The role of frozen section in the management of early endometrioid endometrial carcinoma

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Abstract

Objective: To assess the accuracy of intraoperative frozen section in patients with early endometrioid adenocarcinoma of the endometrium.
Methods: Frozen section was compared with definitive histology in patients with early endometrioid adenocarcinoma of the endometrium. Prognostic factors such as grade, depth of invasion and cervical involvement were compared to assess whether frozen section could make a contribution in identifying patients who were at risk of lymph node metastases.
Results: There were 61 patients who met the inclusion criteria. Frozen section was correct when compared to definitive histology in 93.5% of cases. For depth of invasion and cervical involvement, frozen section was correct in 95.1% and 90% of cases respectively.
Conclusion: Frozen section seems, in this study, to be a useful intraoperative tool to identify patients who are at risk of lymph node metastases.

Introduction

Carcinoma of the uterus is the most common gynaecological malignancy in the developed world. Approximately 2-3% of women develop endometrial cancer in their lifetimes.[1] Since the most common presentation, postmenopausal bleeding, occurs early in the course of the disease, many early-stage cases may be adequately treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH and BSO) alone at the time of primary surgery. Once the cancer has spread outside the uterus, adjuvant therapy is indicated.

Endometrioid adenocarcinoma is by far the most commonly occurring histological type of endometrial cancer, accounting for 80% of cases. Other types include mucinous, papillary serous, clear cell, squamous, undifferentiated and mixed carcinoma. Carcinomas are graded according to their architectural growth patterns and nuclear features into well-differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 3) tumours. Since 1988, according to the International Federation of Gynaecology and Obstetrics (FIGO) classification, patients have been surgically staged according to depth of myometrial invasion, cervical and vaginal extension, extension to uterine serosa, adnexae and peritoneum, and lymph node and distant metastases (Table I).

Table I: Endometrial carcinoma staging, FIGO (1988)

Stage	Definition
IA	Tumour limited to endometrium
IB	Invasion to < 50% of the myometrium
IC	Invasion to > 50% of the myometrium
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
IIIA	Tumour invades serosa and/or adnexae, and/or positive peritoneal cytology
IIIB	Vaginal involvement or metastasis
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastasis including intra-abdominal and/or inguinal lymph nodes

Creasman et al studied 621 women with endometrial adenocarcinoma, and found that the incidence of

pelvic lymph node metastasis was 3% for grade 1 tumours and 9% for grade 2 tumours.[2] Eighteen per cent of patients with grade 3 tumours had lymph node involvement. When the worst prognostic grade (grade 3) is combined with deep invasion of the myometrium, the incidence of pelvic lymph node involvement increased to 34%. More recently, Chi et al studied 349 patients, who underwent full surgical staging for carcinoma of the endometrium.[3] Their findings were that the incidence of pelvic lymph node spread in relation to tumour grade and depth of invasion (none, inner half and outer half) was as follows: grade 1, 0%, 0% and 0% respectively; grade 2, 4%, 10% and 17%; and grade 3, 0%, 7% and 28%.

Since low-grade tumours with minimal endometrial invasion can be treated with surgery alone, it is imperative to determine which patients have high-risk features (poor differentiation, myometrial invasion > 50%, cervical extension and histological types other than endometrioid adenocarcinoma) for pelvic and/or para-aortic lymph node metastases. Thus, the presence of these features would be an indication for assessment of the lymph nodes draining the uterus. Lymph node spread requires adjuvant therapy, whilst the absence of positive lymph nodes negates the need for further radio- or chemotherapy in this potentially bad prognostic group.

Frozen section may be used to identify the subgroup of patients undergoing laparotomy or laparoscopy for carcinoma of the endometrium who may have features of high-risk uterine disease. Previous reports aimed at ascertaining the accuracy of frozen section have had conflicting results. Some studies demonstrated that frozen section was accurate, making it a reliable tool for determining which patients should have a lymphadenectomy.[4,5] Other publications suggested that frozen section was inaccurate, and would lead to a false sense of security.[6,7]

The current study is an analysis of the use and accuracy of frozen section in patients with endometrioid endometrial adenocarcinoma.

Material and methods

Ethics approval for the study was granted by the University of Cape Town's ethics committee.

