



Compatibility of Tumor Grades in Pre-Operative Biopsies, Frozen Sections, and Post-Operative Specimens in Patients with Endometrial Cancer

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OBJECTIVE

The aim of this study was to evaluate the compatibility of tumor grades in pre-operative biopsies, frozen sections and post-operative specimens and to evaluate the adequacy of a selective surgical staging policy based on information obtained from intra-operative frozen sections to avoid lymphadenectomy in patients with endometrial cancer (EC).

METHODS

Ninety patients diagnosed with EC were analyzed. Fifty-four patients were at Stage I (60%), 19 were at Stage II (21%) and 17 (19%) were at Stage III. Fifty-four patients (60%) had grades on pre-operative biopsies, 31 patients (34%) had grades on frozen sections and 88 patients (98%) had grades on post-operative specimens. Depth of myometrial invasion was reported in 54 patients (60%) based on frozen sections and in all patients on post-operative specimens. Eight patients (9%) underwent no lymphadenectomy, 32 patients (36%) underwent pelvic lymphadenectomy and 50 patients (55%) underwent pelvic and para-aortic lymphadenectomy.

RESULTS

There were five patients for whom tumors were up-graded when pre-operative biopsies and frozen sections were. There were 17 patients for whom tumors were up-graded and four patients for whom tumors were down-graded when pre-operative biopsies and post-operative specimens were compared. There were six patients for whom tumors were up-graded when frozen sections and post-operative specimens were compared and the distribution of patients between intra-operatively and post-operatively assigned tumor grade groups was statistically significant.

CONCLUSION

For surgeons who do not perform complete surgical staging for every patient with EC, clinical judgment should only be efficient when augmented with information obtained from frozen sections.

Keywords: Adjuvant; endometrial neoplasms; frozen sections; hysterectomy; lymph node excision; radiotherapy.

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Introduction

Endometrial cancer (EC) is the most common cancer of the female reproductive tract, accounting for 4.8% of

all cancers.[1] Most ECs present with postmenopausal uterine bleeding. Endometrioid carcinoma is the most common type for ECs, often associated with unopposed estrogenic stimulation and endometrial hyper-

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plasia.[2] The cornerstone of treatment is surgery and International Federation of Gynecology and Obstetrics (FIGO) advocate surgical staging including pelvic and para-aortic lymphadenectomy in addition to total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO).[3]

Among prognostic features for ECs, depth of myometrial invasion is particularly associated with pelvic lymph node involvement and parametrium extension, which may alter both staging and therapeutic approaches. The assessment of the depth of myometrial invasion will allow an adequate selection of low-risk cases and avoid unnecessary lymphadenectomy and associated morbidity.[4] The most common usage of intraoperative frozen sections in gynecological oncology is associated with ECs. There is only moderate agreement on tumor grade between pre-operative biopsies and post-operative specimens, with the lowest agreement being observed for Grade 2 tumors. Furthermore, overall agreement for tumor grade between frozen sections and post-operative specimens ranges from 30% to 60%.[5,6] Hence, a selective surgical staging policy based on predictive models to avoid lymphadenectomy should take into account parameters other than tumor grade reported in pre-operative biopsies and frozen sections.

The aim of this study was to evaluate the compatibility of tumor grades in pre-operative biopsies, frozen sections, and post-operative specimens and to evaluate the adequacy of a selective surgical staging policy based on information obtained from frozen sections to avoid lymphadenectomy in patients with EC who were admitted for post-operative adjuvant radiotherapy.

Materials and Methods

Following approval by Sakarya University Faculty of Medicine Research Ethics Committee, 120 patients with EC who applied for adjuvant radiotherapy from 2012 to 2020 were retrospectively analyzed. Ninety patients meeting the required criteria were included in the study. The following data were obtained from the patients' charts: Age, tumor grade from preoperatively obtained biopsies, tumor grade and depth of myometrial invasion from intraoperatively obtained frozen sections, tumor grade, depth of myometrial invasion, lymphovascular space invasion, tumor size, and tumor location from postoperatively obtained specimens.

A three-tiered grading system (as suggested by FIGO) was used to evaluate tumor grade. The depth of myometrial invasion was recorded in millimeters and

grouped as <50% invasion or >50% invasion. Lymphovascular space invasion was defined when malignant cells were present in the endothelial-lined spaces. Tumor size was measured in centimeters in its maximum extension. Tumor location was defined as either involving one subsite or diffusely involving the uterine cavity.

