DIAGNOSTIC PATHOLOGY

Intraoperative Consultation

SECOND EDITION

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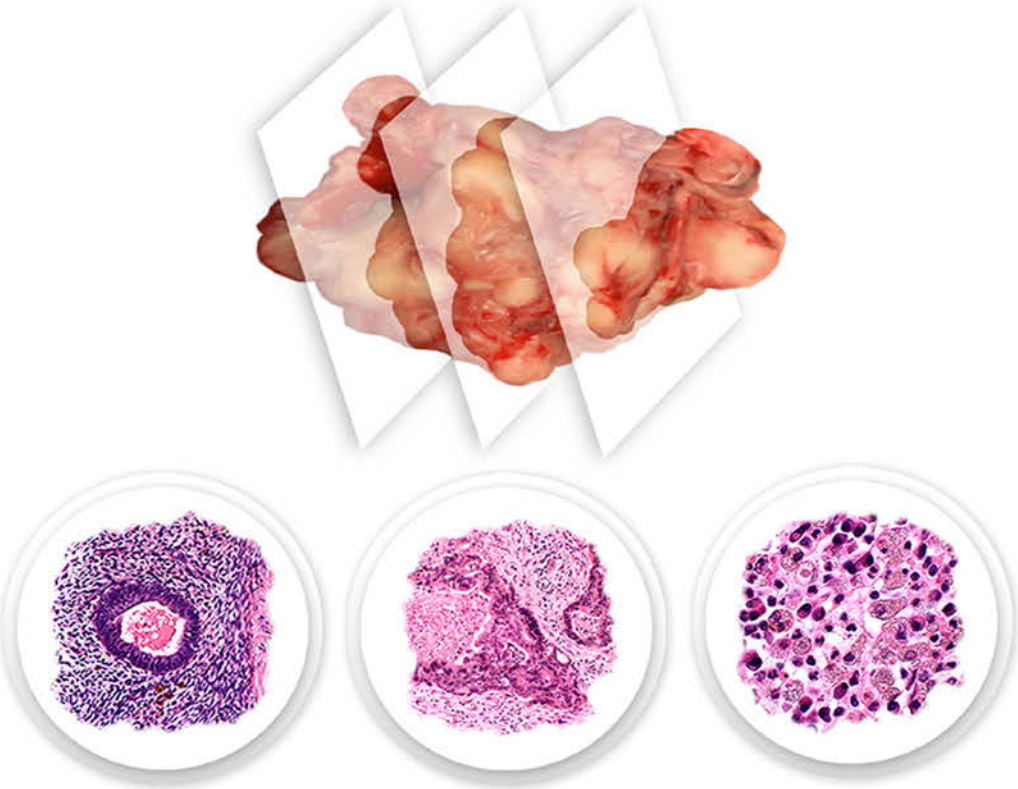

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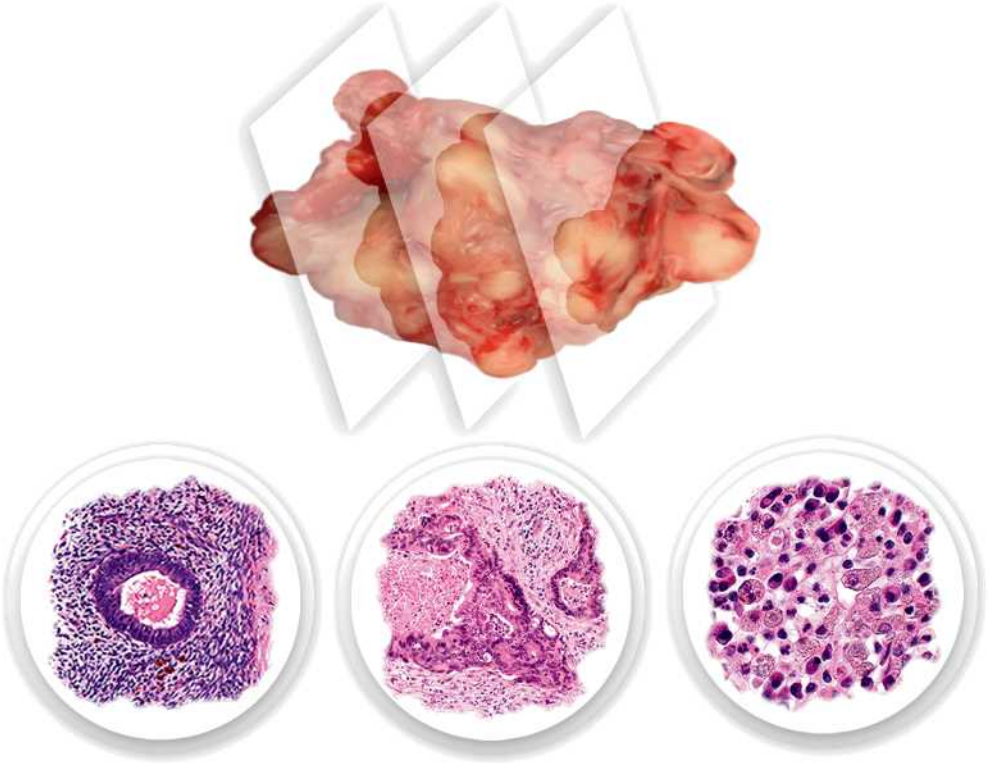

