: surgical staging, diagnostic indices, gross assessment, endometrial cancer.

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ความแม่นยำของการประเมินด้วยตาเปล่าในระหว่างการผ่าตัดประเมินระยะโรคของโรคมะเร็งเยื่อบุโพรงมดลูก

บุณฑรีก์ ไชยประสิทธิ์, วัชรินทร์ เฉิดฉิม

บทคัดย่อ

วัตถุประสงค์: *เพื่อวัดดัชนีการวินิจฉัยของการประเมินด้วยตาเปล่าในการผ่าตัดเพื่อกำหนดระยะของมะเร็งเยื่อบุโพรงมดลูก*
วัสดุและวิธีการ: *รวบรวมข้อมูลจากแฟ้มเวชระเบียนและบันทึกการผ่าตัดของผู้ป่วยโรคมะเร็งเยื่อยุโพรงมดลูกที่ได้รับการวินิจฉัยและผ่าตัด เพื่อกำหนดระยะโรคในโรงพยาบาลพระปกเกล้า ระหว่างปี พ.ศ.2557 ถึง พ.ศ. 2562 จำนวนทั้งสิ้น 112 คน เพื่อนำมาเปรียบเทียบ ดัชนีในการวินิจฉัยซึ่งประกอบไปด้วย ความแม่นยำ (specificity) ความไว (sensitivity) ความจำเพาะ (specificity) ค่าทำนายผลบวก (positive predictive value) ค่าทำนายผลลบ (negative predictive value) โอกาสความน่าจะเป็นเมื่อการตรวจเป็นผลบวกและผลลบ (likelihood ratio) ในการประเมินด้วยตาเปล่าในการผ่าตัดเพื่อกำหนดระยะของมะเร็งเยื่อบุโพรงมดลูก กับ การตรวจวินิจฉัยทางพยาธิวิทยาชิ้นเนื้อหลังการผ่าตัดของ 5 ตัวแปร ประกอบด้วย การแพร่กระจายไปยังปากมดลูก ปีกมดลูก กล้ามเนื้อมดลูก ต่อมน้ำเหลือง และขนาดเส้นผ่าศูนย์กลางของก้อนมะเร็ง*
ผลการศึกษา: *การประเมินด้วยตาเปล่าในการผ่าตัดเพื่อกำหนดระยะโรคของมะเร็งเยื่อบุโพรงมดลูกมีความแม่นยำในทุกตัวแปร โดยมีความแม่นยำอยู่ระหว่าง 0.711 ถึง 0.899 ตัวแปรที่มีความแม่นยำมากที่สุดคือ ขนาดเส้นผ่าศูนย์กลางของก้อนมะเร็ง (0.899) ในขณะที่การแพร่กระจายไปที่ปากมดลูก ปีกมดลูก และกล้ามเนื้อเรียบมีความไวน้อย โดยมีความไวร้อยละ 46.7, 18.8, 56.6 ตามลำดับ แต่มีความจำเพาะที่ดี โดยมีความจำเพาะร้อยละ 95.6, 95.5, 90.9 ตามลำดับ ส่วนการกระแพร่กระจายไปต่อมน้ำเหลืองโดยรอบเส้นเลือดเอออร์ต้า มีจำนวนตัวอย่างการตรวจชิ้นเนื้อที่น้อยทำให้มีข้อจำกัดในการแปลผลตัวแปรนี้*
สรุป: *การประเมินด้วยตาเปล่าในการผ่าตัดเพื่อกำหนดระยะโรคของมะเร็งเยื่อบุโพรงมดลูกมี ความจำเพาะและความแม่นยำที่ดี แต่ความไวน้อย จากการศึกษาพบว่าการใช้การประเมินด้วยตาเปล่าในการผ่าตัดนั้นยังเป็นวิธีการที่น่าเชื่อถือ แต่อย่างไรก็ตามยังคงต้องการเครื่องมือหรือวิธีการที่นำมาช่วยในการตัดสินในเพื่อทำการผ่าตัดให้ได้ผลที่ดีที่สุดในผู้ป่วยแต่ละรายต่อไป*

