

Diagnostic problems on frozen section examination of myometrial invasion in patients with endometrial carcinoma with special emphasis on the pitfalls of deep adenomyosis with carcinomatous involvement

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Summary

Frozen-section and paraffin section diagnoses were compared in 55 patients with Stage I endometrial adenocarcinoma. In 44 patients (80%), a corresponding depth of myometrial invasion and in 54 (98%) patients the same tumor grade were found. Regarding the depth of myometrial invasion and histologic grade, sensitivity, specificity, positive and negative predictive values were 70%, 86%, 73%, 83% and 92%, 100%, 100%, 94%, respectively. Concerning myometrial invasion 9% false-positivity and 10% false-negativity rates were noted. The histopathologic characteristics of false-positive and false-negative patients are emphasized because carcinomatous involvement of deeply situated adenomyosis and advanced grade tumors are the main diagnostic pitfalls.

It is important for pathologists to be able to identify carcinomatous involvement of adenomyosis and adjacent foci of minimal myometrial invasion during frozen-section examination which can prevent aggressive surgery.

Key words: Endometrial carcinoma; Frozen section; Myometrial invasion.

Introduction

Endometrial carcinoma is the most frequent malignancy of the female genital tract.

Its incidence is rising in most of Western Europe and the USA [1-3]. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the basic treatment of the disease, but it is not considered adequate in all cases. A number of prognostic parameters determine the need for additional surgical intervention, namely, pelvic and/or paraaortic lymph node dissection, or performance of radical instead of simple abdominal hysterectomy for both therapeutic and staging purposes. These parameters are aggressive histologic types, grade 2 and 3 tumors, deep myometrial invasion (>50%), cervical infiltration and lymph node enlargement in the preoperative radiological workup [4].

Although deep myometrial invasion is uncommon when the tumor is well differentiated, some grade 1 tumors are associated with deep myometrial invasion [5]. Grade determined in the curettings is often inaccurate compared to the final grading found in the surgical specimen. Therefore, information concerning the depth of myometrial invasion is important when making a surgical decision concerning lymph node dissection [3].

In this study we evaluated the correlation between depth of myometrial invasion and histologic grade determined by intraoperative frozen section (FS) and final histology of the surgical specimen. The histopathologic

characteristics of the false-positive and false-negative cases are emphasized.

Patients and Methods

The study group consisted of 55 women with endometrial carcinoma diagnosed by curettage. All were operated on at the Zeynep Kamil Maternity and Children's Hospital from December 1999 to May 2003. None had preoperative radiotherapy nor hormonal therapy.

All patients underwent pelvic washing followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy. After removal of the uterus, the specimen was opened along the lateral margins from the external os to the origin of the fallopian tubes. This method allows a careful inspection of the entire uterine cavity including the endocervical canal. A vertical cut through the tumor bulk and uterine wall is performed. One or occasionally two FS is performed to include the tumor and entire thickness of the myometrium. The depth of myometrial invasion is measured from the endometrial-myometrial junction to the deepest point of tumor penetration. The procedure takes 10-20 minutes.

The depth of myometrial invasion was assigned according to the International Federation of Gynecologists and Obstetricians (FIGO) staging; Stage Ia, tumor limited to endometrium; Stage Ib, invasion to < 1/2 of the myometrium. The grade of the tumor was assigned according to the FIGO grading. Tumors were considered grade 1 if there was less than a 5% solid nonsquamous mass of epithelium, grade 2 if more than 5% but less than 50% of the tumor was composed of a solid mass and grade 3 if more than 50% of the tumor was composed of a solid nonsquamous mass. Nuclear grading was based on the degree of nuclear atypia: grade 1 was used if there was minimal nuclear enlargement and finely dispersed chromatin and grade 3 if most nuclei

displayed significant pleomorphism, coarse chromatin clumping and thick nuclear membranes with irregular contours; grade 2 nuclear atypia showed an intermediate degree of atypia. A combined grading system along the guidelines of FIGO was based on both architectural and nuclear abnormalities. Tumors were graded according to architectural differentiation, as described above, but high-grade nuclear abnormalities increased the grade by one for grade 1 and 2 tumors.

According to the results of the intraoperative FS evaluation, lymph node dissection was performed in patients with deep myometrial invasion or FIGO grade 2 or 3. Standard statistical calculations were used to determine accuracy, sensitivity, specificity, positive and negative predictive values (PNV, NPV) and false-positive and false-negative rates of the method.

