Use of Frozen Section in GU Pathology

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Introduction

Intraoperative frozen section (FS) diagnosis is one of the most challenging areas in the practice of diagnostic surgical pathology due to a variety of reasons, such as constraint of time, incomplete clinical information, suboptimal tissue preparation due to freezing artifacts, and limitation of surgical and/or gross sampling. Similar to any other systems, the purpose of intraoperative FS diagnosis in genitourinary tract (GU) is to provide diagnostic information that is needed for immediate intraoperative decision making for optimal patient care. Although there are general indications for the intraoperative FS request by urologists, these are influenced by a variety of factors including personal preference, training, and institutional tradition of the requesting surgeons. Furthermore, with the advances in surgical and imaging techniques as well as treatment options, the indication and use of FS diagnosis in GU diseases continue to evolve. It is the responsibility of both the urologist and the pathologist to communicate with and educate each other, to understand the reason for the FS and to be aware of the advantages and limitations of intraoperative FS diagnosis.

This presentation will briefly review the recent major advances in urological surgery over the last decade and its impact in the request for intraoperative FS diagnosis. The main indications for intraoperative FS in GU tumors including tumors of prostate, bladder, kidney and testis will be summarized. Finally, some of the major pitfalls and mistakes in the practice of intraoperative FS diagnosis will be highlighted.

Major recent advances in urologic surgery

Laparoscopic or minimally invasive surgery, particularly robotic-assisted surgery, has revolutionized the field of urologic surgery. With the improved ergonomics, greater freedom in movement, and increased magnification, robotic systems allow for better visualization and surgical precision than open surgery. Robotic procedures provide similar short and intermediate-term oncologic outcome as open surgery does, but there is decreased patient morbidity, less blood loss and a shorter hospital stay.\(^1\)\(^-\)\(^4\) Due to heavy marketing and widespread media coverage, an estimated of 80% prostatectomies are currently performed by robotic technique in USA.\(^5\) Robot-assisted radical cystectomy is also picking up speed even though open approach is still more commonly done.\(^3\) Partial nephrectomy has become the standard therapy for organ-confined small renal masses. The criteria for partial nephrectomy continue to expand for larger T1b tumors, endophytic tumors and even tumors near hilar structures. In some centers, essentially all partial nephrectomies are performed via a robotic-approach.

Intraoperative FS for radical prostatectomy

There are two major trends in the radical prostatectomy (RP) in recent years. Firstly, the diagnosis of organ-confined prostate cancer has increased significantly in the last 10-15 years.\(^6\)\(^,\)\(^7\) Secondly, robotic-assisted RP has emerged to become the main surgical approach for radical prostatectomy in USA. The most common reason for intraoperative FS in RPs is the evaluation of the surgical margins and rarely lymph node evaluation of nodal metastasis. The majority of
the RPs do not require intraoperative frozen section evaluation. As a general rule, selective patients with high risk disease, as determined by combination of clinical stage, biopsy Gleason score and PSA levels, are likely candidates for intraoperative evaluation of margin and/or lymph nodes.

FS can reliably determine the surgical margin for the presence of either carcinoma or normal prostatic glands. This information provides the key for the urologist to consider resection of new margins, level of the anastomosis, extent of additional dissection, and to consider whether the neurovascular bundle should be preserved or not.

Recent studies have shown a similar rate and location of positive surgical margins with open, pure laparoscopic and robotic assisted RPs. Our experience also supports that the incidence of positive surgical margins is similar in both open and robotic surgery. The presence of non-neoplastic glands should also be reported to the surgeon, as this finding may indicate inadequate removal of the prostate tissue or capsular incision.