Patient and Tumor Characteristics

Median age was 64 years (30-81 years). Fifty-four patients (60%) were at Stage I (22 in Stage Ia and 32 in Stage Ib), 19 patients (21%) were at Stage II, and 17 patients (19%) were at Stage III (six in Stage IIIa, seven in Stage IIIc1, and four in Stage IIIc2). The distribution of patients according to stage is shown in Table 1.

Fifty-four patients (60%) had tumor grades assigned on pre-operative biopsies. Of these, 25 had Grade 1 tumors (46%), 22 had Grade 2 tumors (41%), and seven had Grade 3 tumors (13%). Thirty-one patients (34%) had tumor grades assigned on frozen sections. Of these, 13 had Grade 1 tumors (42%), 13 had Grade 2 tumors (42%), and five had Grade 3 tumors (16%). Eighty-eight patients (98%) had tumor grades assigned on post-operative specimens. Of these, 18 had Grade 1 tumors (20%), 52 had Grade 2 tumors (60%), and 18 had Grade 3 tumors (20%). Tumor grades by method of assignment are shown in Table 2.

Table 1 Distribution of patients according to stage

Surgical stage	n	%
1A	22	24
1B	32	36
2	19	21
3A	6	7
3C1	7	8
3C2	4	4
Total	90	100

n: Number of patients

Table 2 Tumor grades by method of assignment

Tumor grade	Pre-operative biopsies		Frozen sections		Post-operative specimens	
	n	%	n	%	n	%
Grade 1	25	46	13	42	18	20
Grade 2	22	41	13	42	52	60
Grade 3	7	13	5	16	18	20
Total	54	60	31	34	88	98

Depth of myometrial invasion was reported in 54 patients (60%) based on frozen sections. Of these, 28 had <50% invasion (52%) and 26 had greater than 50% invasion (48%). Depth of myometrial invasion was reported in all patients on post-operative specimens. Of these, 35 had <50% invasion (39%) and 55 had >50% invasion (61%). On post-operative specimens, tumor size ranged from 1 to 10 cm (median, 5 cm). Tumors were localized in only one subsite in the uterine cavity in 38 patients (42%) and diffusely involved the uterine cavity in 52 (58%).

Surgery

Of all patients, 8 (9%) underwent TAH and BSO without lymphadenectomy whereas 32 (36%) underwent pelvic lymphadenectomy in addition to TAH and BSO and 50 (55%) underwent pelvic and para-aortic lymphadenectomy and peritoneal washing in addition to TAH and BSO. Of eight patients who underwent TAH and BSO without lymphadenectomy, seven were at Stage I and the remaining one was at Stage II. Of 17 patients with Stage III disease, 14 underwent pelvic and para-aortic lymphadenectomy and peritoneal washing in addition to TAH and BSO and three underwent pelvic lymphadenectomy in addition to TAH and BSO. For 32 patients who underwent only pelvic lymphadenectomy, the number of dissected pelvic lymph nodes ranged from 3 to 47 (median, 17). For 50 patients who underwent pelvic and para-aortic lymphadenectomy, the number of dissected pelvic lymph nodes ranged from 5 to 44 (median, 21) and the number of dissected para-aortic lymph nodes ranged from 1 to 51 (median, 7).

Radiotherapy

External beam pelvic radiotherapy was given at a dose of 50.4 Gy in 1.8 Gy fractions in 24 patients (27%), 45 Gy in 1.8 Gy fractions in 64 patients (71%), and 46 Gy in 2 Gy fractions in 2 patients (2%). Median total dose of radiotherapy was 45 Gy and median fraction size was 1.8 Gy. Following external beam pelvic radiotherapy, an HDR brachytherapy boost to the vaginal cuff was applied to 69 (77%), patients at a fraction dose of 5-7 Gy (median, 6 Gy) in 2-4 fractions (median, three fractions). Organs at risk dose constraints were calculated using total equivalent dose (EQD2) according to GEC-ESTRO recommendations.[7] External beam and brachytherapy doses sum up to an EQD2 of 60-74 (median, 68).