The records of all patients who had frozen sections during surgery for endometrial carcinoma were obtained from two sources. The first was the records of all the patients with endometrial carcinoma who had surgery at Groote Schuur Hospital, Cape Town. These patients were referred to the combined assessment clinic in the radiotherapy department. The other source was the records of the private pathology laboratory of

Dr J Whittaker and Dr C Baigrie. These patients were primarily managed in private practice in Cape Town.

Data collection started from January 2002 and continued to December 2009, and included all women from these two sources who had frozen sections during surgery for endometrial carcinoma. As this study included patients managed between 2002 and 2009, the 1988 FIGO staging (Tabel) was used, and not the 2009 classification.

The inclusion criteria were that the patients had to have had a frozen section and that the frozen section must have been performed on what was perceived to be stage I endometrial carcinoma. Patients with a uterine neoplasm other than endometrioid endometrial adenocarcinoma, and patients in whom frozen sections were done for reasons other than to grade and stage early endometrial cancers, were excluded. These patients have a different disease progress compared to that of patients with endometrioid endometrial adenocarcinoma. As per protocol, a patient who was found, on frozen section, to have either a grade 3 endometroid adenocarcinoma, or > 50 % infiltration of the myometrium, or cervical stromal involvement, was considered to be a candidate for pelvic lymphadenectomy. This approach has been based on data from the literature. [2,3]

The surgical procedure, according to protocol, entailed entering the abdomen through either a lower transverse incision or a subumbilical mid-line incision. After the abdominal cavity was inspected and washings of the pouch of Douglas were obtained, a TAH and BSO were performed. The specimens were removed and offered to the pathologist. If a lymphadenectomy was indicated, based on the aforementioned risk factors, all the pelvic nodes on both sides along the ileac vessels, from the common ileac vessels, down to the level where the circumflex vein crosses the ileac artery, were removed. The nodes in the obturator fossa on both sides anterior to the obturator vessels were removed. The Groote Schuur Hospital protocol, which was followed, does not require removal of the para-aortic lymph nodes.

The histological approach used during frozen section was as follows:

1. After removal, the uterus was bi-valved.
2. Serial coronal cuts were performed, approximately 5 mm apart.
3. If invasive carcinoma was grossly identified, the depths of invasion, macroscopically, and uninvolved myometrium were measured. A section was taken, from what was estimated to be the deepest area, to assess both stage and grade.
4. If no tumour was macroscopically seen infiltrating

the myometrium, a random section was taken from the area of greatest tumour bulk.

5. If no tumour was macroscopically seen, the specimen was closely examined to see if the site of previous sampling could be visualised, and a section was then taken from this area to assess grade and, if possible, depth of invasion.

6. The endocervical canal was examined closely and, in cases of stage IA or stage IB carcinoma, a section of the endocervical canal was evaluated. This step was not performed with grade 3 or stage IC tumours.

7. Grading of the tumour was done by evaluating the percentage of solid tumour present and degree of pleomorphism, as recommended by FIGO: > 50% solid tumour equalled grade 3; or < 50% and > 5%, with a high nuclear grade or showing pleomorphism, also equalled grade 3.

In this study, all histology slides were reviewed by one of the authors (JW). The frozen section reports were compared with the final paraffin report with regard to discrimination between low and high grade and stages IA and B versus IC lesions. Furthermore, the frozen section findings of the status of the cervix were compared with those of definitive histology. Any differences between frozen section and definitive histology outcomes resulted in the frozen section being scored as inaccurate. The inaccurately diagnosed cases were then further divided into over-scored or under-scored, depending on the comparison. In addition, the inaccuracies were reviewed to determine in which cases the discrepancies resulted in either unnecessary lymph node dissection or omission of necessary lymph node dissection, or if they had no bearing on intraoperative management.

Results

The files of 63 patients were initially drawn. Two of these patients did not meet the inclusion criteria. The reasons for exclusion were that one patient's histology proved, on review, to be a sarcoma of the uterus and, in the other patient, the disease was intraoperatively classified as a stage III tumour and the frozen section was not done to assess early-stage disease.

Specimens of 61 women with endometrioid endometrial adenocarcinoma who underwent intraoperative frozen section for presumed early stage endometrial carcinoma were, therefore, analysed. The median age of these patients was 68 years (range 41-87 years). According to the definitive histology results, 46 of the patients (75.4%) had stage I disease, 10 patients (16.3%) were stage II, five patients (8.1%) were stage III, and none of the patients had stage IV disease (Table II). Histopathological grading on definitive histology found 26 (42.6%), 28 (45.9%) and seven patients (11.4%) with grade 1, 2 and 3 lesions, respectively (Table II).