Results

Characteristics of cases are summarized in Table 1. Comparison of FS and final histology with respect to myometrial invasion is shown in Table 2. FS examination correctly identified (accuracy rate) depth of myometrial invasion in 80% (44/55) of cases. Intraoperative overestimation (false-positive rate) of the depth of invasion was made in 9% (5/55) of cases, while underestimation (false-negative rate) occurred in 10.9% (6/55). In five cases, myometrial involvement were wrongly estimated as deep invasion by FS examination. Final histologic examination with many serial sections of myometrium revealed carcinomatous involvement of deeply situated adenomyosis, in some with adjacent foci of minimal myometrial infiltration (Figure 1).

In six underestimated cases, myometrial involvement was wrongly estimated as superficial invasion by the FS

Table 1. — Patient characteristics.

| | Myometrial invasion | | |
|---------------------------------------|---------------------|----------------------|--------------------------|
| | < 50% n = 27 (%) | ≥ 50% n = 20, (%) | Noninvasive n = 9 (%) |
| Age (years, mean ± SD) | 65.9 ± 6.8 | 63.5 ± 6.8 | 53.8±9.0 |
| <i>Histology of the tumor</i> | | | |
| Endometrioid | 24 (88.8) | 10 (50) | (88.8) |
| Endometrioid+squamoid differentiation | 2 (7.4) | 3 (15) | (11.1) |
| Secretory | | 1 (5) | |
| Clear cell | 1 (3.7) | 2 (10) | |
| Papillary serous | | 2 (10) | |
| Mucinous | | 1 (5) | |
| Undifferentiated | | 1 (5) | |
| <i>Tumor grade</i> | | | |
| 1 | 16 (59.2) | 8 (40) | (88.8) |
| 2 | 9 (33.3) | 3 (15) | (11.1) |
| 3 | 2 (7.4) | 9 (45) | |

Table 2. — Myometrial Invasion: FS versus histological results (n = 55).

| Histopathological myometrial invasion | FS evaluation | | |
|---------------------------------------|---------------|-------|-------------|
| | < 1/2 | > 1/2 | Noninvasive |
| < 1/2 | 22 | 5 | |
| > 1/2 | 6 | 13 | |
| Noninvasive | | | 9 |

a Sensitivity: 70%; specificity: 86%; PPV: 73%; NPV: 83%; accuracy: 80%; false-negative rate: 10%; false-positive rate: 9%.

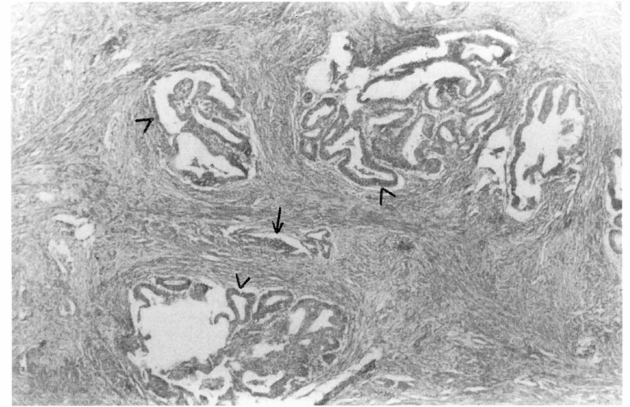


Figure 1. — Carcinomatous involvement of deeply situated adenomyosis (arrowhead), in some with adjacent foci of minimal myometrial infiltration (arrow).

examination but final histologic examination showed deep myometrial invasion; four of which were advanced grade tumors and one was undifferentiated carcinoma. The other two were well-differentiated endometrioid carcinomas. Sensitivity, specificity, PPV and NPV regarding the myometrial invasion were 70%, 86%, 73% and 83%, respectively. Tables 3 and 4 summarize clinical characteristics of the patients in whom depth of myometrial invasion was overestimated and underestimated at intraoperative examinations, respectively.

