



Commentary

Clinical view of gynecologic intraoperative frozen section diagnosis

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ABSTRACT

Intraoperative consultation includes gross evaluation and frozen section, which is an integral component of surgical oncology for many reasons. First, it allows appropriate surgical procedures to be undertaken. Second, it can potentially protect the patient from a second procedure. Third, it helps towards counselling of patients and their family members and lastly, it facilitates early management planning. Utilization of frozen section is justified by the reported sensitivity, specificity, positive and negative predictive values all of which are as high as 90–100% in some studies. It is very important for gynecologists to have good communication with pathologists, especially for cases with an indeterminate, frozen result. Discussion with the pathologist can help the gynecologist understand the diagnostic dilemma and the differential diagnosis, which can help them make best surgical decisions.

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In gynecologic cancers, the implications of frozen section findings can be different depending on the cancer genital tract subsite. For vulvar cancer, frozen section histology is important for sentinel lymph node evaluation. For cervical cancer, sentinel lymph node (SLN) approach is new and evolving, although frozen section histology may be done on the sentinel lymph node, full lymphadenectomy remains a universal standard. On the other hand, tumor size, grade and depth of invasion are all findings from frozen section histology of endometrial cancer that can be utilized to determine the extent of staging procedure necessary.^{3–5}

In vulvar cancer, frozen section is primarily relevant to the evaluation of sentinel lymph nodes. Since the findings of the GROINSS-V study—a European multicenter observational study on the sentinel lymph node

procedure in vulvar cancer—were published, the sentinel lymph node is being utilized increasingly in the management of women with early vulvar cancer. The aim of the procedure is to detect nodal metastases in the “sentinel” node (which primarily drains the tumor), and then to omit a full lymphadenectomy in sentinel node negative patients, thereby decreasing the morbidity associated with a complete inguofemoral node dissection.^{6,7}

All patients who have a positive sentinel lymph node (one or more positive nodes), besides undergoing a full inguofemoral lymph node dissection, should receive radiotherapy to the groins and pelvis if indicated. A subsequent trial, GROINSS-V II, is investigating the efficacy of groin radiation without inguofemoral lymphadenectomy for patients with a single positive sentinel lymph node with 2 mm or less in diameter.^{8,9}

Sentinel lymph node detection for cervical cancer has been evaluated over the last two decades.^{10–12} However, sentinel lymph node is currently not the gold standard for cervical cancer making frozen section lymph node evaluation less impactful. A recent analysis of two French prospective multicentric database on SLN biopsy for cervical cancer (SENTICOL I and II), included patients with IA to IIA1 2018 FIGO stage, that underwent sentinel lymph node biopsy with both frozen section

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examination and subsequently ultra-staging. The sensitivity and the negative predictive value of frozen section examination were 42.3% and 89.7% respectively or 56.4% and 94.1% if individual tumor cells in lymph nodes were excluded. The researchers concluded that frozen section examination of sentinel lymph nodes for cervical cancer had a low sensitivity for detecting micrometastases and individual tumor cells and a high negative predictive value for sentinel lymph node status.¹³

Frozen section examination can be important during cervical cancer surgery in women diagnosed with early-stage cervical cancer, interested in fertility preservation, and undergoing radical trachelectomy.^{14–17} Since the uterine body is being preserved, it is necessary to ensure that the uterine margin is negative. Therefore, a very thin slice of the uterine margin is sent for frozen section and if positive, additional resection can be done until a negative margin is achieved. Furthermore, a suspicious lymph node either during radical trachelectomy or hysterectomy must be sent for frozen section examination. If the lymph node is positive for cancer, the procedure is best abandoned and the patient should be treated with primary chemoradiation therapy.^{18,19}

Unique to endometrial cancer is the utility of frozen section pathology in the management of women with complex atypical endometrial hyperplasia diagnosed in previous endometrial biopsy. This entity carries a concurrent cancer diagnosis rate of 43% at hysterectomy and preoperative consensus amongst gynecologic pathologists regarding the diagnosis is poor. Intra-operative frozen section offers the opportunity for an appropriate one-sitting staging surgery for those with cancer in this group of patients.^{20,21} In patients with preoperatively confirmed low grade endometrioid adenocarcinoma, where the risk of lymph node metastasis is typically low, uterine features of the cancer as assessed by intraoperative frozen section can be used to determine whether surgical assessment of lymph nodes is necessary. This approach protects those patients considered not at risk of lymph node involvement from the morbidity associated with lymphadenectomy whilst ensuring that lymph node involvement does not escape detection in women at higher risk of metastatic disease to lymph nodes.²²

