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Comparing the Intraoperative Frozen Section With Permanent Pathology in Assessing the Depth of Myometrial Invasion, Tumor Size, and Histological Subtype and Grade in Endometrial Cancer

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Abstract

Objectives: Endometrial cancer is one of the most important and prevalent malignancies among women and its treatment and prognosis depends on the severity and spread of the disease in the body. The present study aimed to evaluate the accuracy of the frozen section (FS) as a reliable method for intraoperative decision-making in patients with endometrial endometrioid adenocarcinoma.

Materials and Methods: This study was conducted during September 2016- February 2017 on 50 patients with endometrioid adenocarcinoma, detected by the diagnostic curettage which was the total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO) surgery candidate in the oncology ward of Al-Zahra hospital of Tabriz. Tissue samples of TAH + BSO patients sent for FS pathology were evaluated in terms of histological subtype criteria including endometrioid, serous, clear cell, undifferentiated, tumor grade 1, 2, and 3, tumor size in cm smaller or bigger than 2 cm, and myometrial invasion (MI) rate higher or lower than 50 %. FS results were compared to the final results of the paraffin section (PS) pathology.

Results: The concordance rate between PS and FS regarding the risk factors of endometrioid (k: 0 .492, $P<0.001$), myometrium invasion (k: 0.729, $P<0.001$), tumor size (k: 0.800, $P<0.001$), tumor grade (k: 0.641, $P<0.001$), undifferentiated (k: 0.545, $P<0.001$), adenosquamous (k: 0.390, $P<0.005$), papillary serous (k: 0.658, $P<0.001$), and clear cell (k: 0.479, $P<0.001$) was 49, 73, 80, 64, 54, 39, and 65 %, respectively.

Conclusions: Based on the results, if FS is accurately and precisely implemented, an appropriate decision can be taken for low-risk patients. This method can successfully be adopted by the gynecologic oncologists.

Keywords: Endometrial cancer, Frozen section, Paraffin section, Surgical staging

Introduction

Endometrial cancer is the most prevalent gynecologic malignancy in the world with around 10470 deaths in the United States in 2016. In addition, the incidence rate of endometrial carcinoma increases by 1%-6% each year. Most of the women diagnosed at early stages have a rather good prognosis, yet those with advanced or recurrent diseases have a poor prognosis (1). International Federation of Gynecology and Obstetrics (FIGO) staging is an important determinant of the outcomes of patients with endometrial cancer. Metastatic status of the lymph nodes is the most essential indicator of endometrial cancer stage and as such evaluating the status of pelvic and para-aortic lymph nodes is important in this respect. Therefore, all endometrial cancer patients should undergo a total hysterectomy and bilateral salpingo-oophorectomy, as well as pelvic and para-aortic lymphadenectomy (PLND-PALND). In the case of histological subtype criterion endometrioid adenocarcinoma, FIGO grade 1 and 2, myometrial involvement less than 50%, and tumor size smaller than 2 cm, endometrial cancer would be considered a low risk (1). In these patients, the disease may be treated by the total hysterectomy and bilateral salpingo-oophorectomy since metastasis to lymph nodes is less than 4%. This therapeutic approach has no significant effect on the prognosis and therefore, lymphadenectomy can be ignored to prevent further morbidity and the related costs (2). Only a small proportion of patients with low-risk endometrial cancer may benefit from routine and comprehensive surgery like the lymphadenectomy. However, those with high–risk factors are treated with comprehensive staging surgery including PLND-PALND,

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as well as omentectomy (if needed) without performing frozen section (FS) (2). Accordingly, the key question is how to identify those endometrial cancer patients who may need complete surgical staging.

Using intraoperative FS represents the cornerstone of this intermediate strategy since it should identify low and high-risk features (3). If FS results suggest high-risk attributes such as high grade, deep myometrial invasion, tumor size bigger than 2 cm, then full surgical staging is conducted (4). However, there are contradictory reports on findings related to intraoperative FS and a number of researchers consider these results as a valuable guideline for intraoperative decision making (4). The limitations of the FS approach in endometrial cancer may include the need for an expert pathologist, freezing artifacts introduced by the FS technique, and time limitation (3).

