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RESEARCH

The Guidance of Intraoperative Frozen Section For Staging Surgery in Endometrial Carcinoma

Frozen section in endometrial carcinoma

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Abstract The objective of this study was to evaluate the reliability of an intraoperative frozen section during the endometrial carcinoma staging surgery procedure. The paraffin section reports of 291 cases with endometrial carcinoma were compared with intraoperative frozen section reports, which were diagnosed in the Pathology Department of Cukurova University, Medical Faculty between June 2006 and December 2012. The reports were reviewed for diagnostic accuracy of the frozen section in terms of histological subtype, grade, and myometrial invasion. Concordance values between frozen and paraffin section reports were 86, 84.3, and 91.6 % for histological subtype, grade, and myometrial invasion, respectively. When collectively evaluated, two (0.7 %) of 291 patients were inappropriately operated on due to frozen section reports. Intraoperative frozen section is a reliable guide for surgeons to evaluate the risk group of patients with endometrial cancer and prevent an unnecessary staging surgery operation.

Keywords Endometrial cancer · Intraoperative frozen section · Staging surgery

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Introduction

Intraoperative evaluation of gynecological tumors with a frozen section (FS) is the most common use of FS, and is associated with the frequent incidence of endometrial and ovarian tumors. Additionally, the most reliable guide for a surgeon to make a decision about the surgical staging procedure is the intraoperative FS report.

A total abdominal hysterectomy and bilateral salpingooopherectomy is the first-choice treatment for early stage endometrial cancer. However, it is not adequate for patients who are at risk of lymph node metastasis. The staging surgery procedure, which includes pelvic and para-aortic lymph node dissection, can be added to the primary operation. The risk of lymph node metastasis increases with tumor grade, depth of myometrial invasion (MI), cervical or adnexal involvement, lymphovascular invasion, and poor histological subtype [1]. The reported incidences of pelvic and para-aortic lymph node metastases range from 5 to 34 and 5 to 25 % [2]. Other than the prognostic importance of lymph node metastasis, pelvic and para-aortic lymphadenectomy increases morbidity, so the surgeon has to behave selective while deciding to perform staging surgery.

An intraoperative frozen section (IFS) is obtained for all endometrial cancers at our institute, except in high-risk patients (serous or clear cell carcinoma, grade 3 endometrioid carcinoma), to determine the risk group of the patient. In this retrospective study, we documented our experience with endometrial cancer and determined the diagnostic accuracy and concordance of IFS with paraffin sections at our institute.

Materials and Methods

In this retrospective study, reports of 291 endometrial carcinomas with FS diagnoses between July 2006 and December

2012 were re-evaluated. All cases were diagnosed previously as either complex hyperplasia (27 cases) or endometrial carcinoma (264 cases) by endometrial biopsy or curettage. High-risk patients (serous carcinoma, clear cell carcinoma, or grade 3 endometrioid carcinoma) were excluded, because the staging surgery is performed routinely on available patients. The hysterectomy specimen was intra-operatively delivered to the pathologist for FS. Almost all cases were evaluated by a gynecopathologist both macroscopically and microscopically. The uterus was opened along the both lateral walls, and sliced transversely. One or two slices from the macroscopically deepest invasion sites of the tumor were sampled. These sections included the uterus wall from mucosa to the serosa for appropriate myometrial invasion measurement. Tumor size, histological subtype, grade, MI, cervical and adnexial involvement were reported to the surgeon. The staging surgery procedure (pelvic-para-aortic lymphadenectomy) was performed based on the FS report. At our institute, the staging surgery procedure is performed with the following criteria: Grade 1 or 2 endometrioid carcinoma with MI>50 %; grade 3 tumors; tumors with cervical extension; clear cell or serous carcinoma; tumor size>2 cm.

All FS reports were compared with the paraffin section (PS) final reports. PS diagnoses reported by an experienced gynecopathologist were accepted as accurate diagnoses. The specimens were checked by the same gynecopathologist who evaluated the frozen sections. Twenty-nine cases diagnosed as "complex endometrial hyperplasia with atypia" in IFS were not included in the grade and myometrial invasion correlations. "Over-subtyped" meant high-risk histological diagnoses including serous, clear cell carcinoma reported in the IFS, which were diagnosed as endometrioid adenocarcinoma in PS diagnoses. "Under-subtyped" meant visa versa.

All risk factors were evaluated collectively. The term "inappropriate" was used if the patient had undergone lymphadenectomy after the primary surgery or was unnecessarily operated on during the primary surgery on the basis of IFS diagnoses.

The results between FS and PS were analyzed for discordance, and for diagnostic accuracy of IFS, as well as specificity and sensitivity of IFS.