Common pitfalls in the interpretation of intraoperative FS of margin status include various artefacts induced by surgical tear, crush and thermal changes, as well as freezing artefacts and anatomical histologic variations. Thermal artefact is particular problematic for interpretation of margin status and for distinction of benign from malignant glands. The constellation of multiple features including haphazard infiltrative pattern, enlarged nuclei, prominent nucleoli, lack of basal cells, and circumferential perineural invasion remain very helpful for a correct FS diagnosis. Cauterized nerves or ganglion tissue, and focal dense inflammatory infiltrates can simulate high grade prostate carcinoma. Small vessels with margination of neutrophils can also mislead to a diagnosis of carcinoma or lymphovascular invasion on FS. It is always helpful to have recuts or deeper levels of those areas for a definitive diagnosis. If a definitive diagnosis still cannot be reached after deeper sections, it is advisable to obtain consultation with an experienced colleague or GU pathologist. Do not hesitate to ask for another biopsy for FS which may or may not be technically possible. Otherwise one may have to defer the interpretation for permanent sections evaluation.

Lymph node dissection is an integral part of TNM staging. Frozen sections on pelvic lymph nodes are not routinely done during RP, especially in patients with low risk disease (Gleason score of ≤6 (3+3), low level of PSA and low clinical stage). However, in patients with high risk disease such as high Gleason score (score ≥8) and/or high level of PSA, positive lymph nodes as evaluated by FS may be a reason to halt the RP. Everyone is well aware that the presence of a microscopic focus of carcinoma will not deter the surgeon from doing a RP, but those patients with extensive lymph node metastasis may not benefit from the RP.

The specificity of FS diagnosis of nodal metastasis for prostate cancer is very high, but the false negative rate can be as high as of 33% due to micrometastasis and sampling issue. Therefore, in many centers, intraoperative FS evaluation of pelvic lymph nodes is not routinely done unless specifically requested by urologists.
Intraoperative FS of nephrectomy

More and more small kidney cancers are diagnosed due to imaging procedures for other reasons. For organ-confined renal tumors, the current standard treatment is partial nephrectomy in order to preserve renal function and achieve long term survival. Radical nephrectomy is performed for large and advanced renal cancer and debulking in patients with metastatic disease. Request for intraoperative FS diagnosis for nephrectomy is infrequent.

One of the most frequent intraoperative FS requests is margin evaluation for partial nephrectomy, whereas histologic diagnosis of renal tumor is rarely needed since it usually does not alter the type of surgery. Occasionally, FS diagnosis is requested to distinguish invasive urothelial carcinoma vs high grade renal cell carcinoma since they require different surgery. The role of routine nodal dissection for radical nephrectomy remains undetermined and FS diagnosis of lymph node is rarely requested. The indications for intraoperative FS are also strongly influenced by personal preference and training of urologists, institutional tradition and the types of hospitals.

It is important to emphasize that careful and thorough gross examination is critical for intraoperative pathologic consultation. In many situations, gross consultation rather than FS can provide sufficient information for intraoperative decision making. In fact, FS diagnoses are usually not requested in our hospital, but rather the urologists generally request a gross consultation. In the gross evaluation of the kidney, the location of the tumor, its relationship with surrounding tissue, circumscription, perirenal and hilar tissue invasion, heterogeneity and color of the tumor, presence of cystic change and necrosis are all helpful features. In addition, gross evaluation of the surgical margins (vascular, ureteral and perirenal) is also extremely valuable.

The indications for a partial nephrectomy continue to expand. The renal margin evaluation with FS is by far the most common request during renal surgery even though a positive surgical margin appears to have minimal impact in patients’ survival. FS may be also requested for a specific histologic diagnosis especially when the surgical margin is positive during partial nephrectomy. A definitive diagnosis of a benign tumor such as angiomyolipoma, oncocytoma or metanephric adenoma may negate the need for additional margin or total nephrectomy. Since the tumors selected for partial nephrectomy are usually circumscribed and even encapsulated, gross impression of a negative margin is usually accurate. Recognizing a free parenchymal surgical margin is usually straightforward for a partial nephrectomy specimen. However, inaccurate interpretation of the histology may occur when the specimen has significant cautery and freezing artifacts. Normal or atrophic renal tubules may simulate a neoplasm and conversely, neoplastic tubules of low grade RCC may look similar to benign renal tubules.