Since the possibility of lymph node metastasis in lower-risk tumors is less than 4%, lymphadenectomy may be eliminated to prevent morbidity and costs. Otherwise, bilateral PLND/PALND must be performed. In this study, patients with endometrial cancer undergo comprehensive surgical staging such as the total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO), PLND/PALND in the oncology ward of Al-Zahra hospital. It is supposed that lymphatic metastasis is low in low-risk patients and lymphadenectomy makes no changes in the patient's survival or may even impose mortality upon the patient. Accordingly, the findings of this applied research can be used to eliminate the lymphadenectomy in low-risk patients if FS results match the pathology results. Therefore, this research sought to evaluate the accuracy of FS as a reliable method for intraoperative decision making in patients with endometrial endometrioid adenocarcinoma.

Accordingly, all of the patients suffering from endometrial cancer in Alzahra hospital are subject to surgical treatment and systematic lymphadenectomy (surgical staging) while if uterus is sent to FS during the surgery and signs of low risk factors encompassing endometrioid adenocarcinoma, tumor size smaller than 2 cm, grades 1 and 2, and myometrial involvement less than 50% appear, then lymphadenectomy which comes along with morbidity can be stopped. This review is done in Alzahra hospital by a gynecologic oncologist and a pathologist. Accordingly, this review was conducted to compare the concordance results of FS with those of the permanent pathology. Therefore, in the case there is a concordance between these two factors, then it can be used by all gynecologic oncologists and pathologists as an instruction.

Materials and Methods

The current study was performed during 2016 (September)-2017 (February) on patients with endometrioid adenocarcinoma, detected by diagnostic curettage who were admitted for TAH + BSO and surgical staging in the oncology ward of Al-Zahra hospital in Tabriz. Fifty patients were included in the study, who underwent diagnostic curettage before completing the surgery and their histology result was endometrioid adenocarcinoma, grade1. Non-endometrioid histology, tumor grade 3 results, and patients who represented extrauter in the spread of tumor by the para clinic and intraoperative intra-abdominal and pelvic examination were excluded from the study. TAH + BSO surgery and uterus bivalve were conducted by a surgeon from the cervix to the fundus of the uterine. Then, the tumor size was measured by a ruler and the extent of myometrial invasion (MI) was estimated by the surgeon accordingly. Then, the uterus was sent to the pathology department to perform FS and permanent pathology.

Tissue samples were evaluated by FS in terms of histological subtype criteria including endometrioid, serous, clear cell, undifferentiated, tumor grades 1, 2, and 3, tumor size smaller or bigger than 2cm, and MI rate higher or lower than 50% FS results were compared to the final results of paraffin section (PS). The uterus samples were measured by FS during the surgeries and low-risk symptoms which reduced the chance of metastasis to lymph nodes including grade 1, MI less than 50%, tumor size smaller than 2 cm, and endometrioid carcinoma were identified. FS and permanent pathology results were then compared.

Inclusion criteria were patients undergoing a total hysterectomy and bilateral salpingo-oophorectomy, those with endometrioid adenocarcinoma diagnosis, endometrial invasion <50%, tumor size <2 cm by FS results, and non-extra-uterine intraoperative macroscopic invasion.

Exclusion criteria encompassed pathology other than endometrioid adenocarcinoma and extra-uterine involvement.

Finally, the concordance of subtype, grade, tumor size, and depth of the MI between FS and the permanent section was compared. Data were analyzed using the SPSS software, version 17. Further, Cohen (kappa) statistic was employed to assess the concordance rate between the FS and final pathology with regard to histologic subtype, grade, size, and MI. The results were considered statistically significant at $P < 0.05$.

Results

A total of 50 patients with endometrial cancer on either endometrial curettage pathology or without evidence extrauterus speared of the tumor by the para clinic and pelvic exams were analyzed. FS and PS were performed on all patients for histological subtype, tumor size, depth of MI, and the grade. The concordance rate of histological subtype, grade, as well as the size and depth of the MI between FS and PS were evaluated in all patients. The findings indicated that participants aged between 35 and 71 years with an average of 55.61 years. Thirty-nine out

of 50 patients were positive in PS for the endometrioid carcinoma while 11 others were negative in FS for endometrioid tumor. Furthermore, 38 out of 50 cases were positive in FS whereas 11 patients were negative in PS for endometrioid carcinoma. The concordance rate of endometrioid subtype between permanent pathology and FS is 4%. As represented in Table 1, 45 out of 50 cases are negative for undifferentiated in FS, 2 cases are positive for undifferentiated in PS and FS, and finally, 48 cases are negative for undifferentiated.

