

Accuracy of frozen section diagnosis at surgery in pre- malignant and malignant lesions of the endometrium

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Summary

Objective: The purpose of this study was to correlate the histological diagnosis made during intraoperative frozen section examination of hysterectomies with atypical hyperplasia or carcinoma, with the definitive paraffin section histology. **Study Design:** Frozen section pathology results of patients with a preoperative biopsy showing atypical hyperplasia or endometrial carcinoma (87 patients) were compared retrospectively with paraffin section pathology findings. Those patients with curettage specimens showing atypical hyperplasia or curettings suspicious of endometrioid carcinoma had intraoperative frozen section to determine whether an invasive lesion was present and whether they required pelvic lymphadenectomy. The purpose of frozen section assessment in those patients who had a preoperative curettage specimen showing endometrial carcinoma was to identify poor prognostic pathological factors related to histological subtype, grade, depth of myometrial invasion and cervical involvement. **Results:** The correlation between frozen sections and paraffin histology in patients with endometrial carcinoma was 98.6% (69/70) for histological sub-type and 84.3% (59/70) for grade of differentiation. Depth of myometrial invasion was accurately diagnosed in 94.3% (66/70) while cervical involvement was accurately assessed in 86.7% (52/60). Of the 37 patients with atypical hyperplasia or suspicious curettings on preoperative curettage who had intraoperative frozen section, 23 patients had invasive malignancy, which was confirmed in subsequent paraffin sections. Of the remaining 14 patients with a non-malignant frozen section diagnosis, 11 were confirmed with paraffin sections while three had a small well differentiated invasive lesion, two were FIGO Stage 1a and one had microscopic invasion into the myometrium. **Conclusion:** Intraoperative frozen section is a useful procedure to identify poor prognostic pathological factors as well as to diagnose endometrial cancer in patients undergoing hysterectomy for a preoperative biopsy diagnosis of atypical hyperplasia.

Key words: Frozen section; Endometrial carcinoma; Endometrial hyperplasia.

Introduction

Endometrial cancer is the most common malignancy of the female genital tract in the United States with over 40,000 new cases and 7,000 deaths in 2004 [1]. In the United Kingdom and Ireland uterine cancer accounted for around one in 30 cancer cases and one in 50 cancer deaths in the 1990s, and is the fifth most common cancer in women, with over 90% occurring in women over the age of 50 years [2]. The main risk factors for endometrial carcinoma are associated with prolonged or increased exposure of the uterus to oestrogen and include early age at menarche, low parity, late age at menopause, anovulatory cycles, and obesity as well as unopposed administered oestrogens [2]. There is also a 2-3 fold increase risk of endometrial cancer in women treated with tamoxifen for breast cancer [3, 4].

Endometrial hyperplasia is characterised by an increased endometrial thickness with glandular crowding. In the presence of cytologic atypia the potential for malignancy may be as high as 30% [5-8]. The work of Kurman *et al.* suggested a 1.6% risk of progression to cancer in the absence of cytological atypia compared to a risk of 23% in the presence of atypia [5], and a similar

progression rate of 25% was found by Ferenczy and Gelfand [9]. A common diagnostic problem arises when atypical hyperplasia is diagnosed in the preoperative biopsy histology as it may be difficult to distinguish between atypical hyperplasia and a well differentiated adenocarcinoma, especially in small biopsy specimens. Several morphological features have been described which, when seen in a biopsy, are predictive of myometrial invasion in the uterus [10]. However underdiagnosis of adenocarcinoma and limitations of sampling probably account for the fact that adenocarcinoma is found in 17-43% of hysterectomy specimens performed for a preoperative diagnosis of atypical hyperplasia [8, 11].

The cornerstone of treatment for endometrial cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy. Certain pathological characteristics are associated with a higher risk of nodal involvement and when present are normally regarded as an indication for surgical staging by pelvic lymphadenectomy. These factors include depth of myometrial invasion > 50%, tumour grades 2 or 3, high risk histological subtypes and cervical or adnexal involvement. These patients may also receive post-op adjuvant radiotherapy.

The aim of this study was to establish the accuracy of intraoperative frozen section, when compared to definitive paraffin histology, in identifying those endometrial

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carcinoma patients with poor prognostic factors who require pelvic lymphadenectomy. Secondly, we assessed the accuracy of intraoperative frozen sections in those patients undergoing hysterectomy for atypical hyperplasia or suspicious curettings but no definite preoperative diagnosis of carcinoma, in identifying carcinoma and poor prognostic factors requiring lymphadenectomy.

