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BIOPSY INTERPRETATION: THE FROZEN SECTION

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CONTENTS

PREFACE

Surgical pathology including the practice of frozen section was conceived and developed by surgeons. However, the very first frozen section was accomplished by a pathologist. In 1891, at the newly established Johns Hopkins Hospital, William S. Halsted, the surgeon, requested a frozen section on a breast tumor. The procedure was carried out by the pathologist William H. Welch. The procedure went so well that Halsted did not request another frozen for 25 years. Nonetheless, over the last almost 120 years, frozen section has evolved from a novelty to an accepted, even mundane, part of the practice of what we now recognize as surgical pathology. While the advent of laparoscopic, robotic, and microsurgical techniques has changed the utilization of frozen section and the nature of the questions asked, the essentials are the same: a freezing apparatus to harden tissue, a microtome to shave off thin slices, a staining set-up, a microscope, and a pathologist.

While the general public may be unaware of the active role of the pathologist in the conduct of surgery, intraoperative consultations including frozen section are a mainstay of 21st century patient care and an inseparable aspect of any pathology training program. These consultations take several forms, including the triage of fresh tissue for special studies, gross specimen examination, imprints, or the actual appearance in the operating room by the pathologist to view the operative field and speak directly to the surgeon. Frozen section, despite its associated artifacts and potential sampling error, is regarded as the most definitive form of consultation, since it involves the microscopic examination of tissue designated by the surgeon as important. The consequences of these consultations, and especially frozen section, are potentially dramatic. It is essential that the pathologist know the clinical setting and gross findings as well as the treatment algorithm for a given disease.

Currently, resident training in pathology is centered on organ system specialization. Despite acknowledged organ-specific expertise, faculty members in many university departments regularly participate in the frozen section rotation, which frequently involves organs outside their comfort zone. The downsides of this circumstance are that intradepartmental specialist-consultants need to be available and that the pathologist faces potential credibility issues with surgeons and clinicians outside his or her specialty area. The potential awkwardness for specialists and the mixed educational message notwithstanding, it is in this context that the practice of general surgical pathology persists. There is thus an implied value for pathologists with broadly based clinical medical knowledge, a capacity for practical decision making, an ease in rapid communication, and the possession of excellent morphologic skills. The pathologist's

confidence level is dependent on training and tempered by experience so that good medical judgment dictates what and how much to report, aspects of diagnostic pathology that are sometimes more important than specific lesion identification.

Pathologists regard a frozen section as an emergency requiring cessation of whatever the activity of the moment may be. This is true not only for the pathologist on call but also for any colleague from whom an intradepartmental consultation is sought. While most surgeons and pathologists do recognize that this is a cooperative effort of some gravity, friction is created when it is perceived by the pathologist that a frozen section is frivolously requested. Reporting a frozen section only to discover that the diagnosis had no potential to change what was done, that the surgeon is no longer in the room, or that the patient is already in recovery implies that the information was inherently irrelevant and the pathologist's effort inconsequential.

This book regards frozen section as a selective, clinically relevant interdisciplinary effort. The application of frozen section to all specimens is not mainstream practice and will not be addressed. Readers may wonder why certain topics are or are not included. The specifics of each pathologist's practice related to intraoperative consultations, the rationales for those consultations and specifically frozen sections do differ, possibly are institutionally driven. We acknowledge that the selection of topics is reflective of our respective experiences; however, we hope that at least some information will be applicable to the circumstances of individual readers.

This book is an outgrowth of a recently completed USCAP short course. It is not designed to be a comprehensive traditional listing of entities as would be encountered in a textbook of surgical pathology, nor the promotion of frozen section heroics in the diagnosis of rare conditions. Frozen section is the focus but the central idea is intraoperative consultation. Although unusual entities may be illustrated, the principal concern is the practical use of frozen section in the management of a clinical problem, mostly involving tumors. Emphasis is placed on the morphologic expertise of the surgical pathologist in standard hematoxylin and eosin evaluations. The histologic illustrations, insofar as possible, are actual, frozen sections, with artifacts. Immunostains are not routinely available in this setting and are not diagnostically relevant. It is hoped that this volume will contribute to an informed practice of frozen section and an appreciation of the physician role of the general surgical pathologist for the patients they serve.