คำสำคัญ: *การผ่าตัดเพื่อประเมินระยะโรค, การประเมินด้วยตาเปล่า, ดัชนีการวินิจฉัย, โรคมะเร็งเยื่อบุโพรงมดลูก*

Introduction

Endometrial cancer is the most common female genital cancer in developed countries[1]. For Thailand, which is one of the low and lower middle income countries, endometrial cancer is the 3rd most common after cervical and ovarian cancer at the incidence of 4.5 per 100,000 persons[2]. Up to the present time, primary surgical treatment or surgical staging remains the standard treatment of endometrial cancer, consisting of total hysterectomy, bilateral salpingo-oopherectomy and selective lymph node dissection[3-5]. According to the latest National Comprehensive Cancer Network guidelines (NCCN, 2018)[4], there is still no definite conclusion in the role of lymphadenectomy. Two previous randomized controlled trials had shown no benefit of routinely performed lymphadenectomy in early-stage patients[6, 7]. Currently, lymphadenectomy may be omitted in low risk cases; tumor size < 2 cm, myometrial invasion < 50%, no lymphovascular invasion, no cervical involvement and well or moderately differentiated endometrioid histology[4].

As lymphadenectomy is not routinely performed and depends on the patient's assessment, preoperative and intraoperative assessment become an important matter because it could guide the appropriate surgical treatment and also help in planning for adjuvant treatment for patients. From previous studies, intraoperative assessment was the most accurate tool when compared with the gold standard (final pathological reports)[8]. In the past, many studies assessed the accuracy of gross visual inspection but only in some parameters, with commonly seen parameters being myometrial invasion and cervical involvement[9-15].

In this study we conducted research to find diagnostic indices of all 5 clinical parameters which include cervical involvement, adnexal involvement, myometrial invasion, tumor diameter, and lymph node involvement. The purpose of this study was to find the diagnostic indices of intraoperative assessment in the surgical staging of endometrial cancer patients. The other objective was to find demographic data, risk factors, and pathological findings of endometrial cancer patients at Prapokklao Hospital.

Materials and Methods

This study was approved by the Ethics Committee of Prapokklao Hospital for study from the medical records; no informed consent was required.

This research was a diagnostic accuracy study. The study design was a retrospective cross-sectional descriptive study. For data collection, we retrospectively reviewed the medical records and operative notes of newly diagnosed endometrial cancer patients at the Department of Obstetrics and Gynecology of Prapokklao Hospital between Jan 2014 and July 2019. The exclusion criteria were inoperable patients, patients with no pathological reports, and patients with no documented operative findings. The collected data included the baseline characteristics of age, body mass index, co-morbidities, parity, family history of cancer, procedural information, and pathological information.

Endometrial cancer was classified as low-grade and high-grade disease. Low grade endometrial cancer includes grade 1 and grade 2 endometrioid adenocarcinoma. High grade endometrial cancer consists of grade 3 endometrioid adenocarcinoma and non-endometrioid histologies[16].

In Prapokklao Hospital, there is no routine guideline of preoperative assessment whereby transvaginal ultrasound, computed tomography, or magnetic resonance imaging are used differently depending on the physicians' decision and severity of the patients' disease. All surgical staging was done by expert oncologists. The procedures include hysterectomy and bilateral salpingo-oophorectomy and peritoneal washing. Pelvic and para-aortic lymphadenectomy were performed in patients for whom it was indicated by the clinical parameters (non-endometrioid type, tumor grade 3, cervical invasion, tumor size larger than 2 cm, tumor invasion of more than 50% of myometrial thickness)[3]. Radical hysterectomy was performed in patients with cervical involvement. Pelvic lymph nodes consisted of external iliac, internal iliac, and obturator lymph nodes. The para-aortic lymphadenectomy involved dissection below the inferior mesenteric artery.

For intraoperative gross assessment, all parameters

were assessed by gynecologic oncologists. The uterus was incised and opened along the uterine fundus to the cervix in antero-posterior fashion to assess cervical involvement, adnexal involvement and myometrial invasion. For tumor size, we defined on the basis of more or less than 2 cm, which we used for values from the maximal diameter of the tumor. Information was then recorded by residents. For pathological reports, all were finalized by pathologists and will be reported as official reports.