Statistical Analysis

Patient characteristics were compared with a Chi-square test. Histological grade (Grade 1 vs. Grade 2 and Grade

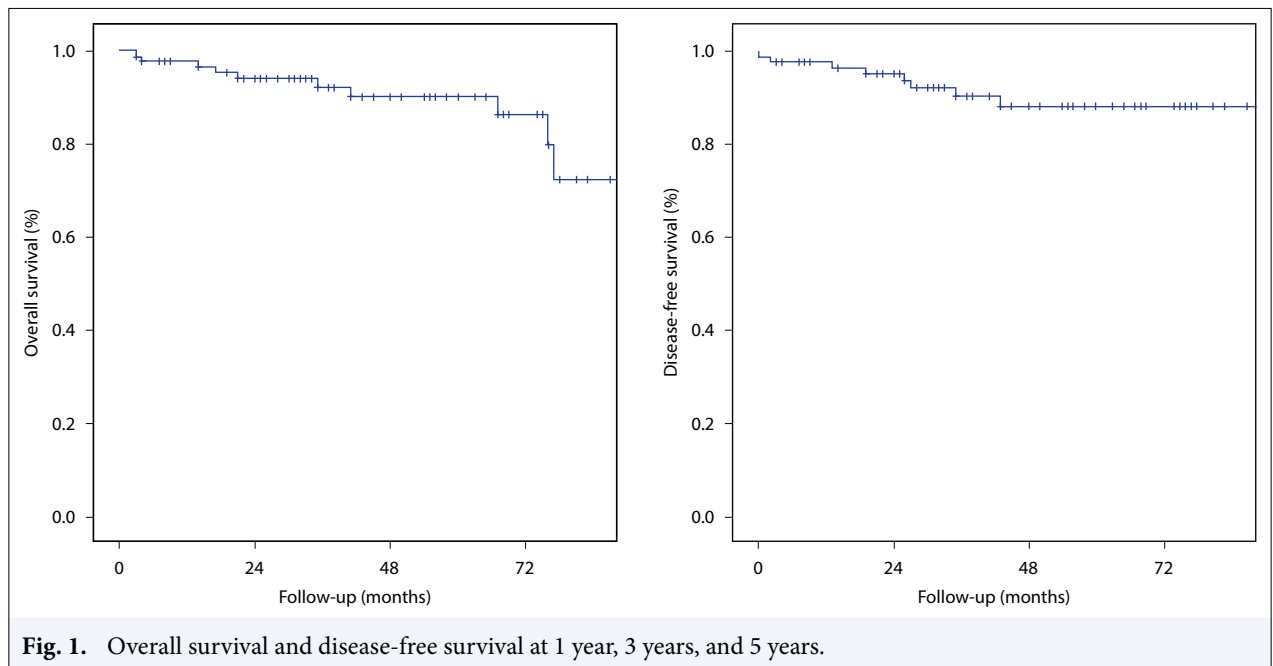
3) and depth of myometrial invasion were used as categorical variables. Survival analysis was performed using the method of Kaplan and Meier method. Overall survival and disease-free survival were calculated starting from the date of the biopsy. Statistical analysis was carried out using the SPSS 21.0 software package. $P \leq 0.05$ was used as the statistical significance level.

Results

There were 19 patients for whom a tumor grade was assigned both preoperatively and intraoperatively. Tumors were upgraded for five of these patients and downgraded for one. The distribution of patients between preoperatively and intraoperatively assigned tumor grade groups was statistically significant ($p=0.05$, $\chi^2=3.52$). There were 52 patients for whom a tumor grade was assigned both preoperatively and postoperatively. Tumors were upgraded for 17 of these patients and downgraded for four. The distribution of patients between preoperatively and postoperatively assigned tumor grade groups was not statistically significant ($p=0.19$, $\chi^2=1.72$). All patients who were downgraded had Grade 2 tumors on pre-operative biopsies. There were 31 patients for whom a tumor grade was assigned both intraoperatively and postoperatively. Tumors were upgraded for six of these patients and downgraded for none. The distribution of patients between intraoperatively and postoperatively assigned tumor grade groups was statistically significant ($p<0.001$, $\chi^2=12.52$). All patients who were upgraded had Grade 2 tumors on post-operative specimens.

There were 54 patients for whom depth of myometrial invasion was assigned both intraoperatively and postoperatively. Depth of invasion was upgraded for six of these patients and downgraded for none. The distribution of patients between intraoperatively and postoperatively assigned depth of myometrial invasion groups was statistically significant ($p<0.001$, $\chi^2=34.47$). Information on lymphovascular space invasion was available on post-operative specimens in 75 patients (83%). Of these patients, lymphovascular space invasion was reported in 21 (28%).