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BIOPSY INTERPRETATION SERIES

BIOPSY INTERPRETATION: THE FROZEN SECTION

1

THE FROZEN SECTION: HISTORICAL BACKGROUND AND QUALITY ASSURANCE

ANTHONY G. MONTAG

HISTORY OF THE FROZEN SECTION

The history of the frozen section as intraoperative consultation is intertwined with the development of pathology as a clinical specialty. Prior to the late 19th century, pathology, or pathologic anatomy, was an exercise in the gross correlation of premortem symptoms and physical examination with postmortem findings. As pathology developed into a distinct specialty in the late 19th century, its focus was largely research oriented; the correlation of pathologic findings to clinical disease continued to be carried out by practicing clinicians, predominantly surgeons, well into the 20th century. The frozen section served a pivotal role in bringing microscopy into the clinical practice of medicine and the pathologist into the clinical management of patients.

Although autopsies were performed by ancient Greek and Egyptian physicians, the father of pathologic anatomy is regarded to be Giovanni Morgagni, who published his treatise, *The Seats and Causes of Disease*, in 1761, detailing clinical and gross pathological correlation of 700 autopsies (1). Morgagni correlated his autopsy findings with the clinical impressions of Antonio Valsalva, his physician collaborator, and recognized the association of clinical symptoms with a specific organ, such as jaundice with abnormalities of the liver. His treatise argued against the humoral theory of disease, which had been dominant since Galen.

The French morbid anatomist Marie Francois Xavier Bichat published *Treatise on Membranes in General and on Various Membranes in Particular* in 1800, followed in 1801 by *Physiological Researches on Life and Death* (2). Bichat realized that organs were themselves complex structures composed of tissues, or membranes, and described 21 separate types, including cartilage, fibrous tissue, serous membrane, glands, and hair. This reductionist approach to anatomy, breaking an organ into tissue components, led Bichat to be considered as the father of histology.

Ironically, his observations were made using only a hand lens; the microscopes available in the late 18th century had poor resolution and were regarded as unreliable novelties by most anatomists.

Pathology as an independent specialty of medicine has its origins in Vienna with Karl Rokitansky, who founded the first institute for pathology, and is said to have supervised 70,000 autopsies and performed 30,000 autopsies (3). Between 1842 and 1846, Rokitansky published his treatise *General Pathologic Anatomy*, putting forth a general classification of diseases, including blood dyscrasias, new growths, and congenital abnormalities. Rokitansky also made little use of the microscope, although he did publish one treatise with the help of microscopy: *On Connective Tissue Tumors of the Nervous System*.

Rudolf Virchow, Rokitansky's pupil working at the Charity Hospital in Berlin, popularized microscopy in the study of pathology and is regarded as the father of modern pathology (4). Virchow realized that at a more fundamental level cells, rather than Bichat's tissues, were the probable root of disease. In 1858, he published *Cellular Pathology as Based Upon Physiological and Pathological Histology*, which was widely accepted and established microscopic anatomy as integral to the understanding of pathology and medicine. His other major contribution was to refute the tenet of spontaneous generation of cells from inanimate material, which still lingered in the cell theory published in 1839 by Theodor Schwann and Matthias Schleiden. Virchow asserted "Omnis cellula e cellula," or that all cells come from cells. Ironically, in spite of the rise of cellular pathology as a concept, Virchow was primarily an experimental and autopsy pathologist, and the diagnosis of disease on living patients continued to be based on clinical impression and gross features as judged by the surgeon (5). Only rare attempts at diagnosis from a tumor fragment or biopsy had been attempted, and Virchow had his own reasons to be reluctant about the reliability of biopsy as a diagnostic technique. One of Virchow's first attempts at biopsy diagnosis occurred in 1887 on specimens from the German Emperor Frederick III, who had developed a laryngeal mass. Virchow rendered a benign diagnosis, however, Frederick died the following year from laryngeal carcinoma (6). Although the lesion was probably inoperable at the time of biopsy, Frederick's death led to the ascension of the more militaristic Wilhelm II, and may have contributed to the development of World War I. More directly, there was a lingering distrust of the technique of microscopic evaluation of biopsy specimens, which resulted in reluctance and disinterest in using microscopic pathology to direct the care of living patients.