Intraoperative FS diagnosis of renal tumors relies on familiarity with features of classic types of benign and malignant renal neoplasms and consideration of inherent FS artifacts. In most situations, a diagnosis of renal cell carcinoma (not specified) or benign renal tumor is sufficient intraoperatively. Difficult situations may arise in tumors with oncocytic cytoplasm, tumors with papillary growth or cystic changes, high grade carcinomas including urothelial carcinoma, and angiomyolipoma. In some situations, a definitive histologic diagnosis may not be possible.
Nodal dissection is not routinely performed during total nephrectomy and its role is not well established. Clinically unsuspected nodal metastasis occurs in less than 5% of cases. Nodal metastasis is often suspected preoperatively by imaging, thus obviating the need for FS in most instances. Since enlargement of a lymph node may be due to processes other than metastatic RCC, i.e., reactive lymphoid hyperplasia, lymphoma, sarcoidosis, etc, a FS may be requested.

**Intraoperative FS of cystectomy for bladder cancer**

Radical cystectomy with pelvic nodal dissection is standard treatment for patients with muscle invasive bladder cancer, recurrent tumors or tumor resistant to intravesicle therapy. The most frequent reason for intraoperative FS diagnosis is to evaluate the surgical margin status of the ureter, urethra, and rarely soft tissue margins during radical cystectomy. For a partial cystectomy specimen, evaluation of surgical margins is also commonly requested.

Urothelial neoplasia is frequently multifocal and may involve the mucosal resection margins including ureteral and urethral mucosal margins, in the form of urothelial carcinoma in-situ or pagetoid mucosal spread of adjacent urothelial carcinoma (pagetoid in situ carcinoma) or rarely separate foci of invasive carcinoma. Although the effectiveness of routine FS of ureteral margin has been questioned in a number of studies, the goal of achieving negative ureteral margin whenever feasible is highly desirable in order to reduce the risk of recurrence at the ureterointestinal anastomosis. The incidence of high-grade dysplasia/carcinoma in situ of the ureteral margins ranges from 4.8% to 9%. If the margin is positive for high grade dysplasia/carcinoma in situ, additional ureteral tissue with new margin may be taken if clinically feasible. FS of the distal prostatic urethra is requested to ensure that no high grade dysplasia/carcinoma in situ is present at the urethral margin before performing urinary diversion with construction of an orthotopic neobladder. In situations when the clinical examination and surgical findings are equivocal, FS might be requested to determine the resectability or adequacy of tumor resection.

FS diagnosis of severe dysplasia/carcinoma in-situ in ureteral and urethral margins is frequently challenging, because it is often accompanied by inflammation, treatment effect, cautery or freezing artifacts. The diagnoses may be divided into three broad categories: non-dysplastic, atypia not further classified, high grade dysplasia/carcinoma in situ or invasive carcinoma. One must keep in mind that normal urothelium frequently looks distorted and atypical on the FS slide. Therefore, the diagnosis of severe dysplasia/carcinoma in-situ should be reserved for those cases exhibiting clear cut nuclear atypia, apoptosis and mitotic activity in addition to loss of polarity. The diagnosis of low grade or moderate dysplasia should be avoided at it has poor diagnostic reproducibility, lacks standard treatment options and probably does not have clinical significance. The interpretation of perivesical soft tissue margins is usually straightforward.

Partial cystectomy is reserved for highly selected patients. The most common indications for partial cystectomy include solitary tumor located in the dome of the bladder, tumor associated with bladder diverticulum or urachal adenocarcinoma. FS may be requested for margin evaluation. The diagnoses of mucosal high grade dysplasia/CIS and its pitfalls are similar to those encountered for the ureteral and urethral margins. Invasive tumor in subepithelial tissue,
muscularis propria, and perivesical fat can occasionally be seen. Small foci of urachal adenocarcinoma of mucinous or signet ring cell type may show only intramural mucin pools.

During radical cystectomy, colorectal or gynecologic surgery, incidental bladder lesions may be visualized on the bladder wall by the surgeon, either in the form of a peritoneal nodule, irregular thickening, or areas of discoloration. FS is requested to identify the nature of these lesions. The diagnosis rarely changes the course of the surgery, but may be part of the staging procedure. The most frequent diagnostic entities include mesothelial hyperplasia, fibrotic and hyalinized nodule, chronic inflammation, calcification, endometriosis, endocervicosis, endosalpingiosis, and, rarely, metastatic carcinoma. In these situations, awareness of the clinical history and histologic features of these lesions will provide an accurate diagnosis.