Table 3. — Characteristics of patients with overestimated myometrial invasion at FS examination (n = 5).

| | |
|--|------------|
| Age (years, median/range) | 58 (47-62) |
| <i>Tumor histological type</i> | |
| Endometrioid | 5 |
| Endometrioid+Squamoid differentiation | |
| Endometrioid+Clear cell component | |
| Undifferentiated | |
| <i>Tumor grade</i> | |
| G1 | 5 |
| G2 | |
| G3 | |
| Deep adenomyosis with carcinomatous involvement | 4 |
| Deep adenomyosis with carcinomatous involvement and adjacent minimal foci of myoinvasion | 1 |

Table 4. — Characteristics of patients with underestimated myometrial invasion at FS examination (n = 6).

| | |
|--|------------|
| Age (years, median/range) | 49 (42-72) |
| <i>Tumor histological type</i> | |
| Endometrioid | 3 |
| Endometrioid+Squamoid differentiation | 1 |
| Endometrioid+Clear cell component | 1 |
| Undifferentiated | 1 |
| <i>Tumor grade</i> | |
| G1 | 2 |
| G2 | |
| G3 | 4 |
| Deep adenomyosis with carcinomatous involvement and adjacent minimal foci of myoinvasion | 1 |

FS correctly identified (accuracy rate) FIGO grade of tumors in 98% (54/55) of the cases. Intraoperative overestimation of FIGO grade was not observed in any case, while underestimation (false-negative rate) occurred in 3% (1/55); a case with FIGO grade 3 (histologic grade 3 and nuclear grade 3) stated as FIGO grade 2 (histologic grade 2, nuclear grade 2). Sensitivity, specificity, PPV and NPV concerning the grade are 92%, 100%, 100% and 94% respectively.

Discussion

The correlation between the potential risk of lymph node metastases and myometrial invasion is well established [3]. Therefore, intraoperative information concerning the depth of myometrial invasion and histologic grade might be helpful in the decision of whether or not lymph node dissection should be performed [3]. This is of particular importance in patients with operative risks [3]. Depth of myometrial invasion is difficult to predict preoperatively. Pelvic ultrasound, computed tomography and magnetic resonance imaging have been used to estimate depth of myometrial invasion with varying success [6-10]. Besides being expensive and inconvenient for the patient, these imaging studies appear to lack the accuracy needed to be clinically useful [6].

Tumor grade has been the most common measurable preoperative factor used to guide surgical aggressiveness in staging patients with endometrial cancer. Unfortunately, tumor grade on the preoperative endometrial biopsy and the final hysterectomy specimen do not always agree [6, 11, 12]. Office biopsy and dilatation and curettage under-grade lesions in 26% and 10% of patients, respectively [13]. On the other hand intraoperative FS evaluation by the pathologist has accurately predicted myometrial invasion and histologic grade in 87-94% and 85.1-91.0% of cases, respectively [14-19].

In this study we evaluated myometrial invasion depth and histologic grade by intraoperative FS examination. Regarding the depth of myometrial invasion and histologic grade, a correlation was found in 81% and 98% of cases, respectively. When deep adenomyosis with carcinomatous involvement was present with or without adjacent foci of minimal myoinvasion, intraoperative evaluation by FS was overestimated. These were patients with well-differentiated endometrioid carcinomas. Our results are different from other publications with lower rates of accuracy due to a relatively high percentage of overestimated cases. This is probably due to the high frequency of cases with adenomyosis involved by carcinoma in our series. Atad *et al.* [3] also considered adenomyosis as a cause of underestimation. In conclusion, during FS evaluation in grade 1 cases, caution regarding the diagnosis of deep myometrial invasion should be taken. The possibility of adenomyosis with carcinomatous involvement should be kept in mind and excluded by investigating the residual benign endometrial glands and stroma at the margins of carcinomatous foci. By obtaining three to four serial frozen sections overestimation can be avoided and

it would take an additional couple of minutes at most.

Recent publications report that adenocarcinomas involving adenomyosis, even with adjacent foci of minimal myoinvasion, were characterized by low histologic grade and excellent prognosis [20-28]. It is important therefore for pathologists to be able to identify carcinoma involving adenomyosis and adjacent foci of minimal myometrial invasion. Involvement of adenomyosis and minimal invasion from this area should be separately commented on in the FS results and final pathology report in such cases. This distinction is important from the standpoint of staging, treatment and prognosis.

The role of CD-10 staining in distinguishing invasive endometrial adenocarcinoma from adenocarcinoma involving adenomyosis has been analysed in some difficult cases [29, 30]. It is obvious that differentiation in this situation of FS examination will be more difficult.

Analysis of the characteristics of underestimated patients showed that they had tumors of advanced grade. We should be cautious about the diagnosis of no or superficial myometrial invasion in patients with high grade tumors. By taking thinner sections at macroscopic examination and with serial frozen sections myometrial invasion can be accurately determined. Figge *et al.* [31] tried to estimate the depth of myometrial invasion by gross examination of the sectioned uterus at the time of surgical removal. In many publications intraoperative gross examination of myometrial invasion appears to be a fast, accurate and easily available method for identifying patients at marked risk for extrauterine metastases [6, 11-13, 32-34]. However, the obvious true advantage of FS over gross examination is its accuracy in determining tumor grade.