Several technical developments in the field of microscopy in the latter half of the 19th century led to its adoption as a reliable technique (3). The microscope itself was improved with the introduction of achromatic and apochromatic lenses to correct distortion and by the invention of the substage condenser and oil immersion lens by Ernest Abbe. Consequently, German microscope manufacturers became the leaders in microscopy,

and high-quality instruments were readily available. Histochemical stains from natural dyes were introduced in the mid-1800s, but the development of the aniline dye industry in Germany led to the introduction of many new stains between 1870 and 1900, including methylene blue, Gram, Congo red, and Mallory trichrome stains (7). Microtomes, including freezing microtomes, were introduced by the 1870s, and the introduction of formalin fixation and wax embedding led to more uniform histology.

Surgical practice also underwent a revolution in the late 19th century. In 1846, the first public demonstration of anesthesia using ether was carried out at the Massachusetts General Hospital. Oliver Wendell Holmes published his treatise on puerperal fever in 1847, establishing that it was frequently carried by the obstetrician from patient to patient, and called for more sanitation in hospitals and in the operating room. In 1867, Joseph Lister published on antisepsis, and proposed hand washing, gloves, and the use of carbolic acid. The result was that surgery became less painful, and the patient was more likely to survive. It also gave the surgeon the luxury of time, to better define the disease, and to tailor an operation that would not have been possible with a writhing patient.

By the end of the 19th century, all the elements were in place for surgical pathology to emerge as a clinical specialty, yet the use of biopsy to make a definitive diagnosis before surgery was seldom done. Pathology emerged as an academic pursuit, using microscopy to correlate gross and microscopic findings with clinical history and to classify disease, however in most cases only on autopsy or material from definitive surgeries. For most surgical cases, clinicopathologic evaluation was performed by the surgeon, often by gross examination only. This practice was reinforced by the tradition of academic surgeons spending a year or two in pathology departments in Europe, virtually none of which were handling biopsy material and most of which were grounded in autopsy pathology and experimental pathology. This dichotomy continued in academic centers past the middle of the 20th century with the tradition of having a separate group of research faculty involved in autopsy pathology. As a consequence, many of the advances in the application of pathology to living patients took place in departments of surgery or gynecology, or in clinically oriented private hospitals and clinics.

William Halsted, Chief of Surgery of the new Johns Hopkins hospital, requested the first intraoperative frozen section be done by the pathologist William Welch in 1891 (8). Welch had studied pathology extensively in Europe and had established the first hospital pathology laboratory in Bellevue Hospital Center, New York, prior to being recruited to Johns Hopkins. Halsted scheduled the frozen section on a suspected breast cancer case, and Welch prepared a slide using a carbon dioxide freezing microtome, but not before Halsted had concluded the case. Subsequently, Thomas Cullen, who had studied in Germany and learned a technique for freezing formalin fixed tissue, published a frozen section method in the Johns Hopkins' bulletin in 1895. The fixation step prior to freezing the tissue block meant the procedure still took nearly an hour to complete.

Although several other rapid frozen section methods were subsequently published in Europe, it is generally accepted that the standard cryostat method used today was first published in *JAMA* in 1905 by Louis Wilson of the Mayo Clinic (9). Wilson used a dextrin solution to embed the tissue and a carbon dioxide freezing microtome. By using methylene blue and reading the slides without permanent mounting the technique could be performed in a few minutes as opposed to an hour for Cullen's method. This method rapidly became a routine at the Mayo Clinic, and was adopted by other clinical centers. Most centers today include a brief fixation prior to staining in hematoxylin and eosin, followed by permanent mounting, but the essential technique is largely unchanged (10).

Unfortunately, standard textbooks of pathology in the early 20th century continued to feel that the rapid frozen section technique was unreliable, and the technique was not widely adopted until after the late 1920s. In many academic centers, pathologists continued to regard diagnostic pathology as outside the interest of the pathology department. The American Society of Clinical Pathology was formed in 1922 to elevate the status of the pathologist as a physician who provided clinical services for live patients, and the frozen section consultation was one of the first services promoted by the organization (11,12).

A strong proponent of the frozen section was Dr Joseph Bloodgood, a surgeon at Johns Hopkins. Prior to the 1920s, he had been skeptical of the frozen section technique, believing that an experienced surgeon could recognize the nature of a tumor with the naked eye (13). Beginning in 1927, Bloodgood began a campaign to promote the frozen section as a medical standard (14). He submitted editorials to major regional medical journals and, in an editorial in *JAMA* in 1927, extended the invitation to surgeons and pathologists to visit the laboratory at Johns Hopkins. Several times a year, approximately 40 people a day attended seminars on the technique. In a 1929 editorial, Bloodgood hinted that a growing public enlightenment required that the diagnosis of cancer be made on a frozen section. He also recognized the need to specifically train pathologists for diagnostic microscopy, stating "There is a greater demand today for pathologists . . . than for operators."