The sample size was calculated by using values from a previous study[13], which revealed the accuracy of intraoperative gross assessment of myometrial invasion at 90.3%. The sample size was then estimated using one-sample comparison of proportion to the hypothesized value, with the probability of a type one error of 0.05 and power of 0.8, so at least 95 patients were required to be included in this study. The demographic data and other pathological information were demonstrated using mean and frequency. The diagnostic indices of intraoperative assessment and final histological value were calculated using sensitivity, specificity, negative predictive value, positive predictive value, and likelihood ratio with a 95% confidence interval. Statistical analysis was performed by Stata 12.1.

As we retrospectively reviewed the operative notes, we encountered a problem of data collection. We found that there was incompleteness of operative note recordings. Complete operative note recording was defined as all parameters that had been surgically performed were noted and correlated with the final pathological reports while incomplete operative note recording was defined as an incomplete filling of the operative note findings of each parameter while there was actually a final pathological report.

Results

A total of 188 patients were newly diagnosed with endometrial cancer at Prapokklao Hospital between January 2014 and July 2019. Of these, 76 patients were excluded due to an inoperable condition (n = 16), no operative note (n = 7), and a lack of operative note records (n = 53). As a result the number of remaining participants to be included in the study was 112 patients (Fig. 1).

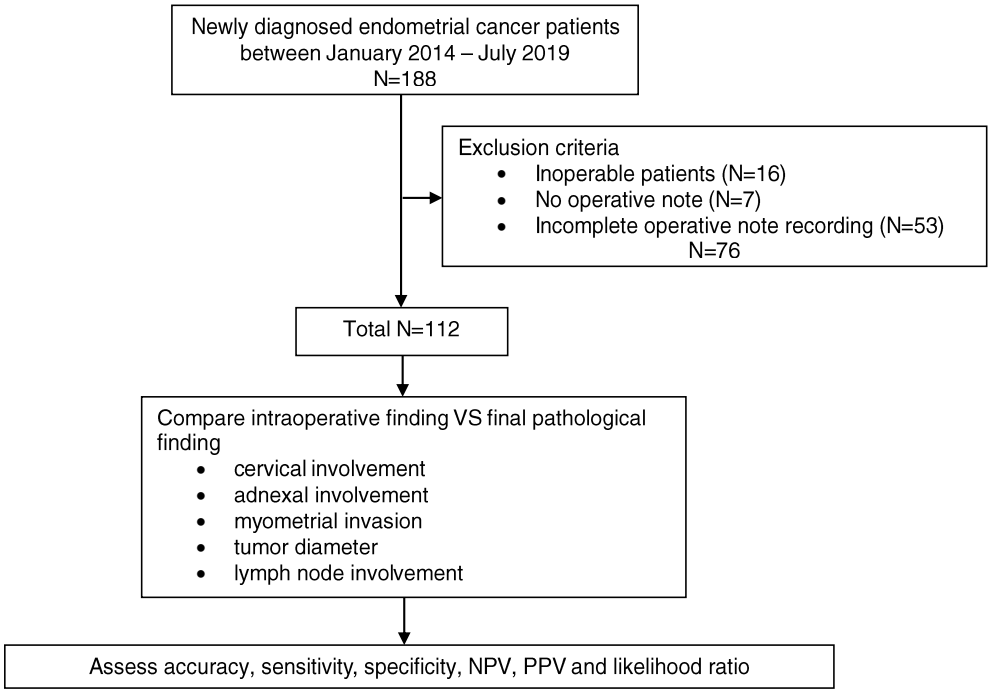

Fig. 1. Study flow.