According to our results, gross examination to predict myometrial invasion would be even more difficult especially in cases with deep adenomyosis involved by carcinoma with or without adjacent foci of minimal microinvasion.

References

- [1] Greenlee R.T., Murray T., Bolden S., Wingo P.A.: "Cancer statistics, 2000". *CA Cancer J. Clin.*, 2000, 50, 7.
- [2] Cancer facts and figures. Atlanta, GA: American Cancer Society, 1997.
- [3] Atad J., Weill S., Ben-David Y., Hallak M., Klein O., Lurie M., Abramovici H.: "Intraoperative frozen section examination of myometrial invasion depth in patients with endometrial carcinoma". *Int. J. Gynecol. Cancer*, 1994, 4, 352.
- [4] Hacker N.F.: "Uterine cancer". In: Berek J.S., Hacker N.F. (eds.), *Practical Gynecologic Oncology* (3rd ed.). Philadelphia: Lippincott Williams & Wilkins, 2000, 407.
- [5] Creasman W.T., Monrow C.L., Bumdy L.: "Surgical pathological spread patterns of endometrial cancer". *Cancer*, 1967, 60, 2035.
- [6] Larson D.M., Connor G.P., Broste S.K., MS, Krawisz B.R., Johnson K.K., PA: "Prognostic significance of gross myometrial invasion with endometrial cancer". *Obstet. Gynecol.*, 1996, 88, 394.
- [7] Artner A., Bosze P., Gonda G.: "The value of ultrasound in pre-operative assessment of the myometrial and cervical invasion in endometrial carcinoma". *Gynecol. Oncol.*, 1994, 54, 147.
- [8] Dore R., Moro G., Andrea D.Z.F., La Fianza A., Franchi M., Bolis P.F.: "CT evaluation of myometrium invasion in endometrial carcinoma". *J. Comput. Assist. Tomogr.*, 1987, 11, 282.