The acceptance of the frozen section as a diagnostic tool in the setting of a one-step surgical procedure eventually led to the acceptance of biopsy techniques to allow a presurgical diagnosis. Although today performed only on a small percentage of all surgical cases and representing a small fraction of the typical pathology laboratory's activity, the frozen section played a pivotal role in the acceptance of microscopy in the clinical management of patients and the development of modern surgical pathology.

INDICATIONS FOR FROZEN SECTION

Intraoperative consults, with or without frozen section, should be limited to the following indications (15,16):

1. Provide a diagnosis that will allow the surgeon to make an intraoperative decision regarding further surgery during that operative event. For example, a benign ovarian tumor requires no additional staging as opposed to a malignant ovarian tumor.
2. Assess margins when additional excision to attain a negative margin is an option.
3. Assess adequacy of diagnostic tissue in a biopsy specimen from an open or complicated procedure. For example, a bone biopsy in the operating room may yield only reactive bone, and a second biopsy procedure may be avoided with the frozen section.
4. Plan the workup of the specimen. The need for cytogenetics, flow cytometry, and other special studies should reasonably be evaluated prior to fixation. Tissue for protocols or banking may need to be sampled.
5. Plan for resources. Scheduling of operating room time for definitive procedure pending permanents may require faster diagnosis. For example, placement of chemotherapy catheters during initial biopsy if the diagnosis is malignant, instead of a second anesthesia.

A CAP Q-probe study evaluated 9,164 cases with intraoperative frozen section from 472 institutions for indications (17). Surgeons at the participating institution cooperated in completing questionnaires as to the rationale behind their request for a frozen section consultation. The study found the most common indications were to establish diagnosis to determine type of surgery (51%), confirm adequacy of margins (16%), plan further studies or workup (10%), allow the surgeon to inform the patient of the diagnosis (8%), confirm adequacy of tissue (8%), abate surgeon's curiosity (3%), plan resources (3%), and establish academic protocol (1%). The findings suggest that approximately 10% of frozen sections are done for illegitimate reasons. Another Q probe found that frozen sections were requested in 5.7% of all surgical procedures (18). The frozen section rate was proportional to institutional size, with a 15% rate in hospitals with more than 600 beds. This probably reflects increased complexity of cases at large tertiary centers.

Illegitimate reasons for requesting a frozen section include the following:

1. *Curiosity.* Some frozen sections are requested entirely out of curiosity. The author has personally been requested to perform a frozen section on a "pelvic lesion" specimen, which proved to be seminal vesicle. The surgeon indicated that there was a wager as to whether the pathologist would recognize the normal organ.
2. *Preliminary report to family in the recovery room.* It should be emphasized that because of sampling and technical issues, the diagnosis can only be preliminary, and that any change in diagnosis will be the responsibility of the surgeon to explain.
3. *Surgeon's habit.* Some surgeons perform exactly the same surgery regardless of the outcome of the frozen section.

Obviously there are times when, based on these considerations, a frozen section should be refused, albeit after a conversation with the clinician. Other important considerations that might lead to refusal of a request for frozen section include the following:

1. When the specimen is for primary diagnosis, represents the entire available sample of the lesion, and it is not possible to leave anything nonfrozen for permanent sections. This especially applies to pigmented skin lesions.
2. When the entire specimen appears uniform and grossly benign, for example, a serous cyst, and a frozen section to inspect for subtle microscopic disease would be taken entirely at random.
3. The specimen has a high likelihood of having an infectious agent such as tuberculosis and there are insufficient back-up cryostats to allow one to be decontaminated during the workday.

The Mayo Clinic is perhaps unique in that nearly all operative cases receive a diagnosis rendered entirely by frozen section. In a review of 1 year's experience, Ferreiro et al. reported 24,880 cases with frozen section analysis at the Mayo Clinic (19). By contrast, the percentage of cases undergoing frozen section at most laboratories is nearer to the 5.6% rate reported in a Cap Q-probe study (20). The Mayo Clinic experience includes many intraoperative consultations on cases that would not be considered eligible for frozen section at nearly any other pathology laboratory. For this reason, data regarding frozen section performance and quality assurance from the Mayo clinic cannot be compared to data from other institutions or CAP Q probes (21).