Moreover, the concordance rate of undifferentiated subtype between permanent pathology and FS is 54.5%. Based on Table 1, 45 patients are negative while 4 cases are positive for adenosquamous in FS. Finally, 5 cases are found positive while the remaining 45 cases are negative for adenosquamous in PS.

Additionally, the concordance rate of adenosquamous subtype between the permanent pathology and FS was 39%. 49 out of 50 cases were negative in terms of papillary serous in FS and only 1 patient was positive in this regard. Eventually, 48 patients were found negative as regards papillary serous in PS while 2 cases were detected positive. As shown in Table 1, the concordance rate of papillary serous subtype between the permanent pathology and FS is 66%.

Based on the data in Table 2, considering 50% MI as a cutoff, the concordance of the depth of MI is 73% between FS and PS. Further, 41 tumors in FS and 41 tumors in PS have an MI < 50%. 7 tumors in PS have an MI > 50%.

Table 1. Concordance Rate Between Permanent Pathology and FS in Histologic Subtype Diagnosis

		FS		Kappa Coefficient	*P*
		Yes	No		
Endometrioid P	Yes	34	5	0.492	<0.001
	No	4	7		
Undifferentiated P	Yes	2	3	0.545	<0.001
	No	45	0		
Adenosquamous P	Yes	2	2	0.390	0.005
	No	43	3		
Papillary serous P	Yes	1	0	0.658	<0.001
	No	1	48		
Clear cell	Yes	1	1	0.479	<0.001
	No	1	47		

P, permanent pathology.

Table 2. Concordance Rate Between Permanent Pathology and FS in Myometrial Invasion and Tumor Size Diagnosis

		Myometrium P		Kappa Coefficient	*P*
		>50%	<50%		
Myometrium F	>50%	7	2	0.729	<0.001
	<50%	2	39		
		Tumor size P			
		≤2 cm	>2 cm		
Tumor size F	≤2 cm	22	2	0.800	<0.001
	>2 cm	3	23		

F, Frozen Section; P, permanent pathology.

Tumor size more than 2 cm was considered a risk factor for lymph node metastatic while that of less than 2 cm in the group is a low risk factor. As shown in Table 2, among all 50 cases, 24 tumors are < 2 cm while 26 tumors are > 2 cm in FS. Furthermore, 25 tumors are <2 cm while the remaining 25 tumors are >2 cm in PS. The concordance rate of tumor size between FS and PS is 80% (Table 2).

As represented in Table 3, among all the 50 cases, 12 tumors are grade 1 while 12 tumors are grade 2 in PS and FS. In addition, 14 tumors are grade 3 in PS and FS. The concordance rate of grade between FS and PS is 64%.

The results of the correlation rate between FS and PS for endometrioid subtype had KAPP coefficient (K) value of 0.492 and was significant at $P < 0.001$ (Table 1). Moreover, the concordance level of myometrium above and below 50% (MI) had a K value of 0.792 and a $P < 0.001$ (Table 2). As regards the tumor size, the concordance between the two methods had a K value of 0.800 and was significant at $P < 0.001$ (Table 2). The K value for the concordance rate in tumor grade was 0.641 and it was significant at $P < 0.001$ (Table 3). Additionally, the results regarding the undifferentiated indicated that K and significance values were 0.545 and < 0.001, respectively (Table 1). Finally, the concordance rate for papillary serous demonstrated a K value of 0.658 and a significant level of < 0.001 (Table 1).

Discussion

The main surgical treatment for endometrial cancer is the total hysterectomy and bilateral salpingo-oophorectomy and surgical staging. In addition, the status of para-aortic and pelvic lymph nodes affects both the continuance of post-surgery adjuvant treatment and survival (5). Total systemic lymphadenectomy during surgical staging is approved by most researchers and applicable to high-risk patients. However, the role of total lymphadenectomy is not clear for the low-risk patients at the early stages of the disease (6-10).

In a study, the concordance rate of endometrial cancer results between FS and PS methods was 100, 89.3, 97.3, and 95.5% in terms of histological subtype, grade (100/112), MI (109/112), and tumor size (107/112), respectively. Further, it was revealed that intraoperative FS diagnosis regarding the endometrioid was highly effective for surgical staging (2).