Recurrences were observed in eight patients: At para-aortic lymph nodes in one, as liver metastases in one, as abdominal implants in one, and as pulmonary metastases in five. The patient presenting with a recurrence at para-aortic lymph nodes was initially treated with TAH and BSO without lymphadenectomy due to the absence of a tumor grade on frozen section. Of recurrent patients, five died of their disease at 3-41



months (median, 17 months). The remaining three patients were alive with disease at 34-91 months (median, 67 months) following treatment with palliative chemotherapy. Five patients died due to causes not related to their disease at 14-77 months (median, 67 months). At a mean follow-up of 44 months (ranging from 3 months to 104 months), overall survival at 1 year, 3 years, and 5 years was $98\pm 2\%$ ($n=80$), $92\pm 3\%$ ($n=47$), and $90\pm 4\%$ ($n=29$), respectively, and disease-free survival at 1 year, 3 years, and 5 years was $98\pm 2\%$ ($n=80$), $90\pm 4\%$ ($n=45$), and $88\pm 4\%$ ($n=27$), respectively (Fig. 1).

Discussion

Tumor grade and the depth of myometrial invasion are important prognostic variables that determine the presence of extrauterine disease in EC. The incidence of pelvic lymph node metastases in Grade 1 tumors is reported to be 3%, in comparison to 9% for Grade 2 tumors and 18% for Grade 3 tumors.[8] Similarly, the reported incidence of distant metastases is 2% in Grade 1 tumors, compared with 10% for Grade 2 tumors and 39% for Grade 3 tumors.[9] Hence, tumor grade (as well as the depth of myometrial invasion) should be evaluated by means of several pre-operative and intra-operative parameters to avoid both overtreatment and undertreatment.[10] In a systematic review, moderate agreement has been reported between tumor grades on pre-operative biopsies and post-operative specimens (with the lowest agreement being for Grade 2 tumors)

and clinically relevant upgrading has been found in 8% of patients.[5] On the other hand, the correlation rate between frozen sections and post-operative specimens can reach 88% in experienced institutions.[11] Therefore, frozen sections are almost routinely used in many institutions to assess tumor grade (and the depth of myometrial invasion) to guide intraoperative decisions for lymphadenectomy. Despite the confidence in frozen sections, they are not universally available. Furthermore, determination of tumor grade on frozen sections has not been considered reliable at many institutions since most departments are staffed with general attending pathologists instead of dedicated gynecological pathologists.[6]

The primary aim of this study was to evaluate the compatibility of tumor grades in various specimens. However, not all patients in the study had tumor grades assigned on more than 1 specimen. Tumor grades were reported in pre-operative biopsies in 60%, frozen sections in 34%, and post-operative specimens in 98% of patients. To obtain comparable data, those patients having reports on at least two separate occasions were selected for analysis. When tumor grades on pre-operative biopsies and frozen sections were compared, tumors were upgraded in 26% of patients. Similarly, when tumor grades on pre-operative biopsies and post-operative specimens were compared, tumors were upgraded in 33% of patients. On the contrary, when tumor grades on frozen sections and post-operative specimens were compared, tumors were upgraded in only 19% of patients.

In a retrospective study evaluating tumor grade concordance in 118 patients, frozen sections and post-operative specimens were in agreement in 56% and tumors were upgraded in 44% of 73 patients with Grade I tumors in post-operative specimens, whereas frozen sections and post-operative specimens were in agreement in 80% and tumors were upgraded in 13% and downgraded in 7% in 45 patients with Grade 2 tumors in post-operative specimens. Overall, the concordance in terms of tumor grade between frozen sections and post-operative specimens was 65%.[12] In a study by Batista et al.[6] reporting on 79 patients with EC, the overall level of agreement between pre-operative and post-operative grading was regarded as “fair.” Concordance was 61% for the overall group, 67% for G1 tumors, 44% for G2 tumors, and 40% for G3 tumors. Tumors were upgraded in 15% of patients with Grade I tumors in post-operative specimens. In another retrospective report of 653 patients, pre-operative biopsies correctly identified grading in post-operative specimens in 77% of cases. The authors concluded that pre-operative biopsies were only modest predictors of post-operative specimens.[13]

In a retrospective analysis, the accuracy of frozen sections in determining the depth of myometrial invasion was reported to be high. The concordance between frozen sections and post-operative specimens amounted to 93% for all patients and the accuracy of the frozen sections was not influenced by overall stage. Sensitivity and specificity for all patients were 98% and 89%, respectively.[14] In their study on 460 patients, Quinlivan et al.[15] reported an accurate detection rate of 88% for the depth of myometrial invasion. In another study by Kumar et al.,[12] the depth of myometrial invasion was assessed in 146 patients. Out of 47 patients who were reported to have no evidence of myometrial invasion on frozen sections, 68% were in agreement on post-operative specimens whereas the remaining 32% had varying degrees of myometrial invasion. On the other hand, for 99 patients who were reported to have <50% of myometrial invasion on frozen sections, 74% were in agreement, 12% had no myometrial invasion, and 14% had \geq 50% myometrial invasion. The overall concordance for the presence of myometrial invasion between frozen sections and post-operative specimens was 72%.