The mean age of endometrial cancer patients was 57.72 ± 1.08. Mean body mass index was 26.84 ± 0.51 kg/m^2. Most were postmenopausal, accounting for 74.55%. For parity, nulliparity was 27.68% while grand multiparity was only 8.03%. Comorbidities were in association with metabolic syndromes, showing that 32.14% had diabetes mellitus, 51% had hypertension, 35% had dyslipidemia, while only 15% had other comorbidities. Concerning the family history of cancer, colon cancer was the most common, shown in 8 patients (7.14%). Also reported was abnormal Pap smear including atypical glandular cell (7.14%) and adenocarcinoma (2.68%). Most of the patients were in stage I of the disease accounting for 66.07% (Table 1).

Table 1. Baseline characteristics of participants.

Characteristics	n	(%)
Age (years) mean (±SD)	57.72 ± 1.08	
Body mass index	26.84 ± 0.51	
Menopausal status		
Pre-menopause	30	26.79
Post-menopause	82	73.21
Parity		
0	31	27.68
1-4	72	64.29
>4	9	8.03
Comorbidities		
Diabetes mellitus	36	32.14
Hypertension	51	45.54
Dyslipidemia	35	31.25
Others	15	11.88
Family history of cancer		
Endometrial cancer	2	1.79
Breast cancer	2	1.79
Ovarian cancer	1	0.82
Colon cancer	8	7.14
Others	9	8.04
Pap smear		
Normal	78	69.64
Glandular cell abnormality	8	7.14
Adenocarcinoma	3	2.68
Squamous cell abnormality	3	2.68
Squamous cell carcinoma	2	1.79
No data	18	16.07
Stage		
I	74	66.07
II	8	7.14
III	23	19.64
IV	7	7.14

SD: standard deviation

Histological reports from final pathological specimens are shown in Table 2. and can be categorized as 90 endometrioid type (80.36%) including of grade 1 = 44, grade 2 = 34 and grade 3 = 12 and 22 non-endometrioid type (23.21%).

Procedural information (Table 2.) revealed that most patients underwent fractional curettage and extrafascial hysterectomy. Most patients had negative peritoneal cytology and grade 1 tumors. Most patients underwent transabdominal operation mode.

Table 2. Procedure and histopathologic information.

Characteristics	n	(%)
Endocervical curettage		
Positive	43	38.39
Negative	30	26.79
Not done	39	34.82
Tissue diagnosis (pre-operative)		
Fractional curettage	79	70.53
Office endometrial sampling	13	11.61
Others	20	17.86
Hysterectomy		
Extrafascial	105	95.45
Radical	7	6.25
Operation mode		
Transabdominal	107	95.45
Laparoscopic	5	6.25
Histological cell type		
Endometrioid	90	82.14
Non-endometrioid	22	17.86
Tumor grade		
Grade 1	57	50.89
Grade 2	37	33.04
Grade 3	18	16.07
Peritoneal cytology		
Positive	3	2.68
Negative	101	90.2
Not done	8	7.14

Details of completeness of operative note recordings are shown in Table 3. This problem may affect the overall results because it may reduce the number of sample cases to be included in the study.

For the main objective, we focused on comparisons between the intraoperative gross findings and final pathological results in five clinical parameters as previously mentioned. Comparisons of findings are shown in Table 4. From the final pathological reports, 14.56% and 2.78% had pelvic lymph node and para-aortic lymph node involvement. The diagnostic indices were then calculated and are shown in Table 5. for cervical involvement (n = 106); sensitivity 46.7%, specificity 95.6%, positive predictive value (PPV) 63.6% negative predictive value (NPV) 91.6%, likelihood ratio (LR) 10.62, 0.56, accuracy

0.887. Adnexal involvement (n = 105); sensitivity 18.8%, specificity 95.5%, PPV 42.9%, NPV 86.7%, LR 4.17, 0.85, accuracy 0.838. Myometrial invasion (n = 108); sensitivity 56.6%, specificity 90.9%, PPV 85.7% NPV 68.5%, LR 6.23, 0.48, accuracy 0.741. Tumor diameter (n = 79); sensitivity 91.8%, specificity 66.7%, PPV 97.1% NPV 40%, LR 2.75, 0.12, accuracy 0.899. Lymph node involvement (pelvic; n = 97, para-aortic: n = 54); sensitivity 73.3%, 0%, specificity 70.7%, 87.3%, PPV 31.4%, 0%, NPV 93.5%, 96.5%, LR 2.75, 0.38, and 0.38, 1.15, accuracy 0.711, 0.846, respectively.