For ovarian cancer, frozen section histology is critical for women who are being taken for cytoreductive or staging surgery without a preoperative diagnosis of cancer. Approximately 75% of ovarian cancer patients have stages III-IV disease at the time of initial diagnosis. For this advanced stage disease patients, a good proportion now get their treatment via the neo-adjuvant chemotherapy approach following confirmation of diagnosis from ascitic fluid cytology or histology from image guided tissue biopsies.^{23,24} Patients with advanced ovarian cancer who are suitable for upfront cytoreductive surgery are typically not sent for image guided biopsy preoperatively as this invasive procedure can be very uncomfortable for patients. Therefore, intraoperative frozen section is necessary to confirm diagnosis even though debulking rather than staging surgery is done. For the small proportion of ovarian cancer patients who present with early-stage disease, frozen section pathology is extremely important for many reasons. First, these patients typically have a pelvic cystic mass with a good chance that malignancy if present is confined to the cystic mass, making a preoperative image-guided biopsy that has a potential for intraperitoneal spread ill-advised. Second, appropriate staging surgical steps during the surgery depends on malignancy confirmation. Lastly, there are many patients that prefer removal of all their internal reproductive appendages should cancer be confirmed yet prefer to keep the contralateral adnexal and the uterus if intra-operative findings are benign making the extent of surgery done depend solely on frozen section. A Cochran database analysis of available studies conclude the following: In a hypothetical population of 1000 patients (290 with cancer and 80 with a borderline tumor), if a frozen section positive test result for invasive cancer alone was used to diagnose cancer, on average 261 women would have a correct diagnosis of a cancer, and 706 women would be correctly diagnosed without a cancer. However, four women would be incorrectly diagnosed with a cancer (false positive), and 29 with a cancer would be missed (false

negative).²⁵ If a frozen section result of either an invasive cancer or a borderline tumor was used as a positive test to diagnose cancer, on average 280 women would be correctly diagnosed with a cancer and 635 would be correctly diagnosed without. However, 75 women would be incorrectly diagnosed with a cancer and 10 women with a cancer would be missed. The largest discordance is within the reporting of frozen section borderline tumors. Investigation into factors leading to discordance within centers and standardization of criteria for reporting borderline tumors may help to improve accuracy. Some centers may choose to perform surgical staging in women with frozen section diagnosis of a borderline ovarian tumor to reduce the number of false positives. In their interpretation of this review, readers should evaluate results from studies most typical of their population of patients.²⁵

Ovarian borderline tumor accounts for about 15% of all primary ovarian neoplasms. One study concluded that although frozen section analysis was highly accurate in the diagnosis of benign and malignant ovarian tumors, but only moderately useful in the diagnosis of borderline tumors.²⁶ In a study of 354 ovarian borderline tumors, the overall agreement between the frozen section and the permanent pathological diagnosis was only 64.4%. Mucinous histology was the only predictor for under-diagnosis by frozen section analysis.²⁷ The study indicated that frozen section for mucinous borderline tumors was not very accurate and association with a high degree of under-diagnosis and over-diagnosis.²⁷ More studies concluded that ovarian mucinous borderline tumors are underdiagnosis more commonly than serous borderline tumors, because mucinous tumors tend to be larger and frequently contain benign, borderline, and malignant components that can be missed with sampling errors by pathologists.^{28,29} Given the significance of a frozen section diagnosis and the potential morbidities of surgical staging, strategies to help reduce surgical intervention in patients with ovarian borderline tumor have been an area of interest. Since the presence of peritoneal implants has prognostic significance, and the most common sites of implants include the omentum and peritoneal surface, at the University of Texas MD Anderson Center, after a frozen section diagnosis of borderline ovarian tumor, surgical staging includes pelvic washings, omental biopsy, thorough inspection of the peritoneal cavity and retroperitoneal structures with biopsy of any abnormal sites, palpation of the pelvic and aortic lymph nodes with removal of any abnormal nodes, and unilateral or bilateral salpingo-oophorectomy with or without hysterectomy depending on the patient's menopausal status and wishes regarding fertility preservation.³⁰ Although multiple studies shown the low utility of an appendectomy in detecting carcinoma in patients with a normal-appearing appendix,^{31,32} it has been common practice for patients with mucinous borderline tumors to undergo an appendectomy as part of their surgical staging regardless of the appearance of the appendix.³⁰

Although frozen section diagnosis will never be perfectly accurate, they certainly can provide guidance for most gynecological cases. The expertise of the pathologist is a key component in determine accuracy. It is very important for gynecologists to have good communication with pathologists, especially for cases with an indeterminate frozen section result. Communicating to the pathologist relevant information, such as preoperative imaging findings, clinical information, tumor marker status, and intraoperative findings, can likely aid the pathologist in trying to arrive at the correct diagnosis on intraoperative frozen section analysis.^{29,33} Full discussion with the pathologist can help the gynecologist understand the diagnostic dilemma and the differential diagnosis, which can guide the best surgical decisions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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