Materials and Methods

One hundred and sixty-two patients with a preoperative diagnosis of endometrial carcinoma or of atypical hyperplasia/curettings 'suspect of endometrioid carcinoma' were treated at the Kent Cancer Centre in Maidstone, Kent, UK from December 2002 to December 2005. Patient ages ranged from 37 to 88 years with a median age of 66 years. Of these patients 87 had frozen sections performed at the time of surgery and were included for analysis. Of the 162 patients there were 46 patients with a preoperative diagnosis of atypical hyperplasia/suspicious curettings but no definite diagnosis of carcinoma. Of these 46 patients 37 had intraoperative frozen section assessment.

Intraoperative examination of hysterectomies and attached adnexal structures was performed to identify patients at high risk of regional lymph node metastasis. Specifically, gross dissection and subsequent frozen section microscopy were performed to determine depth of myometrial invasion, cervical involvement and adnexal involvement by tumour. In addition, tumour subtype and grade were assessed and compared with the preoperative curettage diagnosis. Upon receipt of the fresh specimen in the laboratory the external surfaces of the uterus and adnexal structures were briefly examined and the adnexa were then sliced with inspection of the cut surfaces. Any adnexal nodules suspicious of metastasis that were visible with the naked eye were submitted as frozen sections. The uterus was then bisected in the coronal plane followed by sequential transverse slicing at 3 mm intervals through each half of the uterus. During this dissection the depth of tumour invasion into the myometrium and any involvement of the cervix were assessed with the naked eye. Tissue slices incorporating the maximum depth of myometrial invasion were submitted as frozen sections (either as one or two sections depending on the thickness of the uterine wall). One section of the cervix was normally also examined, though this was omitted when the tumour was clearly invading into the outer half of the myometrium. Tissue slices were placed on metal chucks in cryomatrix embedding medium and frozen with Envirotech 1,1,1,2-tetrafluoroethane freezer spray. Sections with a thickness of 4 μ were cut in a Leica CM 1900 semi-automated cryostat and stained with haematoxylin and eosin before presentation to the reporting pathologist. Between one to five frozen sections were examined per case and the whole process from receipt to telephoned result was 10 to 15 minutes in duration. After formalin fixation further sections were taken for routine processing and paraffin embedding (depending on the case, typically four more sections of cervix, four to five of tumour, one of background endometrium and four of the adnexal structures). The paraffin section report and frozen section result were reviewed by an experienced gynaecological pathologist.

Results

Eighty-seven frozen sections cases were performed during the study period and all cases subsequently had definitive paraffin histology.

Four cases had benign histology on both frozen section and paraffin assessment. One of these cases was referred with a small focus of well differentiated endometrioid adenocarcinoma and three with atypical hyperplasia on polypoid curettings. Neither intraoperative frozen section assessment nor subsequent paraffin histology showed any residual pathology.

Thirteen cases had a frozen section diagnosis of atypical hyperplasia. Ten of these were confirmed on paraffin while three cases also showed an underlying coexisting well differentiated endometrioid adenocarcinoma. Two of these carcinomas were confined to the endometrium and the other showed a small 5 mm focus of infiltration into the inner half of the myometrium. Although the invasion was not detected at frozen section, neither of these cases were undertreated as lymphadenectomy was not indicated for such small tumours.

Histological subtyping

Seventy cases had a frozen section diagnosis of endometrial carcinoma and of these 65 were diagnosed as endometrioid, three were serous papillary, one was clear cell and one was mixed Mullerian tumour. Correlation of frozen and paraffin assessment of histological subtype was almost perfect for these cases although one case diagnosed as a poorly differentiated endometrioid adenocarcinoma on frozen section was subsequently shown to be poorly differentiated mixed serous/endometrioid on paraffin histology. Management was not affected by the minor discrepancy in this case as both diagnoses were of poorly differentiated tumours for which lymphadenectomy was indicated. Overall correlation for histological subtyping was 98.6%.