Table II: Patient characteristics (n = 61)

Median age	68 (range 41–87 years)
Final staging[a]	
Stage I	46 (75.4%)
Stage II	10 (16.3%)
Stage III	5 (8.3%)
Stage IV	0
Grade	
Grade 1	26 (42.6%)
Grade 2	28 (45.9%)
Grade 3	7 (11.4%)

[a] Based on definitive histology

Of the 61 patients, 16 (26.2%) were found to have high-risk lesions (grade 3, > 50% myometrial invasion or cervical stromal involvement) on frozen section. Forty five patients (73.8%) were found to have lesions at low risk for lymphatic spread based on frozen section findings. This was compared with the definitive histology results, from which it was determined that 20 patients (32.8%) had high-risk lesions and 41 (67.2%), low-risk lesions. Lymphadenectomy was, therefore, performed in the 16 patients (26.2%) who, according to their intraoperative frozen section findings, had uterine lesions at high risk of lymph node metastasis. The definitive histology findings were that 20 patients (32.8%) had cancers that were at high risk of lymph node metastasis. The sensitivity of frozen section for identifying patients with high risk lesions (grade 3 lesions, > 50% myometrial invasion, and/or cervical involvement) was found to be 75% and the specificity 97.6% with a positive predictive value (PPV) of 93.8% and a negative predictive value (NPV) of 88.9% (Table III).

Table III: Comparison of frozen section with definitive histology for identifying lesions at high risk of lymph node metastasis

		Definitive histology results		
		High risk	*Low risk*	*Total*
Frozen section results	*High risk*	15	1	16
	Low risk	5[a]	40	45
	Total	20	41	61

Sensitivity = 75.0%, specificity = 97.6%, PPV = 93.8%, NPV = 88.9%

[a] In one patient, both grade and depth of invasion were under-called

A comparative analysis between frozen section and definitive histology showed that results were concordant in 37 (60.7%) cases, where grade and myometrial depth of the lesions were identical on frozen section and definitive histology. In 24 (39.3%) patients, there were differences in findings between frozen section and definitive histology. In five of

the 24 patients with discordant results (8.2% of all patients), the patients were incorrectly assessed as low risk when the definitive histology found them to have lesions at high risk of lymph node spread. In one patient (1.6%), a lesion assessed as high risk on frozen section was later found to be low risk on definitive histology. Therefore, in six patients (11.4%), the frozen section outcome had a deleterious influence on intraoperative management. In the remaining 18 patients (29.5%), the differences did not bear any clinical relevance (Table IV).

Table IV: Concordance of results between frozen section and definitive histology

	Number of patients	Percentage of total
Total frozen sections	61	100.0%
Concordant results	37	60.7%
Inaccuracies	24	39.3%
Insignificant changes	18	29.5%
Changed from low to high risk	5[a]	8.2%
Changed from high to low risk	1	1.6%

[a] In one patient, both grade and depth of invasion were under-called

When assessing high-grade (grade 3) lesions, frozen section identified five, whereas definitive histology found eight patients to be have high-grade lesions. Thus, the sensitivity of frozen section for identifying high-grade lesions was 62.5% and the specificity 98.1%, with a PPV of 83.3% and a NPV 94.6% (Table V). Frozen section was found to be accurate in 95.1% of cases.

Table V: Comparison of high-grade lesions identified on frozen section with definitive histology results

		Definitive histology: grade		
		Grade 3	Grade < 3	Total
Frozen section: grade	Grade 3	5	1	6
	Grade < 3	3	52	55
	Total	8	53	61

Sensitivity = 62.5%, specificity = 98.1%, PPV = 83.3%, NPV = 94.6%

Depth of myometrial invasion > 50% was on frozen section in 11 patients, compared with 14 on definitive histology. The sensitivity of frozen section for identifying deeply invasive lesions was found to be 78.57% with a specificity of 100%, a PPV of 100% and a NPV of 94% (Table VI). Frozen section was correct in 95.1% of cases.