Results

The total number of frozen sections studied over a 5-and-a-half-year period was 4239. A total of 698 (16.5 %) of these cases were gynecological tumors. The distribution of cases was as follows: 299 (42.8 %) ovarian masses, 291 (41.7 %) endometrial tumors, 49 (7 %) smooth muscle tumors or polyps, 24 (3.4 %) cervix uteri tumors, 35 (5 %) other various benign lesions.

The mean age of the patients was 54.5 years (range, 27–81 years).

Histological Subtype

The distribution of final PS diagnoses of the 291 endometrial tumors was as follows: 271 (93.1 %) endometrioid adenocarcinomas, 8 (3.1 %) malignant mixed Mullerian tumors (MMMT), 7 (2.4 %) endometrioid and mucinous, 2 (0.7 %) endometrioid and clear or serous carcinomas, 1 (0.3 %) serous, 1 (0.3 %) endometrioid + mucinous + serous, and 1 (0.3 %) undifferentiated + endometrioid carcinoma. The diagnostic accuracy of FS was 87 % based on the PS histological subtype diagnoses.

FS and PS histological diagnoses were concordant in 253 of 291 cases (87 %). Twenty-nine cases (10 %) were false-negatives, six (2.1 %) were under-subtyped, and three (1 %) were over-subtyped based on PS diagnoses. The FS diagnoses of 25 of the 29 false-negative cases were complex hyperplasia with atypia, the remaining four cases were diagnosed as endometrial polyps. The final PS reports of all 29 cases were endometrioid adenocarcinoma, FIGO Grade 1, with minimal or no myometrial invasion. The surgical procedure was sufficient with no additional staging surgery necessary in these 29 patients, because of their low-risk category.

The histological subtypes of nine of the 291 cases were discordant. Of the nine cases, six were histologically under-subtyped as endometrioid adenocarcinoma. Their final PS diagnoses were two cases of MMMT, two cases of endometrioid + clear or serous carcinoma, one serous carcinoma, and one endometrioid + mucinous + serous carcinoma. Four of these under-subtyped cases did not allow additional staging surgery, because they showed other high-risk factors such as myometrial invasion>50 %, grade 3, and/or low uterine segment invasion. The other two of six cases were re-operated for staging surgery (0.7 %).

Three of nine cases were over-subtyped as endometrioid + serous or clear cell carcinoma on the FS. Final PS diagnoses of all three cases were endometrioid adenocarcinoma, FIGO Grade 3. Finally, the patients were in the high-risk group, so the surgical staging procedure was performed for these three cases, as the PS diagnoses required. These cases were not allowed to undergo unnecessary operations up to the FS report.

Grade

Of the 291 cases, 29 were not diagnosed as carcinoma, so they were not graded. Concordances between FS and PS diagnoses in terms of grades 1, 2, and 3 were 94.2, 75, 66.7 % respectively, and 84.3 % overall. Thirty (12.2 %) of 262 cases were upgraded and 11 (10.1 %) cases were downgraded in the PS reports. Of the 153 cases reported as grade 1 on FS, 129 were diagnosed as grade 1 (no additional operation), 23 as grade 2 (19 cases with myometrial invasion<50 %, three with>50 %, one with low uterine segment invasion), one as grade 3 (the

staging procedure was performed during the first operation because of myometrial invasion>50 %) in PS (Table 1).

Six of the 92 cases reported as grade 2 in FS were upgraded to grade 3 on the PS. These cases were tumor size>2 cm and/or myometrial invasion>50 %. So, these cases underwent the staging procedure during the first operation because of other high-risk factors. Eight cases were downgraded from grade 2 to grade 1 in the PS. These cases did not require re-operation when collectively evaluated with other risk factors.

Three of the 17 grade 3 cases were downgraded to grade 2 in PS. These cases showed other high-risk factors in FS, so they underwent the staging procedure during the operation. Specificity and sensitivity of IFS was 99 and 67 % based on histological grade. Additionally, positive predictive value (PPV) and negative predictive value (NPV) was 0.82 and 0.97 respectively.

No operative changes because of grading discordance were present in this study.

Myometrial Invasion

Twenty-nine cases, which were not diagnosed as carcinoma in IFS, were excluded from the MI analysis. Of the 262 patients, 231 (88.2 %) showed MI. Four of the 52 cases with MI>50 % in the FS were overestimated (Table 2). One of these four cases was grade 2 with a tumor size>2 cm, one case showed cervical invasion. Thus, these two cases did not allow for an additional operation. The other two cases were low-risk patients in the final report, and the staging procedure was performed during the operation according to the FS report. Eight of 210 cases with no MI or MI≤50 % in FS were underestimated (Table 2). Four cases were grade 3 and two cases were grade 3 with cervical invasion, so staging surgery was performed. The other two cases were grade 1 with 52 % and 55 % MI. These two patients underwent the staging surgery during the first operation, because tumor size was> 2 cm in the former, and MI was 50 % in the FS of the latter. An operative change because of discordance on MI was present in two cases.