Similarly, another research demonstrated that lymph nodes metastasis was low in low-risk endometrioid cancer and that lymphadenectomy had no beneficial

Table 3. Concordance Rate Between Permanent Pathology and FS in Grade Diagnosis

		Grade F			Kappa Coefficient	*P*
		2	2	3		
Grade P	1	12	2	1	0.641	<0.001
	2	7	12	0		
	3	0	2	14		

P, permanent pathology.

effect on such patients (11). Furthermore, the results of another study indicated that metastasis to lymph nodes was 0.8% (12). Therefore, performing lymphadenectomy for all endometrioid patients imposes additional costs and treatments and increases the rate of mortality. Accordingly, using the FS method helps diagnose the histological subtype, tumor grade and size, MI, and even lymphovascular space involvement. Moreover, FS method acts as a guide for diagnosing the metastasis to para-aortic and pelvic lymph nodes in high-risk patients and avoids performing lymphadenectomy in low-risk patients (13).

The present study was implemented to compare the results of the FS with permanent pathology so that to determine metastatic factors to pelvic and paraaortic lymph nodes. The risk factors included: histological subtype, tumor size smaller than 2cm, 1 and 2 grade, and myometrial involvement less than 50% (7).

Based on lymphadenectomy during the surgery in the early stage, endometrial carcinoma depends on lack of any low risk factors. Therefore, focusing on lymphadenectomy was highlighted in this study regarding the low risk factors. However, a systematic lymphadenectomy vs. lack of lymphadenectomy was not intended in the research.

In the case of endometrioid adenocarcinoma, FIGO grade 1, 2, myometrial involvement less than 50%, and tumor size smaller than 2 cm, the endometrial cancer is considered low risk, and thus lymphadenectomy is probably eliminated in this patients (2).

Based on the results of the present study, the concordance rate of the risk factors endometrioid, myometrium, tumor size, grade, undifferentiated, adenosquamous, pupillary serous, and clear cell was 49, 54.5, 39, 65, 64, 73, and 80%, respectively. These results suggest that if FS is performed accurately and precisely, an appropriate decision can be made for the patient's state. Additionally, the results indicated that high concordance rate between FS and final pathology belonged to histological subtype ($P<0.001$), MI ($P<0.001$), and grade ($P<0.001$), tumor size ($P<0.001$).

The results of this study are in line with the results of several other published reports, confirming the reliability of intra-operative FS in guiding the management of early-stage endometrial cancer. The method minimizes over-treatment and morbidity while allowing gynecologic oncology to select those patients for whom lymphadenectomy is a possible therapeutic, prognostic, and treatment-planning information (14).

Results of the research conducted on 111 patients during (January) 2013-(December) 2014 indicated that employing FS for diagnosing the low-risk cases before comprehensive staging was highly useful in reducing the risk. In addition, the results revealed that there was a significant relationship between the histological type and invasion depth in PS and FS methods and that FS helped the oncologists make the final decision (15).

Further, based on the findings of another research on 116 patients, an association was found between PS and FS results in terms of subtype (97.5%), grade (88%), and MI depth (98.2%), respectively. Furthermore, it was reported that a total of 7 patients were diagnosed with atypical complex hyperplasia in FS method while they were diagnosed with cancer in PS and that eventually, two patients were not treated completely (14). Research on tumor grade suggests that the correlation between the two methods is 56%-97% (16-19). Several other studies using transvaginal ultrasound highlighted a 58%-95% sensitivity in diagnosing MI and a 71%-92% specificity for this method (20-25). Moreover, various studies revealed that the concordance between PS and FS was 98.7%, 58%-98%, and 54%-96.6% regarding histological subtype, grade, and MI, respectively (26-31). However, some studies reported a poor relationship between PS and Fs methods (27, 28)

The results of the present study are in conformity with the related literature, indicating that using the FS method for diagnosing the pathological risk factors of lymphadenectomy may lead to rather successful treatment. The current results demonstrate that FS is an effective and appropriate method for treating patients with low-risk endometrial cancer.

Conclusions

In general, high rates of concordance were found between FS and PS respecting histological subtype, MI, as well as grade and size of the tumor. This study was conducted in gynecology oncology diagnostic center where experienced gynecologic pathologists and gynecologic oncology work. Therefore, the results may not be generalized to smaller diagnostic centers where these specialists do not work. Eventually, gynecology oncology diagnostic centers are recommended to implement a separate study in order to review the accuracy of FS for guiding the intra-operative decision regarding lymphadenectomy.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences under the number IR.TBZMED.REC.1397.341. Written informed consent was obtained from all participants in the study.

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