Histological grade

The frozen section assessment of grade for the 65 cases of endometrioid adenocarcinoma was 36 as grade 1, 26 as grade 2, and three as grade 3. There was a 100% correlation for assessment of tumour grade between frozen section and paraffin sections for grade three cases (and the five non-endometrioid cases were all considered grade 3 by definition). Thirty-one out of 36 well differentiated and 20 out of 26 moderately differentiated endometrioid tumours also correlated for grade. Five cases diagnosed as grade 1 were subsequently upgraded to grade 2: in two of these there was no myometrial invasion so treatment was not affected by the undergrading but the other three cases were undertreated. Three cases of frozen section grade 2 were downgraded to grade 1 on paraffin but all three underwent lymphadenectomy: for involvement of the outer half of the myometrium in two cases and endocervical glands in the other. Three cases of frozen section grade 2 were upgraded to grade 3 after paraffin histology, but all three had lymphadenectomy due to other poor pathological features of deep myometrial, cervical and adnexal involvement. The correlation

for grading in our series was 84.3%, and only three out of 70 carcinomas were undertreated because of under-grading (Table 1).

Table 1. — Correlation for grade between frozen section and paraffin histology.

Frozen section	Paraffin histology			
	Grade 1	Grade 2	Grade 3	Other histological types
Grade 1 (n = 36)	31	5*	0	0
Grade 2 (n = 26)	3	20	3*	0
Grade 3 (n = 3)	0	0	3	0
Other histological types (n = 5)	0	0	0	5

* clinically important errors.

Depth of myometrial invasion

The accuracy of assessment of the depth of myometrial invasion by tumour was also investigated. Of 70 cases of carcinoma identified intraoperatively, nine were reported as limited to the endometrium on frozen section. In the subsequent paraffin sections three of these cases showed a small focus of invasion into the inner half of the myometrium. One of these cases was a well-differentiated tumour and so management was not affected but the other two cases were microinvasive grade 2 tumour which would undergo lymphadenectomy at our institution. Forty cases were reported as invading the inner half of the myometrium at frozen section assessment and 39 of these correlated with the paraffin histology. One case was a well-differentiated tumour which infiltrated into the outer half of the myometrium and was undertreated. Nineteen cases were reported as infiltrating the outer half of the myometrium, and these were all confirmed on paraffin sections. There was one case of serosal breach and one case with ovarian deposits, which were diagnosed on both frozen and paraffin sections. Correlation for the assessment of depth of myometrial invasion was 94.3% (66 out of 70 cases). Misinterpretation of the depth of invasion at frozen section led to inappropriate management in three cases (Table 2).

Table 2. — Correlation for myometrial invasion between frozen section and paraffin histology.

	No myometrial invasion	Inner 1/2	Outer 1/2	Serosa/adnexal involvement
Frozen section	9	40	19	2
Paraffin histology	6	42	20	2

Cervical involvement

A comparison was made of the frozen section and paraffin section assessment of cervical involvement by tumour. A total of 60 cases (out of 70 cases of carcinoma) underwent cervical assessment by intraoperative examination of a frozen section. Ten cases did not have frozen section assessment of the cervix as they already had

adverse prognostic factors prompting lymphadenectomy. Eight of 51 cases, which were reported as negative for cervical involvement on frozen section, were subsequently found to have endocervical involvement in paraffin sections (four showed gland and superficial stromal involvement and four showed only gland involvement). In four of these cases the degree of involvement in the paraffin sections was a microscopic deposit up to only 1 mm across and all of these were discontinuous with the uterine lesion. A fifth case was a 3 mm focus of endocervical gland involvement continuous with the lower edge of the uterine tumour. Frozen sections positively identified four cases with endocervical gland involvement and five with endocervical stromal invasion and this was confirmed in paraffin sections. Overall accuracy of assessment of cervical involvement by tumour at frozen section was 86.7% (Table 3). Misinterpretation of cervical involvement at frozen section assessment led to inappropriate management in four cases while the other four cases had lymphadenectomy performed on other histological grounds.

Table 3. — Correlation between frozen section and paraffin histology for cervical involvement.

Frozen section	Paraffin histology		
	No cervical involvement	Endocervical glands	Stromal involvement
No cervical involvement (n = 51)	43	4*	4*
Endocervical glands (n = 4)	0	4	0
Stromal involvement (n = 5)	0	0	5

* clinically significant.

The overall correlations between frozen section and paraffin section assessment of the various factors described for the series of 70 cases of carcinoma identified at frozen section are detailed in Table 4.

Table 4. — Overall correlation between frozen section and paraffin histology for cases of endometrial cancer.