QUALITY ASSURANCE INDICATORS IN FROZEN SECTION

The College of American Pathologists includes standards for the performance of intraoperative frozen sections. The CAP standards are frequently updated. The following discussion is based on the most recent standards (22,23).

General Considerations

Specimens for frozen section are subject to all the CAP standards for specimen identification in the surgical pathology gross room. Particularly when multiple cases for frozen section are handled simultaneously, the risk of switching specimens or introducing cross-contamination is increased. In general, only one frozen section case should occupy each grossing area. Frozen section blocks typically bear no attached accession information while being cut, and a system for identifying the block and slides should be established. One practice is to have a labeled cassette in the cryostat to act as a cradle for the frozen chuck when it is removed from the microtome. Slides should be labeled prior to cutting the sections and if not used, discarded. Unlabeled slides should never be used. In our own

laboratory, each frozen section specimen is assigned a unique color for the slide label, cassette, and mounting media during accessioning to reduce the chance of identification errors.

The frozen section slides must be permanently mounted and retained in the archive with the permanent sections from the case. The frozen section block must be processed to a paraffin block and permanent sections produced for correlation with the actual cryostat sections. This is an essential quality assurance tool for the evaluation of discrepancies between frozen and permanent sections. It is also a useful teaching tool for recognizing artifacts and sampling issues in frozen section. Occasionally, the actual frozen section block may be saved frozen for molecular or other studies. This is allowable if there is a policy specifying the types of specimens or situations for which permanent section follow-up may be omitted.

The cryostat must be periodically cleaned and the interior wiped down with 70% alcohol. In most cases this is done once a day, but if the cryostat is used frequently, it is advisable to clean out shavings more frequently to avoid cross-contamination between specimens. Cryostats in daily use should be thawed weekly and decontaminated with a tuberculocidal disinfectant. Less frequently used machines can be decontaminated on a longer cycle. A written procedure and schedule should be followed and documentation of maintenance kept for each cryostat. If a frozen section is performed on tissue from a patient known or suspected to be positive for tuberculosis, hepatitis B or C, human immunodeficiency virus—related disease, or prion disease such as Creutzfeldt-Jakob, the cryostat must be decontaminated before further use.

Several CAP requirements deal with the documentation and transmission of the intraoperative report. Intraoperative consultations must be documented in writing and signed by the pathologist who made the diagnosis. If a verbal report is given, it should correspond to the written documentation and should be given directly to the surgeon, not through an intermediary. Any additional clinical information acquired during the verbal report should be documented on the written report if it influenced the final diagnosis. When a verbal report is given, a routine identification check should be made to confirm that the information is being relayed to the correct surgeon on the correct patient. The intraoperative consultation must be made part of the final surgical pathology report, including the name of the pathologist who rendered the intraoperative diagnosis.

Frozen Section Turnaround Time

The CAP standard for frozen section turnaround time states that 90% of cases should have slides prepared within 15 minutes of receipt of the specimen and the interpretation communicated within 20 minutes of receipt of the specimen. Although CAP requires frozen section turnaround monitoring, it does not specify what percentage of frozen sections must be sampled, or how frequently the sampling should be done. Some pathology computer systems now include a time stamp for receipt and completion of

frozen section consultation, which would allow for capture of nearly all cases. However a smaller and less frequent sampling is acceptable if the monitoring procedure is defined, followed, and the results documented, evaluated, and tracked for changes and opportunities for improvement.

The CAP turnaround time standard specifically does not include the transport time prior to receipt of the specimen by the laboratory. Obviously the clinician's impression of the actual timeliness of service may be dependent on transportation factors rather than laboratory performance. The standard also allows exclusion of cases where multiple sequential studies are performed on a single specimen, such as margins. Complex cases requiring additional studies or correlation, for example, examination of radiographs or extensive intradepartmental consultation, can also be excluded from the analysis (24). CAP specifies that if the 90% standard for completion of frozen sections is not met, an analysis of the outliers should be made to ascertain the reason for noncompliance. In practice, our laboratory tracks all frozen sections with a time stamp, and the pathologist of record may indicate if there is a reason for an exclusion from the turnaround time standard. Monthly performance is tracked including percentage of cases with exclusions, number of cases eligible for analysis, and, of those, the percentage, which have met the standard.