Table VI: Comparison of depth of myometrial invasion on frozen section with definitive histology results

		Definitive histology: myometrial invasion		
		> 50%	< 50%	Total
Frozen section: myometrial invasion	> 50%	11	0	11
	< 50%	3	47	50
	Total	14	47	61

Sensitivity = 78.6%, specificity = 100.0%%, PPV = 100.0%, NPV = 94.0%

In one patient, both the depth of invasion and the grade on frozen section were different from the definitive histology results. Therefore, in six patients (9.8%), the frozen section findings differed from the definitive histology and resulted in incorrect intraoperative management.

Out of the 61 frozen sections performed, cervical involvement was not assessed intraoperatively in 31 patients. Cervical involvement was assessed in the remaining 30 patients, and stromal involvement was found in four patients (13.3%) on frozen section, as opposed to seven (23.3%) on definitive histology (Table VII). In 90% of cases, frozen section was accurate when compared to definitive histology. In 15 of the 31 patients (48.4%) in whom cervical involvement was not commented on, lymphadenectomy was already indicated, based on the depth of invasion or grade of the lesion. In the remaining 16 patients, this missing information would have been useful to further guide the surgeon in deciding whether to proceed with lymphadenectomy, or not.

Table VII. Comparison of cervical involvement identified on frozen section with definitive histology results

		Definitive histology: cervical involvement		
		Involved	Not involved	Total
Frozen section: cervical involvement	Involved	4	0	4
	Not involved	3	23	26
	Total	7	23	30

Sensitivity = 57.1%, specificity = 100.0%%, PPV = 100.0%, NPV = 88.5%

Discussion

Accurate intraoperative risk assessment in endometrial cancer is of importance in determining which patients are at high risk of lymph node metastasis. Since low-risk lesions rarely metastasise to lymph nodes and

high-risk lesions have a greater propensity for lymph node spread, it follows that patients with high-risk lesions will benefit from full surgical staging involving lymphadenectomy.[2] Data from the literature discussing grade 1 carcinoma of the endometrium suggest that, in a best-case scenario (stage IA1), the incidence of positive pelvic nodes is close to 0% while, in a worst-case scenario (stage IC3), the incidence of positive pelvic nodes is approximately 34%.[2] It is, therefore, reasonable to treat patients with early-stage (< 50% myometrial invasion and grade 1 and 2 tumours) endometrioid adenocarcinoma of the endometrium with TAH and BSO alone, without lymphadenectomy. On the other hand, in patients with > 50% myometrial invasion and/or a grade 3 tumour, it is imperative that a lymphadenectomy is performed. Knowledge of lymph node involvement may be of assistance in deciding which of these patients will require adjuvant therapy. Patients who are found to be node negative may only receive vaginal brachytherapy to minimise the risk of vaginal vault recurrence whereas, in patients with positive nodes, radical radiotherapy, possibly extending to the para-aortic lymph node groups in addition to vaginal brachytherapy, may be considered.

Since many patients with endometrial cancer are obese and medically unfit, with possible co-morbid diseases such as hypertension, ischaemic heart disease and diabetes, one would hesitate to subject all patients at low risk for lymph node metastasis to a lymphadenectomy. Some authors, however, strongly advocate full surgical staging in all patients with endometrial cancers, irrespective of grade.[6,8]

But, lymphadenectomy is not without risk. Operating time is increased by 30-45 minutes, and complications may arise in 17-19% of patients.[9,10] Vascular injuries, postoperative bleeding and lymph cysts occur far more frequently in patients undergoing lymphadenectomy than those patients who do not have this procedure. Furthermore, nerve and ureteric injuries have been reported in 3% of cases.[11] Postoperative hospital stay is also longer in patients undergoing lymphadenectomy.[9] In addition, the economic cost of the procedure is increased by longer anaesthetic time, operating time and hospital stay. These costs rise even more if complications occur.