Histological subtypes	69 out of 70 cases	98.6%
Depth of myometrial invasion	66 out of 70 cases	94.3%
Cervical involvement	52 out of 60 cases	86.7%

A subgroup of 46 patients were operated on with a pre-operative biopsy histology of either atypical hyperplasia (33 cases) or suspicious curettings, but not diagnostic of carcinoma (13 cases). Thirty-seven of these cases had intraoperative frozen sections and all had definitive paraffin histology.

Of these 37 cases, three cases showed no residual pathology on both frozen section and paraffin examination. Eleven were reported as showing atypical hyperplasia on frozen section and eight of these diagnoses were unchanged in the paraffin sections. In the three discrepant cases a small focus of co-existent well differentiated endometrioid adenocarcinoma was detected in the paraffin sections (Table 5). Two tumours were limited to the

endometrium while the other showed a microscopic focus of invasion of 5 mm depth into the inner half of the myometrium. In all three cases surgical staging with lymphadenectomy was not indicated.

Table 5. — Correlation between frozen sections and paraffin histology in cases with a preoperative diagnosis of atypical hyperplasia/suspicious curettings.

(n = 37)	Atypical hyperplasia	Invasive tumour	No residual abnormality
Frozen sections	11	23	3
Paraffin histology	8	26	3

At frozen section an endometrial carcinoma was detected in 23 of the 37 cases with a preoperative diagnosis of atypical hyperplasia/suspicious curettings and all of these were confirmed in subsequent paraffin sections. Table 6 details the pathological characteristics of the 26 invasive tumours ultimately detected in those patients with no definite preoperative diagnosis of malignancy who underwent frozen section as well as three cases which were not identified at frozen section as detailed above. Fourteen cases had adverse factors requiring lymphadenectomy and eight of these were picked up during frozen section assessment. Of the six cases that were undertreated, three cases had a microscopic deposit on endocervical glands while one case was a moderately differentiated carcinoma thought to be limited to the endometrium but was found to have a small focus invading the inner half of the myometrium. Two well-differentiated adenocarcinomas diagnosed as Stage 1b on frozen section were subsequently found to be moderately differentiated in one case and with cervical stromal deposits in the other.

Table 6. — Pathological characteristics of the 26 invasive tumours ultimately detected on paraffin sections in the subgroup of 37 patients with a preoperative diagnosis of atypical hyperplasia/suspicious curettings who underwent frozen section.

	Paraffin section findings	
Grading	Grade 1	18
	Grade 2	6
	Grade 3	2
Depth of myometrial invasion (DMI)	Nil	2
	Inner 1/2	20
	Outer 1/2	4
Cervical involvement	Negative	18
	Endocervical glands	5
	Stroma	3

Discussion

Pelvic lymphadenectomy plays an important role in surgical staging of endometrial carcinoma. The therapeutic role of lymphadenectomy is still debated. A retrospective study by Kilgore *et al.* of 649 surgically managed patients with endometrial adenocarcinoma showed a significantly better overall survival for patients managed

with multiple-site pelvic node sampling relative to patients without node sampling ($p = 0.0002$) [12]. There was also a better survival for both low-risk and high-risk cancer groups ($p = 0.026$ and 0.0006 , respectively). It is anticipated that some questions relating to the benefit of lymphadenectomy in endometrial cancer may be answered following publication of results from the ASTEC multicentre randomised controlled trial investigating the impact of lymphadenectomy and adjuvant external beam radiotherapy in the treatment of endometrial cancer [13].

In our centre FIGO Stage 1a and 1b well differentiated carcinomas and FIGO Stage 1a moderately differentiated carcinomas are treated and staged by total abdominal hysterectomy, bilateral salpingo-oophorectomy and peritoneal washing cytology. Complete pelvic lymphadenectomy is performed for cases of poorly differentiated endometrioid tumours and high-risk histological subtypes (serous, clear cell, squamous, mixed Mullerian tumours) irrespective of stage; for Stage 1c or above irrespective of the grade and for moderately differentiated endometrioid tumours Stage 1b or above [14]. Postoperative adjuvant external beam radiotherapy is normally given to node positive cases while node negative Stage 2 cases are treated with adjuvant vault brachytherapy alone. The latter is in accordance with a number of reports suggesting that if pelvic lymph nodes are negative for tumour it is reasonable to omit external beam therapy and administer brachytherapy alone to prevent vault recurrence, saving treatment time, cost and reducing potential side-effects from combined treatment [15-20].