A FS diagnosis of a bladder tumor may be rarely requested to provide an immediate diagnosis for selection of the surgical procedure. The reasons may include unsuccessful previous biopsy or a need to secure adequate specimen for diagnosis and staging. This usually involves confirmatory diagnosis of a bladder tumor and evaluation of the depth of invasion. Because the invasion into muscularis propria is a major indication for radical cystectomy, the diagnosis must be accurate and must be differentiated from a tumor-induced desmoplastic myofibroblastic reaction or invasion into hyperplastic muscularis mucosae. It should be emphasized, however, that this distinction may be impossible in small tissue samples.

Bilateral pelvic lymph node dissection is part of the standard procedure in radical cystectomy. Some investigators recommend extending the node dissection to the aortic bifurcation or the inferior mesenteric artery to include the common iliac and pre-sacral lymph nodes. Intraoperative FS diagnosis of lymph node may be used to determine extent of nodal dissection, but presence of metastatic disease in lymph node is not an absolute indication to terminate the radical procedure. FS is highly accurate in detecting nodal metastasis. Diagnostic pitfalls include: micrometastasis, unusual tumor variants such as micropapillary, plamacytoid or lymphoma-like carcinoma, and post-neoadjuvant therapy.

**Intraoperative FS in testicular surgery**

Intraoperative FS of testicular germ cell tumor is rarely needed since the use of imaging techniques and serum tumor markers permit the detection of most neoplasms prior to orchiectomy. Large testicular germ cell tumors are treated by radical orchiectomy through the inguinal approach. FS diagnosis of the tumor and margin evaluation is almost never required since the diagnosis would not alter the surgery. However, asymptomatic testicular or paratesticular lesions without imaging or serologic evidence of malignant germ cell tumor may be candidates for partial orchiectomy, particularly in young patients. FS consultation may be requested in this context for a definitive diagnosis. These lesions may include: a) tumors in prepubertal patients; b) nonpalpable testicular tumors detected by ultrasonography performed because of infertility, pain, or other symptoms; and c) non-neoplastic tumoral lesions such as inflammatory/infectious process. Distinguishing benign from malignant testicular lesions by FS is highly accurate if one is aware of the common pitfalls in testicular pathology.
Factors such as age of the patient, clinical presentation, imaging and serologic information are very helpful for a presumptive diagnosis. Non-neoplastic or benign processes include infectious/inflammatory lesions, sperm granuloma, Leydig cell tumor, sex cord stromal tumors, adenomatoid tumor and paratesticular lipomatous tumor. Malignant non-germ cell tumors include paratesticular mesenchymal neoplasms, mesothelial tumors, lymphoma and metastatic tumors.

FS diagnosis may rarely be requested during retroperitoneal lymph node dissection for metastatic germ cell tumor. If possible, the type (seminoma vs. non-seminomatous tumor) and relative percentage of germ cell tumor should be reported. In patients who have had chemotherapy or radiation, the FS may exhibit only benign tissues such as fibrosis or necrosis or differentiated elements such a mature teratoma. In these cases the key is to find viable germ cell tumor. Fortunately, FS are infrequently required in retroperitoneal lymph node dissection.

Table. Common Indications of Frozen Section Diagnosis in GU Surgery

PROSTATE
- Margin evaluation during radical prostatectomy
- Tissue histologic identification
- Diagnosis of pelvic lymph node metastasis during radical prostatectomy

KIDNEY
- Margin evaluation during partial nephrectomy
- Definitive histologic diagnosis of a renal mass (e.g. RCC vs. TCC)
- Diagnosis of lymph node metastasis and adrenalectomy

URINARY BLADDER, URETER, AND URETHRA
- Margin evaluation during radical or partial cystectomy
- Diagnosis of bladder peritoneal nodules or masses
- Diagnosis of pelvic lymph node metastasis during cystectomy

TESTIS
- Diagnosis of testicular/paratesticular lesions for possible testis-sparing operation
- Diagnosis of lymph node metastasis during retroperitoneal nodal dissection

References