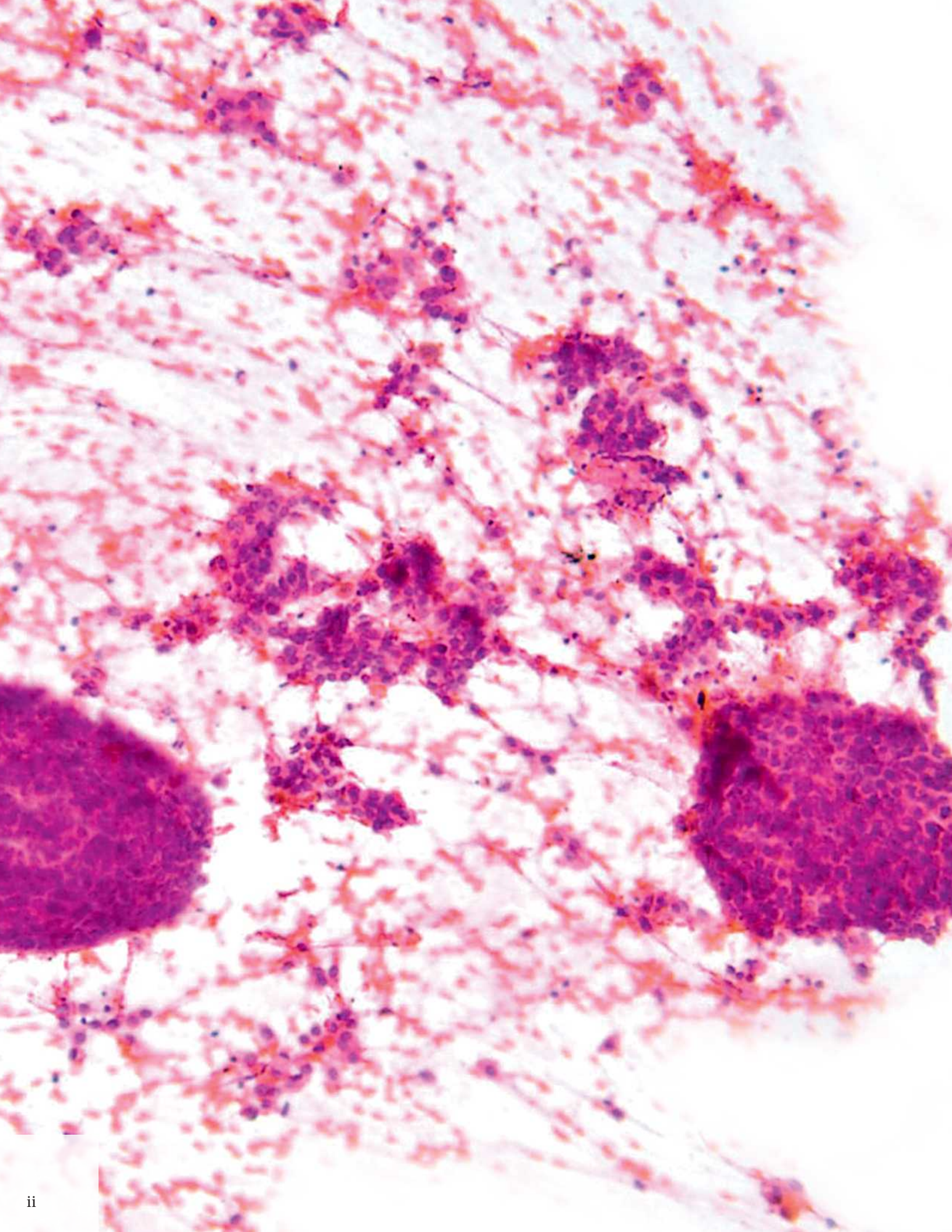

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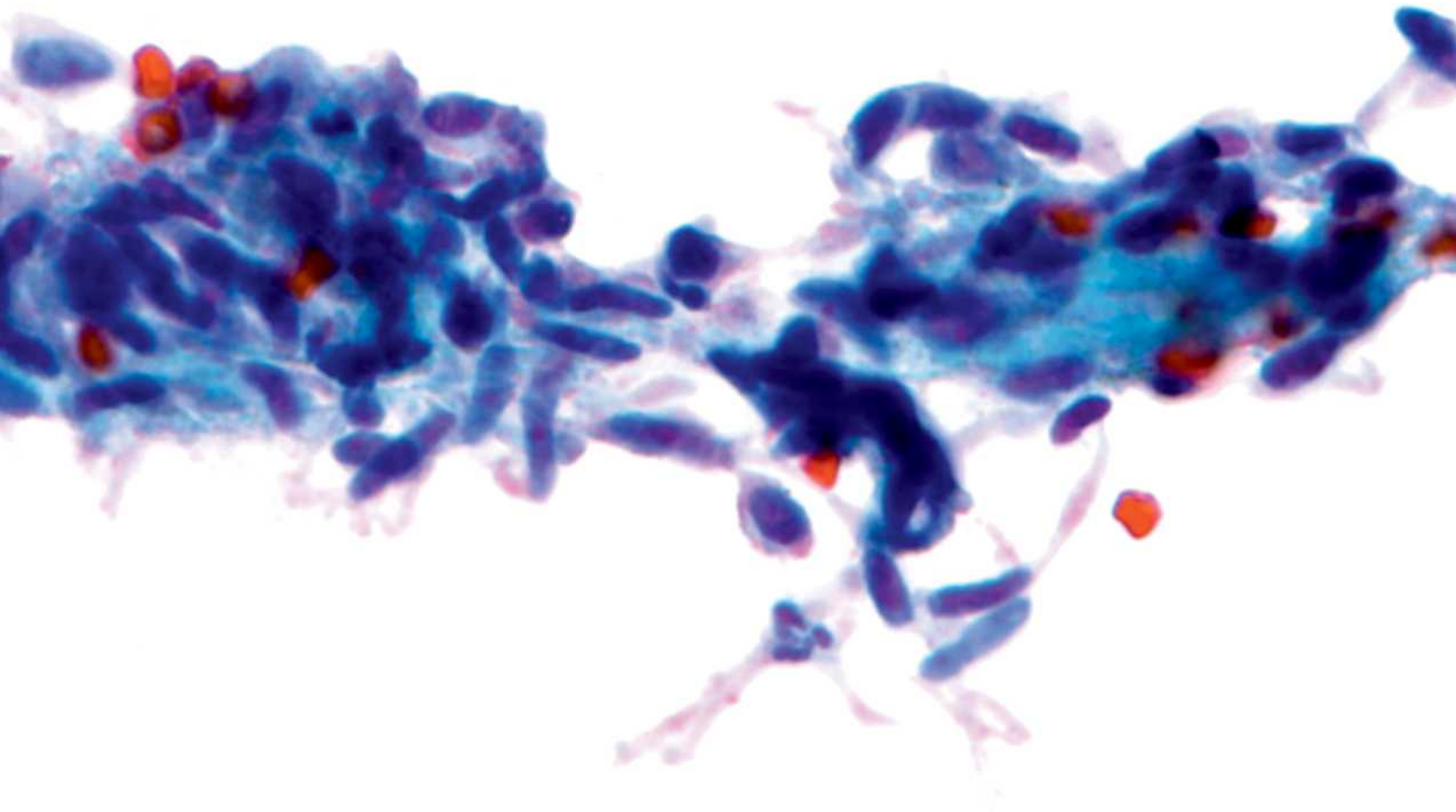
Dedication

This book is dedicated to all the pathologists whose hearts race when alerted by the frozen section pager, to the support staff in the intraoperative consultation room who are always there to assist them, to the surgeons who request essential information to help guide their operations, and most of all, to the patients who have entrusted their care into our hands.