The secondary aim of this study was to evaluate the adequacy of frozen sections in attempt to avoid lymphadenectomy in patients with EC. Along with other pathological features such as the depth of myometrial invasion, cervical stromal involvement, and

lymphovascular space invasion, tumor grade impacts the likelihood of nodal spread and disease recurrence. [8] Correlative studies evaluating the association of pathological features with the risk of nodal spread and disease recurrence have fueled the debate on surgical staging policies.[16,17] These studies have mainly analyzed pathological features on post-operative specimens, as opposed to pre-operative biopsies or frozen sections. For surgeons who do not perform complete surgical staging (consisting of pelvic and para-aortic lymphadenectomy and peritoneal washing) for every patient with EC, previous clinical experience is often relied on to assess which patients would benefit from lymph node sampling and clinical judgment is augmented with information obtained from frozen sections and these imprecise individual algorithms preclude any standard to exist. Many surgeons advocate for the assessment of the depth of myometrial invasion intraoperatively as an adjunct to tumor grade on pre-operative biopsies, since this information is frequently used to determine the extent of the surgical staging procedures. When relevant information is not available preoperatively, however, even the assessment of tumor grade intraoperatively becomes an unparalleled factor that is readily available for risk stratification during surgery. When frozen sections are not available for all patients, as were the case in this study, the decisions on the extent of the surgical staging procedures simply based on the information available through pre-operative biopsies harbor an intrinsic margin of error.

Helpman et al.[13] reported on 1329 patients treated for EC, of whom 653 had central review of their pre-operative biopsies by a dedicated gynecologic pathologist. Of 255 patients whose pre-operative biopsies were reported as Grade 1 tumors, 29% were either found to be low-grade tumors with deep myometrial invasion or were reclassified as high-grade tumors on final pathology. Based on these shifts, the authors recommended that omitting surgical staging in preoperatively diagnosed G1 tumors without deep myometrial invasion would result in missing nodal involvement in only 1% of cases. On the contrary, Frumovitz et al.[18] reported on 129 patients with Grade 1 or Grade 2 tumors with a depth of myometrial invasion less than 50% on frozen sections, based on the evaluations by a gynecologic pathologist, who were considered at risk for metastatic disease underwent lymph node sampling. The authors combined the parameters on frozen sections to develop a decision analysis model to predict pelvic and para-aor-

tic lymph node metastasis and categorize the corresponding post-operative specimens into risk groups in accordance with GOG-33. In their study, the evaluation of histologic grade and depth of myometrial invasion in combination on frozen sections did not correlate well with post-operative specimens and the model suggested a significant risk of lymphatic spread even for patients with seemingly low-risk disease. Therefore, the authors recommended complete surgical staging for all of the patients with EC until the existence of better markers for lymphatic spread. In a retrospective cohort study on 83 patients, surgical treatment for early-stage ECs without systematic lymphadenectomy did not seem to decrease survival outcomes and presented low rates of surgical morbidity, however at the expense of a high rate use of adjuvant therapy.[19] On the contrary, in another retrospective cohort study on 128 patients with EC undergoing surgical treatment including systematic (pelvic or pelvic and para-aortic) lymphadenectomy, the indications for lymphadenectomy per pre-operative biopsies were maintained in 76% of patients and 20% of patients had nodal metastases among those with an indication of lymphadenectomy. A lymphadenectomy was indicated per post-operative specimens in all of the patients with nodal metastases. Furthermore, a lymphadenectomy was indicated per post-operative specimens (but not per pre-operative biopsies) in 33% of patients, including 32% of patients with nodal metastases.[20]

Most management guidelines recommend TAH and BSO without lymphadenectomy (only if complemented with intraoperative assessment of the surgical specimen) for patients who have been diagnosed with Grade 1 and Grade 2 tumors based on their pre-operative biopsies, whereas pelvic (and para-aortic) lymph node dissection remains as the staging procedure of choice for all of the remaining patients. Of eight patients who underwent TAH and BSO without lymphadenectomy in this study, only one was at Stage II (hence receiving the less than adequate surgical procedure). However, if the information available through intraoperative specimens had been disregarded, the margin of error in terms of the adequacy of the surgical procedure would have been 40% based on the comparison of tumor grades on pre-operative biopsies and post-operative specimens. These findings suggest that for surgeons who do not perform complete surgical staging for every patient with EC, clinical judgment should only be efficient when augmented with information obtained from frozen sections.

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