It is, therefore, important to weigh up the need for full surgical staging versus the risks involved in performing unnecessary lymphadenectomy in a, largely, surgically unfit population. At the same time, it must be borne in mind that the surgeon would either want to know the lymph node status of the patient, or be confident that, having not performed the lymphadenectomy, the patient is indeed at low risk for lymph node spread. Frozen section may provide an intraoperative means of

determining the histological type of the tumour, as well as the grade of the disease and the depth of invasion. Many studies have attempted to determine whether or not frozen section is an accurate tool. Kayikçioğlu et al found, in a study involving 154 patients, that final histology results concurred with frozen section results in 134 (87%) in terms of depth of invasion and, in 132 (86%), tumour grade.[4] Quinlivan et al found, in 209 patients, that the accuracy of frozen section was 88.6%, 94.7% and 100% for grade, depth and cervical invasion, respectively.[5] Frumovitz et al, however, reported only a 67% correlation in depth of invasion, and 58% in histological grade.[6] Case et al also concluded that frozen section results were inaccurate when compared with the final histopathological findings.[7] These last two studies recommend comprehensive surgical staging, including pelvic and para-aortic lymphadenectomy, for all patients with endometrial carcinoma, as patients were frequently under-staged using frozen section. Such an approach will, however, result in unnecessary lymphadenectomy, with equally unnecessary complications.[2,9-11]

Errors of frozen section diagnosis are either due to incorrect interpretation or incorrect sampling. The major technical problem is decreased histopathological detail due to suboptimal fixation as a result of freezing artefaction, compared with paraffin samples. Secondly, fewer sections are done with frozen section compared to paraffin samples due to time constraints, and because some tissue must be left for paraffin embedding. The freezing process may also damage the tissue as a result of freezing compression and nuclear freezing artefaction.[5,12] Lastly, it is well documented that frozen sections done by specialist gynaecological pathologists will render better results than those done by general pathologists.[13]

Our study found that, for lesions at high risk of lymph node metastasis, the sensitivity of frozen section when compared with definitive histology was 75% and the specificity 97.56%, with a PPV of 93.6% and an NPV of 88.9%. For identifying high-grade lesions, the sensitivity of frozen section was 62.5% and the specificity 98.1%, with a PPV of 93.8% and an NPV of 88.9%. Lesions at high risk of myometrial invasion were more readily identified on frozen section, with sensitivity of 78.5%, specificity of 100%, PPV of 100% and NPV of 94%.

Five (8.2%) of the total number of frozen sections performed resulted in lesions being under-called and, in only one case (1.6%), a lesion was over-called. In one patient, both the depth of invasion and the grade on frozen section were under-called when compared to the definitive histology results. Therefore, in six patients (9.8%), the frozen section findings differed from the definitive histology and resulted in incorrect intraoperative management. This means that frozen section was accurate in 90.2% of cases, and could

guide the surgeon in deciding whether or not a lymphadenectomy was indicated.

In three patients, the depth of invasion was found on definitive histology to be > 50% whereas, on frozen section, this was missed. This means that, in only 4.9% of cases, a lymphadenectomy was not performed when it should have been. In 95.1% of cases, the assessment of depth of invasion on frozen section was correct.

Since cervical involvement was only assessed in 30 patients, this represents a small sample size, with sensitivity of only 57.14%. As previously mentioned, the cervical data are under-reported and no comment was made on cervical involvement in 16 of the patients in whom these data would have been important for correctly staging the cancer. It is of note that, in only two (11.1%) out of 18 patients who had a pelvic lymphadenectomy, positive nodes were found. This is considerably less than the 17-28% quoted in the literature.[2,3] It may be that the number of lymph nodes removed, although not counted and actually the subject of another analysis, had an influence on this finding.

This study has a number of limitations. Although the exact number is not known, not all frozen sections were done by a specialist gynaecological pathologist. It can be argued that, if a specialist gynaecological pathologist had been involved in all cases, the accuracy might have been enhanced.[13] Secondly, where these findings might have made a difference, the endocervix was not assessed on frozen section in all cases. This assessment should be part of standard frozen section for patients with endometrial carcinoma. Thirdly, the focus in this analysis was on the value of frozen section, and not on the issue of which patients with endometrial carconoma are at risk for lymph node metastases and should undergo lymphadenectomy. Finally, the total number of patients entered into the study is not large, but the findings still give an indication that frozen section would be a useful tool in the management of patients with endometrial carcinoma.

Conclusion

In this study, endometrial frozen section was found to be accurate in more than 90% of cases, guiding the surgeon in deciding whether or not a lymphadenectomy was indicated. This makes it a reasonably reliable method of intraoperatively assessing the grade and stage of early-stage endometrial carcinoma, to determine whether the patient is at risk for lymph node involvement.

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