Frozen Section Error Rate

CAP requires that frozen sections be compared to the permanent diagnosis and discordance noted and reconciled. This exercise provides the opportunity to track performance over time and identify problem areas and opportunities for improvement (25). The possible sources of discrepancy are as follows:

1. Technical issues
   - **a.** The tissue was difficult to cut; technical problems with mounting or staining, mechanical issues with the cryostat.
2. Sampling error
   - **a.** The lesion is present on permanents of the frozen block, but was not present in the actual cryostat section.
     - **i.** Was the block adequately faced and leveled?
   - **b.** The lesion was not present in the block frozen, but is present in other samples from the submitted specimen.
     - **i.** Was the lesion appropriately sampled?
3. Diagnostic error
   - **a.** Disease process missed, for example, metastasis to a lymph node.
   - **b.** Disease process recognized, but misclassified.
     - **i.** No effect on management.
     - **ii.** Effect on management.
4. Errors in communication of diagnosis

The most recent CAP frozen-section Q probe excluded certain types of discordant cases from analysis (26). These included the following:

1. Discordance in type of carcinoma when it has no effect on management, for example, small cell carcinoma versus non–small cell carcinoma affects operative management, while the diagnosis of squamous cell carcinoma versus adenocarcinoma does not.
2. Discordance in degree of differentiation when it has no effect on management.
3. Discordance in the grade of dysplasia or carcinoma in situ.
4. Discordance in breast biopsy or excision where an area is frozen for calcifications, with no gross lesion.
5. Discordance in well-circumscribed follicular lesions of the thyroid.
6. Frozen sections of breast or other organs undertaken to assess the adequacy of tissue for estrogen and progesterone binding proteins.
7. Discordance in the evaluation of tumor margins when the block is cut en face.

These categories recognize the limitations of frozen section in analyzing certain specimens with a limited sampling and with the artifact inherent in frozen sections. The grading of dysplasia in skin or mucosa section is particularly difficult. The practice of freezing small or mammographically detected breast lesions to confirm diagnostic material for radioimmunoassay of estrogen and progesterone receptors has been supplanted by immunohistochemistry and should be discouraged.

Given limited sampling, frequent paucity of clinical information, and the various artifacts introduced by the freezing process, the frozen section technique is remarkably accurate. A 1991 College of American Pathologist Q-probe study found 4.2% deferral of diagnosis rate and discordance with permanent diagnosis of 1.7%. Major sources of discordance were gross tissue sampling (44.8%), misinterpretation (40%), and sectioning (12.7%). Only 2.5% of discrepancies were felt to have a major impact on patient management. A subsequent Q probe found 1.42% discordance rate, with gross tissue sampling (31.4%), misinterpretation (31.8%), and the presence of diagnostic tissue in the permanents of the frozen block which was not present in the original frozen sections (30%) as major contributors to error (17). Sampling, either of the gross specimen or microscopically by insufficient leveling of the block, accounts for approximately two-thirds of frozen section discrepancy. Diagnostic error at frozen section accounts for less than a third of cases, amounting to a rate of less than 0.5%.

Sources of Discordance in Frozen Sections

The most frequent anatomic sites with discordant frozen section diagnoses in the CAP Q-probe series are skin (17.1%), breast (16%), gynecologic sites (10.2%), lymph nodes for metastases (10%), thyroid (6.1%), lung/mediastinum (5.3%), and gastrointestinal tract (5.2%). The most common source of discordant diagnosis was the false-negative diagnosis of tumor (67.8%) as compared to the 11% false-positive diagnosis rate. Obviously,

the actual risk of a discordant diagnosis by anatomic site depends on the volume of cases from that site, and this denominator is not provided in the CAP Q-probe data. The limited sampling done during the frozen section procedure is particularly problematic for large heterogenous tumors such as soft tissue and ovarian tumors. For ovarian mucinous tumors, the predictive value of the frozen section diagnosis is 99% for malignant, 95% for benign, and 65% for borderline lesions (27). Poor technical quality of the prepared slides was cited as a factor in 3% to 5% of cases in Cap Q-probe data. Interestingly, lack of adequate clinical history was cited as a contributing factor in nearly 15% of discrepancies from hospitals with less than 150 beds as opposed to less than 5% of hospitals with more than 450 beds (18).

The frozen section technique played a critical role in the development of diagnostic histopathology in the 19th century and the acceptance of surgical pathology as a specialty in the 20th century. The technique is remarkably accurate when technical and sampling limitations are considered. Frozen section and permanent material should be compared and sources of discordance tracked. The average rate of diagnostic error in published series is less than 0.5%.