Table 3. Completeness of operative notes.

Parameters	Operative note (n)	Final pathological report (n)	Completeness of operative note (n %)
Cervical involvement	108	109	99.08
Adnexal involvement	107	110	97.27
Myometrial invasion	109	111	98.20
Tumor diameter	88	98	89.80
Lymph node involvement			
Pelvic lymph node	99	103	96.12
Para-aortic lymph node	65	72	84.72

Table 4. Comparison of findings of intraoperative gross assessment and final pathologic reports.

Parameters	Gross assessment n (%)		Final pathologic reports n (%)	
Cervical involvement				
Yes	11	10.19	16	14.68
No	97	89.15	93	85.32
Adnexal involvement				
Yes	7	6.54	18	16.36
No	100	93.46	92	83.64
Myometrial invasion				
< 50%	74	67.89	58	52.25
≥ 50%	35	33.02	53	47.75
Tumor diameter				
< 2 cm	13	14.77	7	7.14
≥ 2 cm	75	85.23	91	92.86
Lymph node involvement				
Pelvic lymph node				
Yes	36	36.36	15	14.56
No	63	63.64	88	85.44
Para-aortic lymph node				
Yes	8	12.31	2	2.78
No	57	87.69	70	97.22

We also conducted a subgroup analysis, divided patients into low risk and high risk histopathology group to assess the diagnostic indices. Low risk and high risk group were divided on the basis of histopathology. Low risk group consisted of endometrioid grade 1 and grade 2 (n = 72) and high risk group consisted of endometrioid grade 3 and non-endometrioid cell type (n = 40). The result of diagnostic indices after subgroup analysis are shown in Table 5, which almost all the results were similar when compare with the whole population diagnostic indices, except for adnexal involvement and tumor diameter. For adnexal involvement, high risk group showed less sensitivity (low risk = 40% vs high risk = 9.14%) and accuracy (low risk = 0.912 vs high risk = 0.703). For tumor diameter, high risk group showed much better in all diagnostic accuracy indices.

Table 5. Diagnostic indices of intraoperative gross assessment versus final pathologic reports.

Gross assessment	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio	Accuracy
Cervical involvement						
Total (106)	46.7	95.6	63.6	91.6	10.62, 0.56	0.887
Low risk (69)	44.4	96.7	66.7	92.1	13.33, 0.57	0.898
High risk (37)	50.0	93.5	60.0	90.6	7.75, 0.53	0.865
Adnexal involvement						
Total (105)	18.8	95.5	42.9	86.7	4.17, 0.85	0.838
Low risk (68)	40.0	95.2	40.0	95.2	8.40, 0.63	0.912
High risk (37)	9.14	96.2	50.0	71.4	2.36, 0.95	0.703
Myometrial invasion						
Total (108)	56.6	90.9	85.7	68.5	6.23, 0.48	0.741
Low risk (69)	53.1	94.6	89.5	70.0	9.83, 0.50	0.754
High risk (39)	61.9	73.3	81.3	65.2	3.71, 0.46	0.718
Tumor diameter						
Total (79)	91.8	66.7	97.1	40.0	2.75, 0.12	0.899
Low risk (58)	88.9	50.0	96.0	25.0	1.78, 0.22	0.862
High risk (21)	100	100	100	100	-, 0	1
Lymph node involvement						
Pelvic lymph node						
Total (97)	73.3	70.7	31.4	93.5	2.75, 0.38	0.711
Low risk (68)	71.4	65.6	19.2	95.2	2.07, 0.44	0.662
High risk (29)	75.0	85.7	66.7	90.0	5.25, 0.29	0.828
Para-aortic lymph node						
Total (54)	0	87.3	0	96.5	0, 1.15	0.846
Low risk (35)	0	86.7	0	97.5	0, 1.15	0.848
High risk (19)	0	88.9	0	94.1	0, 1.13	0.842

Discussion

In our study, we examined the diagnostic indices of intraoperative assessment in all five clinical parameters, including cervical involvement, adnexal involvement, myometrial invasion, tumor diameter, and lymph node involvement. We found that all had good specificity and accuracy but relatively poor sensitivity, which was consistent with the findings from previous studies[9-15]. However, when compared to previous studies[9-15], our studies demonstrated slightly less accuracy because intraoperative assessment was associated with many factors such as the surgeon's experience, study methodology which was retrospective design, and diversity of the disease which may be different from those previous studies.