Sensitivity and specificity of IFS based on MI was 86 and 98 % respectively, PPV was 0.92 and NPV was 0.96.

When all of the histological risk factors were considered, 2 (0.7 %) of the 291 cases (two cases overestimated) were inappropriately operated on due to IFS reports.

Discussion

Surgical staging for endometrial carcinoma provides information about prognosis and postoperative adjuvant chemotherapy. This procedure includes a pelvic and para-aortic lymphadenectomy, in addition to a hysterectomy and bilateral salpingooferectomy. Hence, the lymphadenectomy increases the risk of morbidity, and several methods of identifying the high-risk group of patients have been investigated. Some examples of these methods are predictive modeling using trans-vaginal ultrasound [3], magnetic resonance imaging [4], or computerized tomography scans [5]. These methods provide information about tumor size and MI but they do not provide an assessment of histological subtype or grade, which are also important to decide to do the staging surgery. For this reason, widely used IFS has been questioned by several authors and diverse results occur in the literature [6–9].

In this study, 2 (0.7 %) of 291 patients were inappropriately operated on according to the FS report when all risk factors were considered. This ratio was 1.3 % in a prospective study from the Mayo Clinic [10] and 5.3 % in another study [6].

Kumar et al. detected 31 (4 %) histologically discordant cases of 784 in their study [10]. This number was 38 (13 %) of 291 cases in the present study. The diagnostic accuracy for histological subtype was 87 % in our study. The majority of discordant cases was focally present endometrioid adenocarcinoma, grade 1 with no or minimal MI- in complex hyperplasia with atypia (25 cases) and in endometrial polyps (four cases). These focal carcinoma areas were not sampled with FS. However sufficient surgery was performed. The other nine discordant cases were diagnosed as mixed carcinomas either in the FS or PS report. These cases showed other high-risk factors, so the staging surgery was performed during the first operation. Discordance of the histological subtype may be

Table 1 Preoperative and postoperative results of grade. Twenty-nine cases with no carcinoma diagnoses in frozen section are not included

Frozen section report	Paraffin section report			Total
	Grade 1	Grade 2	Grade 3	
Grade 1	129	23	1	153
Grade 2	8	78	6	92
Grade 3	0	3	14	17
Total	137	104	21	262

Table 2 Preoperative and postoperative results of myometrial invasion. Twenty-nine cases with no carcinoma diagnoses in frozen section are not included

Frozen section report	Paraffin section report			Total
	No MI	MI ≤50 %	MI >50 %	
No MI	27	6	0	33
MI ≤50 %	4	165	8	177
MI >50 %	0	4	48	52
Total	31	175	56	262

MI myometrial invasion

related to limited sampling during intraoperative FS, and the effects of freezing artifacts on microscopic appearance.

The concordance between FS and PS in terms of grade ranges from 58 to 98 % in the literature [10–13]. This number was 84.3 % in our study. The highest concordance was in grade 1 (94.2 %), then grade 2 (75 %), and grade 3 (66.7 %). Of the 137 grade 1 cases in PS, eight were downgraded from grade 2 and none from grade 3. Of the 104 grade 2 cases, 23 were upgraded from grade 1, three were downgraded from grade 3. Of the 21 grade 3 cases, six were upgraded from grade 2 and one was from grade 1. All of these discordant cases in terms of grade showed other high-risk factors, so the grade was not decisive alone for the operative change made in this study.

The highest concordance between FS and PS was detected in MI in the present study (91.6 %). This value ranges from 54 to 95 % in the literature [10, 11, 14–16, 7]. Eight (3 %) cases were underestimated and four (1.5 %) cases were overestimated. This was 10.6 and 4 % in another study [11]. The reason for the higher underestimation rate of that study was that they included cases without carcinoma in the FS. That group was not included in the MI analysis in our study. Of the 12 discordant cases, two were staged even though they were low-risk patients according to the PS report.

The major cause of inaccurate IFS reporting for inappropriate surgery was MI in the present study. Four cases showed narrow MI invasion ranging from 38 to 53 %. This difficulty has been documented in the literature [6]. In this situation, if the patient does not have other high-risk factors the surgeon tends to perform the staging surgery in absentia of comorbidity risk of the patient such as obesity or adhesions.

The major advantage of the IFS is the ability to evaluate various risk factors at the time of the operation. Thus, the possibility of an inappropriate operation decreases in the presence of any other high-risk factor that directs the surgeon to make the decision for staging surgery.

In conclusion, we showed that IFS was an accurate method for endometrial carcinomas and helped in making a decision regarding staging surgery, which prevented unnecessary procedures that could increase patient morbidity.

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