Intraoperative frozen section assessment is performed in many centres to identify patients with poor prognostic factors who require lymphadenectomy and to identify low-risk patients who may be spared extensive surgery and possible complications and morbidity.

Our results have shown a good correlation between frozen sections and paraffin histology in the assessment of factors, which influence the decision to perform lymphadenectomy. Frozen section assessment in our series was 98.6% accurate for histological subtype, 84.3% accurate for grade, 94.3% for depth of myometrial invasion and 86.7% for assessment of cervical involvement. This is comparable with the published literature reporting accuracies of assessment of 60-98% for grade, 80-96.6% for depth of myometrial invasion and 60-94% for cervical involvement [21-31].

There was a frozen section accuracy rate of 84.3% in assessing tumour grade in our series. Reports in the literature have frequently shown a poor correlation between the grade of carcinoma in preoperative curettings or pipelle biopsy and the final grade in the resected uterus, and the poorest correlation is for biopsy grade 1 tumours which may subsequently be upgraded in 20-40% of cases [32,33]. Several of the cases in our series tended to show a somewhat better differentiated component of tumour lining the cavity with relatively more solid areas in the myoinvasive component. Of the five cases, which were upgraded from grade 1 to grade 2 in our series, the dis-

crepancy in grading led to undertreatment in three cases. Three cases were downgraded from grade 2 to 1 and three were upgraded from grade 2 to 3 but in all of these cases there were other poor prognostic factors prompting lymphadenectomy.

The overall accuracy of frozen sections in assessing the depth of myometrial invasion was 94.3% in our series. Discrepancy in the assessment of depth led to undertreatment in only three cases according to our protocol (two small grade 2 tumour infiltrating the inner half of the myometrium and a grade 1 tumour with outer half myometrial invasion). There was 95.5% accuracy in detecting those tumours infiltrating into the outer half of the myometrium in our series. This compares very favourably with the reported accuracy of preoperative MRI in detecting invasion into the outer half of the myometrium (i.e. Stage 1c) with reported results of 81-95% for overall accuracy, 80-82% for sensitivity and 91-100% for specificity [34-37]. We would also make the point that intraoperative frozen section is quicker and much less costly than preoperative MRI.

In our series frozen sections were 86.7% accurate in assessing cervical involvement by tumour when compared to the paraffin section histology. Unsurprisingly there was a lack of sensitivity for detection of microscopic disease in the cervix found only after thorough paraffin section sampling. Indeed, four of the eight foci of cervical involvement not detected at frozen section measured no more than 1 mm across and a fifth measured only 3 mm. Interestingly, most of these cases were microscopic deposits discontinuous from the uterine tumour suggesting a metastatic pathogenesis by detachment from the main tumour, transit through the endocervical canal and implantation into the endocervical mucosa. One could argue that the biological significance of such microscopic disease in the cervix is questionable but follow-up of a large number of patients showing only microscopic cervical disease would be required for clarification. The overall correlation of 86.7% is comparable with other similar studies reporting a range of 60-94% [22, 27, 31]. Studies of preoperative MRI have suggested a radiological accuracy of assessment of cervical involvement of 80-95% with a sensitivity of 33-80% and a specificity of 96-100% [34-37]. The sensitivity and specificity in our series were 52.9% and 100%, respectively, but it is of note that in our study frozen section assessment of the cervix was not performed in ten cases because other obvious poor prognostic indicators were present and so these cases were excluded from analysis of accuracy, sensitivity and specificity.

Of the subgroup of patients (n = 46) referred with a preoperative biopsy histology of atypical hyperplasia or suspicious curettings but no definite diagnosis of cancer, 37 had intraoperative frozen section assessment which detected 23 cases of cancer which were all confirmed on subsequent paraffin histology (Table 5). Eleven were reported as atypical hyperplasia on frozen section, but three of these cases were subsequently shown on paraffin histology to coexist with well-differentiated endometri-

oid adenocarcinomas of Stage 1a (two cases) and 1b. This discrepancy did not lead to undertreatment of the three cases, which were still low-risk. Of the initial 46 cases in this sub-group, paraffin sections ultimately showed 32 cases of carcinoma and lymphadenectomy was indicated in 18 of them. These cases would not normally have been referred to and treated in a Cancer Centre.