It is well known that histopathology is one of the most important aspects to be considered and it is known preoperative. Patients with endometrioid cell type grade 3 and non-endometrioid cell type are defined as high risk histopathology patients whom are indicated for lymphadenectomy even before intraoperative gross assessment. We did a subgroup analysis between these groups and found similar results of diagnostic indices, except for adnexal involvement and tumor diameter parameters. High risk group showed poorer sensitivity and accuracy in adnexal involvement but high risk group showed a very good diagnostic index in tumor diameter.

The incidence of lymph node metastasis detected in our study was 14.56% and 2.78% for the pelvic and para-aortic lymph node, respectively. The result of the pelvic lymph node metastasis incidence was consistent with those previous studies[17, 18]. But for para-aortic lymph node metastasis, according to the results, the number of findings was too limited to represent the population. Thus, we suggested that more sample cases might be included in the future to be able to determine the diagnostic index of this parameter.

However, when we examined our results, we found that patients who were classified as low risk patients (endometrioid type grade 1 or 2, myometrial invasion < 50% and tumor diameter < 2 cm) which may omit lymphadenectomy were just a minority group accounting for 13 of the 122 patients (11.61%). Among these, 1/13 had pelvic lymph node metastasis (7.69%) with no para-aortic lymph node metastasis. Our results were consistent with previous studies[19] which showed that low risk groups presented low rates of nodal metastasis. In conclusion, for our population, a majority of patients still have the criteria to undergo lymphadenectomy because 92.86% of our patients had a tumor diameter > 2 cm.

For the strength of the study, we did calculations of the diagnostic indices of all five clinical parameters that should be included in intraoperative gross assessment. Also, our institute is a medium sized center that has appropriate human resources such as many skilled oncologists, a resident training system, and pathologists. All final pathological results were finalized by our hospital pathologists.

As previously mentioned, one limitation of our study was the data collection. We encountered the problem about incompleteness of operative findings. Each operative finding was recorded by obstetrics and gynecology residents but not all clinical parameters were recorded in every operative note. So, when coming to the diagnostic indices calculation, it reduced the included sample numbers for calculation and this might have affected the final results. Another limitation was that our population distribution which we found that most of our patients had tumor size > 2 cm and low risk for nodal metastasis patients were too limited to conducted a subgroup analysis to assess the diagnostic accuracy indices of this specific group.

As we reviewed, intraoperative gross assessment had the best accuracy in determining which patients need lymphadenectomy[8]. Nowadays, intraoperative frozen section (IFS) is also a helpful tool to determine surgical extent. In a previous systemic review[20] showed that IFS was better in accuracy in endometrial cancer patients with deep myometrial invasion. In our setting, IFS may not be feasible due to the requirement for specialized, skilled, and available pathologists.

In the future, if similar studies were to be performed, we suggest that data collection of operative notes might be conducted in a standard form which includes all the essential parameters that should be included. Moreover, we suggest that a longer time of data collection with more samples included in order to provide the diagnostic accuracy indices. Lastly, for the best results a change of study design to a prospective data collection approach might be more suitable as it would be possible to control all the settings from the beginning of the study.

Conclusion

Gross intraoperative assessment in surgical staging had good specificity and accuracy but poor sensitivity. The results implied that gross intraoperative assessment is an applicable tool. It is also easy to use and is an inexpensive tool. In conclusion, as gynecologists, we learned that surgeons should pay careful attention to intraoperative gross assessment and should always practice their skills. However, modality and intervention should be better combined in order to maximize the diagnostic accuracy and to help decide the best surgical treatment for each individual.

Potential conflicts of interest

The authors declare no conflicts of interest.

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