- [9] Lien H.H., Blomlie V., Trope C., Kaern J., Abeler V.M.: "Cancer of the endometrium: value of MR imaging in determining depth of invasion into the myometrium". *AJR Am. Roentgenol.*, 1991, 157, 1221.
- [10] Lien H.H., Blomlie V., Kjorstad K., Abeler V., Kaalhus O.: "Clinical Stage I carcinoma of the cervix: value of MR imaging in determining degree of invasiveness". *AJR Am. J. Roentgenol.*, 1991, 156, 1191.
- [11] Franchi M., Ghezzi F., Melpignano M., Cherchi P.L., Scrabelli C., Apolloni C., Zanaboni F.: "Clinical value of intraoperative gross examination in endometrial cancer". *Gynecol. Oncol.*, 2000, 76, 357.
- [12] Vorgias G., Hintipas E., Katsoulis M., Kalinoglou N., dertimas B., Akrivos T.: "Intraoperative gross examination of myometrial invasion and cervical infiltration in patients with endometrial cancer: decision making accuracy". *Gynecol. Oncol.*, 2002, 85, 483.
- [13] Larson D.M., Johnson K.K., Broste S.K., Krawisz B.R., Kresl J.J.: "Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer". *Obstet. Gynecol.*, 1995, 86, 38.
- [14] Kayikcioglu F., Boran N., Meydanli M.M., Tulunay G., Kose F.M., Bulbul D.: "Is frozen-section diagnosis a reliable guide in surgical treatment of stage I endometrial carcinoma?". *Acta Oncol.*, 2002, 41, 444.
- [15] Shim J.U., Rose P.G., Reale F.R., Soto H., Tak W.K., Hunter R.E.: "Accuracy of frozen-section diagnosis at surgery in clinical Stage I and II endometrial carcinoma". *Am. J. Obstet. Gynecol.*, 1992, 166, 1335.
- [16] Goff B.A., Rice L.W.: "Assessment of depth of myometrial invasion in endometrial adenocarcinoma". *Gynecol. Oncol.*, 1990, 38, 46.
- [17] Zorlu C.G., Kescu E., Ergun Y., Aydogdu T., Cobanoglu O., Erdas O.: "Intraoperative evaluation of prognostic factors in Stage I endometrial cancer by frozen section: how reliable?". *Acta Obstet. Gynecol. Scand.*, 1993, 72, 382.
- [18] Noumoff J.S., Menzin A., Mikuta J., Lusk E.J., Morgan M., LiVolsi V.A.: "The ability to evaluate prognostic variables on frozen section in hysterectomies performed for endometrial carcinoma". *Gynecol. Oncol.*, 1991, 42, 202.
- [19] Fanning J., Tsukada Y., Piver M.S.: "Intraoperative frozen section diagnosis of depth of myometrial invasion of depth of myometrial invasion in endometrial adenocarcinoma". *Gynecol. Oncol.*, 1990, 37, 47.
- [20] Logacre T.A., Hendrickson: "Diffusely infiltrative endometrial adenocarcinoma: An adenoma malignum pattern of myoinvasion". *Am. J. Surg. Pathol.*, 1999, 23, 69.
- [21] Hall J.B., Young R.H., Nelson J.H.: "The prognostic significance of adenomyosis in endometrial carcinoma". *Gynecol. Oncol.*, 1984, 17, 32.
- [22] Mittal K.R., Barwick W.B.: "Endometrial adenocarcinoma involving adenomyosis without true myometrial invasion is characterized by frequent preceding estrogen therapy, low histologic grades and excellent prognosis". *Gynecol. Oncol.*, 1993, 49, 197.
- [23] Koshiyama M., Suzuki A., Ozawa M., Fujita K., Sakakibara A., Kawamura M. *et al.*: "Adenocarcinomas arising from uterine adenomyosis: A report of four cases". *Int. J. Gynecol. Pathol.*, 2002, 21, 239.
- [24] Takai N., Akizuki S., Nasu K., Etoh Y., Miyakawa I.: "Endometrioid adenocarcinoma arising from adenomyosis". *Gynecol. Obstet. Invest.*, 1999, 48, 141.
- [25] Ichiwara Y., Takano K., Higa S., Tanabe M., Wada A., Sugita M. *et al.*: "Endometrial carcinoma coexisting with pregnancy, presumed derived from adenomyosis: a case report". *Int. J. Gynecol. Cancer*, 2001, 11, 488.
- [26] Hernandez E., Woodruff J.D.: "Endometrial adenocarcinoma arising in adenomyosis". *Am. J. Obstet. Gynecol.*, 1980, 138, 827.
- [27] Sasaki T., Sugiyama T., Nanjo H., Hoshi N., Murakami M., Sugita A. *et al.*: "Endometrioid adenocarcinoma arising from adenomyosis: report and immunohistochemical analysis of an unusual case". *Pathol. Int.*, 2001, 51, 308.
- [28] Jacques S.M., Lawrence W.D.: "Endometrial adenocarcinoma with variable-level myometrial involvement limited to adenomyosis: a clinicopathologic study of 23 cases". *Gynecol. Oncol.*, 1990, 37, 401.
- [29] Nascimento A.F., Hirsch M.S., Cviko A., Quade B.J., Nucci M.R.: "The role of CD 10 staining in distinguishing invasive endometrial adenocarcinoma from adenocarcinoma involving adenomyosis". *Mod. Pathol.*, 2003, 16, 22.
- [30] Srodon M., Klein W.M., Kurman R.J.: "CD 10 immunostaining does not distinguish endometrial carcinoma invading myometrium from carcinoma involving adenomyosis". *Am. J. Surg. Pathol.*, 2003, 27, 786.
- [31] Figge D.C., Otto P.M., Tamimi H.K., Greer B.E.: "Treatment variables in the management of endometrial cancer". *Am. J. Obstet. Gynecol.*, 1983, 146, 495.
- [32] Doering D.L., Barnhill D.R., Weiser E.B., Burke T.W., Woodward J.E., Park R.C.: "Intraoperative evaluation of depth of myometrial invasion in Stage I endometrial adenocarcinoma". *Obstet. Gynecol.*, 1989, 74, 930.
- [33] Malviya V.K., Deppe G., Malone L.M., Sundareson A.S., Lawrence W.D.: "Reliability of frozen section examination in identifying poor prognostic indicators in Stage I endometrial carcinoma". *Gynecol. Oncol.*, 1989, 34, 299.
- [34] Altintas A., Cosar E., Vardar M.A., Demir C., Tuncer I.: "Intraoperative assessment of depth of myometrial invasion in endometrial carcinoma". *Eur. J. Gynaecol. Oncol.*, 1999, 20, 329.

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