In conclusion this series supports other published data reporting that intraoperative frozen section assessment of hysterectomy specimens is an accurate method for the detection of risk factors considered as indications for full surgical staging of endometrial cancer. We also believe that frozen section assessment of hysterectomies removed for a preoperative diagnosis of atypical hyperplasia or suspicion of malignancy is justified to identify the significant fraction requiring lymphadenectomy and spare low-risk patients the morbidity of lymphadenectomy.

References

- [1] Jemal A., Tiwari R.C., Murray T., Ghafour A., Samuels A., Ward E. *et al.*: "Cancer Statistics, 2004". *CA Cancer J. Clin.*, 2004, 54, 8.
- [2] Cooper N.: "Cancer Atlas of the UK and Ireland 1991-2000". Chapter 23; 239. Office for National Statistics Publication.
- [3] Fisher B., Constantino J.P., Redmond C.K., Fisher E.R., Wickerham D.L., Cronin W.M.: "Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project B-14". *J. Natl. Cancer Inst.*, 1994, 86, 527.
- [4] Assikis V.J., Neven P., Jordan V.C., Vergote I.: "A realistic clinical perspective on tamoxifen and endometrial carcinogenesis". *Eur. J. Cancer*, 1996, 32A, 1464.
- [5] Kurman R.J., Kaminski P.F., Norris H.J.: "The behaviour of endometrial hyperplasia: a long-term study of 'untreated' hyperplasia in 170 patients". *Cancer*, 1985, 56, 403.
- [6] Silverberg S.G.: "Hyperplasia and carcinoma of the endometrium". *Semin. Diagn. Pathol.*, 1988, 135.
- [7] Huang S.J., Amparo E.G., Yu Y.S.: "Endometrial hyperplasia: histologic classification and behaviour". *Surg. Pathol.*, 1988, 1, 215.
- [8] Widra E.A., Dunton C.J., McHugh M., Palazzo J.P.: "Endometrial hyperplasia and the risk of carcinoma". *Int. J. Gynaecol. Cancer*, 1995, 5, 233.
- [9] Ferenczy A., Gelfand M.: "The biologic significance of cytologic atypia in progestin treated endometrial hyperplasia". *Am. J. Obstet. Gynaecol.*, 1989, 160, 126.
- [10] Kurman R.J., Norris H.J.: "Evaluation of criteria for distinguishing atypical endometrial hyperplasia from well-differentiated carcinoma". *Cancer*, 1982, 49, 2547.
- [11] Janicek M.F., Rosenshein N.B.: "Invasive endometrial cancer in uteri resected for atypical endometrial hyperplasia". *Gynaecol. Oncol.*, 1994, 52, 373.
- [12] Kilgore L.C., Partridge E.E., Alvarez R.D., Austin J.M., Shingleton H.M., Noojin F. *et al.*: "Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling". *Gynaecol. Oncol.*, 1995, 56, 29.
- [13] "ASTEC: A Study in the Treatment of Endometrial Cancer". MRC Clinical Trials Unit, version 3, 2003.
- [14] Kent Cancer Centre Protocol for the treatment of endometrial cancer. Guidelines Network and Treatment Group 2005.
- [15] Mohan D.S., Samuels M.A., Selim M.A., Shalodi A.D., Ellis R.J., Sameuls J.R. *et al.*: "Long-term outcomes of therapeutic pelvic lymphadenectomy for Stage I endometrial adenocarcinoma". *Gynaecol. Oncol.*, 1998, 70, 165.
- [16] COSA-NZ-UK Endometrial Cancer Study Groups: "Pelvic lymphadenectomy in high-risk endometrial cancer". *Int. J. Gynaecol. Cancer*, 1996, 6, 102.