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BONE AND SOFT TISSUE

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INTRODUCTION

The relative rarity of bone lesions, especially tumors, makes requests for frozen section uncommon. Surgical pathologists may feel uncomfortable in assessing these lesions intraoperatively if major treatment decisions are to be made. It may even occur to pathologists that such requests are unreasonable. However, the recent clinical advances in limb-sparing sarcoma management have created a rationale for intraoperative assessment. The differential diagnosis of bone lesions is considered from clinical, radiological, and pathological perspectives, and a number of cases are provided to illustrate common diagnostic problems and pitfalls.

Most bone lesions have typical clinical presentations and classical radiological features. The pathologist who is able to correlate this information with the morphologic features will avoid making errors in pathological diagnosis by frozen section. If the clinical, radiological, and pathological impressions are concordant, then the pathologist can be reasonably reassured that the diagnosis is correct. However, if any of the three factors is discordant, the diagnosis should be deferred until a permanent section is obtained. It is important to emphasize that the treatment algorithm in the limb salvage era is somewhat backward to what would be ordinarily anticipated:

1. A diagnosis of malignancy made from a frozen section will result in closing of the wound to await permanent sections and confirmation of the diagnosis. After appropriate staging, the definitive limb salvage resection will be preceded by neoadjuvant therapy. If the permanent section and evaluation of nonfrozen tissue reveals a benign diagnosis, the lesion will be reexplored, curetted, and packed with cement or bone chips. The error and possible embarrassment to the pathologist aside, the patient will require a second procedure and the final clinical outcome will be a good one for the patient (1).
2. A benign diagnosis allows the surgeon to curette and pack the lesion directly. If the lesion is in fact benign, then the therapy is complete. If, however, the final interpretation of the frozen and nonfrozen tissue is that the lesion is malignant, then the surgical site has been contaminated and is unsuitable for limb salvage operation. A local recurrence rate of

83% in erroneously diagnosed osteosarcoma treated by limb salvage operation suggests that the patient will require an amputation (2).

Therefore, in conducting intraoperative consultations and analyzing frozen sections for bone lesions, especially tumors, the message for the pathologist is a conservative one. With experience, definitive diagnoses and appropriate treatment can be instituted. However, under any circumstances, if there is a diagnostic question, the interpretation should be deferred for definitive evaluation.

CLINICAL INFORMATION

Most patients with bone lesions present in a characteristic age range of 2 to 3 decades, which can quickly narrow down the clinical differential diagnosis (3) (e-Fig. 2.1). Both chondroblastoma and giant cell tumor occur in younger individuals; but chondroblastoma typically occurs prior to or near the time of epiphyseal closure in the teenage years, while giant cell tumor tends to occur later. Osteosarcoma is the most common malignant bone tumor that occurs in childhood, but it also occurs in older patients.

A history of sickle cell anemia or other potential cause of bone infarct raises the possibility of malignant fibrous histiocytoma of bone. A history of Paget's disease of bone or prior radiation therapy to the region raises the possibility of secondary sarcoma.

A previous history of non-osseous malignancy is particularly helpful. Metastatic lesions to bone are far more common than primary bone lesions: 10% to 15% of patients with metastases of unknown primary tumors present with bone lesions (4) and up to 30% of skeletal metastases constitute the first clinical evidence of a malignancy. As a general rule, any poorly marginated lytic bone lesion in a patient older than 40 years should be suspected to be a metastasis until proven otherwise.

Bone ranks number three (behind lung and liver) as one of the most common sites of clinical metastasis. In autopsy studies, it is the most frequent site of metastasis; up to 60% of patients who die of carcinoma are found to have bone metastases (5). The most common malignancies that metastasize to bone are lung, breast, prostate, kidney, and thyroid malignancies. Although metastases are very uncommon in children, lesions that do metastasize to bone in this population include neuroblastoma, rhabdomyosarcoma, and clear cell sarcoma of the kidney. Metastatic lesions frequently undergo internal fixation, and frozen section confirmation is recommended to avoid the placement of hardware in a primary bone tumor, which results in the loss of the limb in the limb salvage management option.

Fractures may complicate benign or malignant bone tumors, metastases, or may be entirely traumatic in origin but mimic a tumor radiographically. Benign tumors in the small bones of the hand are particularly prone to pathologic fractures (6). Pathologic fractures are uncommon in children, but most frequently occur in association with unicameral bone