- [17] Orr J.W., Holimon J.L., Orr P.F.: "Stage I corpus cancer: is teletherapy necessary". *Am. J. Obstet. Gynecol.*, 1997, 176, 777.
- [18] Fanning J.: "Long-term survival of intermediate risk endometrial cancer (Stage IG3, IC, II) treated with full lymphadenectomy and brachytherapy without teletherapy". *Gynaecol. Oncol.*, 2001, 82, 371.
- [19] Seago D.P., Raman A., Lele S.: "Potential benefit of lymphadenectomy for the treatment of node negative locally advanced uterine cancers". *Gynecol. Oncol.*, 2001, 83, 282.
- [20] Horowitz N.S., Peters W.A., Smith M.R., Drescher C.W., Atwood M., Mate T.P.: "Adjuvant high dose rate vaginal brachytherapy as treatment of Stage I and II endometrial cancer". *Obstet. Gynaecol.*, 2002, 99, 235.
- [21] Quinlivan J.A., Petersen R.W., Nicklin J.L.: "Accuracy of frozen section for the operative management of endometrial cancer". *Br. J. Obstet. Gynaecol.*, 2001, 108, 798.
- [22] Zorlu C.G., Kuscu 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. Gynaecol. Scand.*, 1993, 72, 382.
- [23] Badia J., Chuaqui R., Hamed F., Wild R., Barrena N., Mayerson D., Oyarzun E.: "An intraoperative anatomicopathological study of myometrial penetration in endometrial cancer: its usefulness in making decisions on extending the primary surgical treatment". *Rev. Chil. Obstet. Ginecol.*, 1992, 57, 420.
- [24] 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 cancer?". *Acta Oncol.*, 2002, 41, 444.
- [25] Kir G., Kir M., Cetiner H., Karateke A., Gurbuz A.: "Diagnostic problems on frozen section examination of myometrial invasion in patients with endometrial carcinoma". *Eur. J. Gynaecol. Oncol.*, 2004, 25, 211.
- [26] Homesley H.D., Boike G., Spiegel G.W.: "Feasibility of laparoscopic management of presumed Stage I endometrial carcinoma and assessment of accuracy of myoinvasion estimates by frozen section: a gynecologic oncology group study". *Int. J. Gynecol. Cancer*, 2004, 14, 341.
- [27] Malviya V.K., Deppe G., Malone J.M., Sundareson A.S., Lawrence W.D.: "Reliability of frozen section examination in identifying poor prognostic indicators in Stage I endometrial adenocarcinoma". *Gynecol. Oncol.*, 1989, 34, 299.
- [28] Frumovitz M., Slomovitz B.M., Singh D.K., Broaddus R.R., Abrams J., Sun C.C., Bevers M., Bodurka D.C.: "Frozen section analyses as predictors of lymphatic spread in patients with early stage uterine cancer". *J. Am. Coll. Surg.*, 2004, 199, 388.
- [29] Kucera E., Kainz C., Reinhaller A., Sliutz G., Leodolter S., Kucera H., Breitenecker G.: "Accuracy of intraoperative frozen section diagnosis in Stage I endometrial adenocarcinoma". *Gynecol. Obstet. Inv.*, 2000, 49, 62.
- [30] Fanning J., Tsukada Y., Piver M.S.: "Intraoperative frozen section diagnosis of depth of myometrial invasion in endometrial adenocarcinoma". *Gynecol. Oncol.*, 1990, 37, 47.
- [31] 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.
- [32] Obermair A., Geramou M., Gucer F., Denison U., Kapshammer E., Medl M. *et al.*: "Endometrial cancer: accuracy of the finding of a well differentiated tumour at dilatation and curettage compared to the findings at subsequent hysterectomy". *Int. J. Gynecol. Cancer*, 1999, 9, 383.
- [33] Petersen R.W., Quinlivan J.A., Casper G.R., Nicklin J.L.: "Endometrial adenocarcinoma - presenting pathology is a poor guide to surgical management". *Aust NZ J. Obstet. Gynaecol.*, 2000, 40, 191.
- [34] Manfredi R., Mirk P., Maresca G., Margariti P.A., Testa A., Zannoni G.F., Giordano D., Scambia G., Marano P.: "Local regional staging of endometrial carcinoma: role of MRI in surgical planning". *Radiology*, 2004, 231, 372.
- [35] Shibutani O., Joja I., Shiraiwa M., Asakawa T., Miyagi Y., Kudo T., Hiraki Y.: "Endometrial carcinoma: efficacy of thin section oblique axial MR images for evaluating cervical invasion". *Abdom Imaging*, 1999, 24, 520.
- [36] Cunha T.M., Felix A., Cabral I.: "Preoperative assessment of deep myometrial and cervical invasion in endometrial carcinoma: comparison of MRI and gross visual inspection". *Int. J. Gynecol. Cancer*, 2001, 11, 130.
- [37] Frei K.A., Kinkel K.: "Staging endometrial cancer: role of MRI. Review article". *J. MRI*, 2001, 13, 850.

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