SCL



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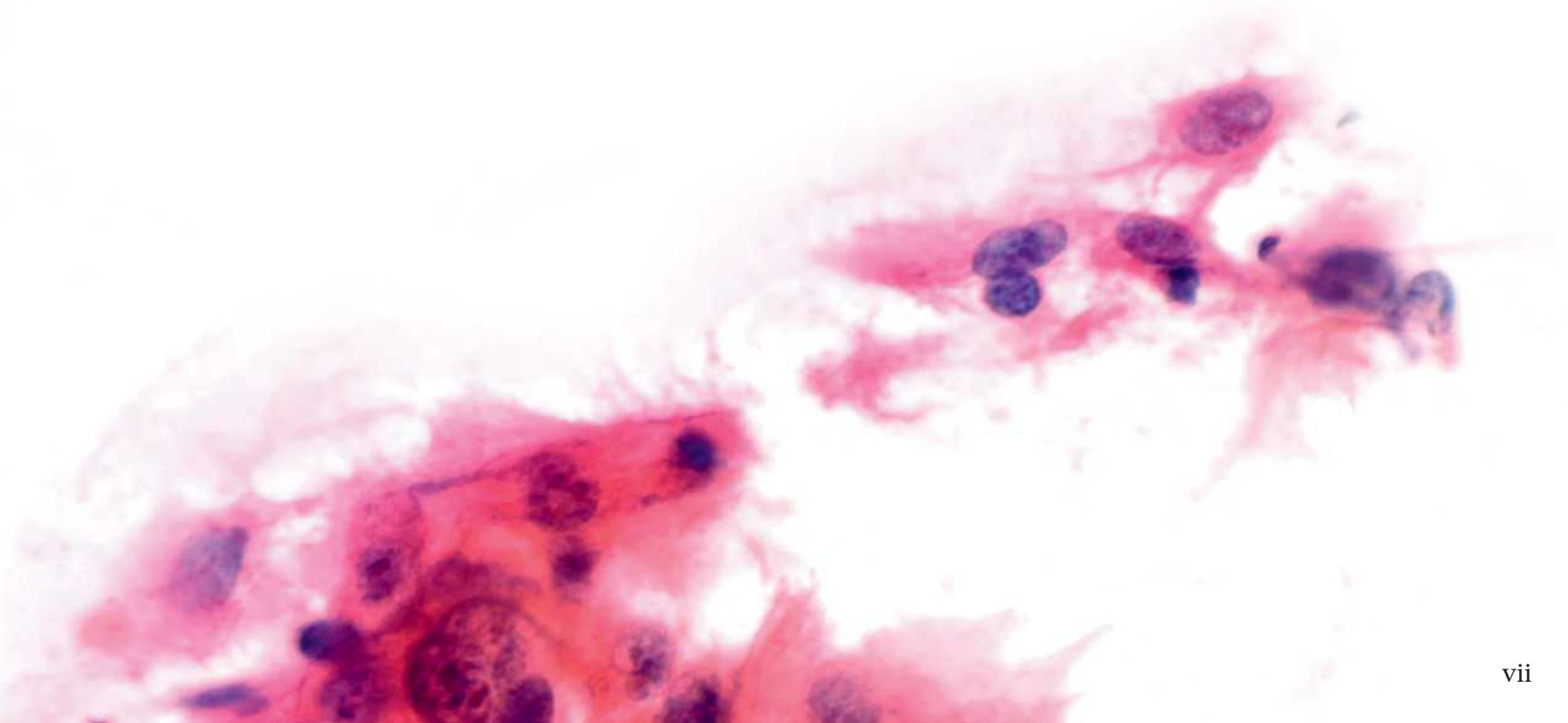

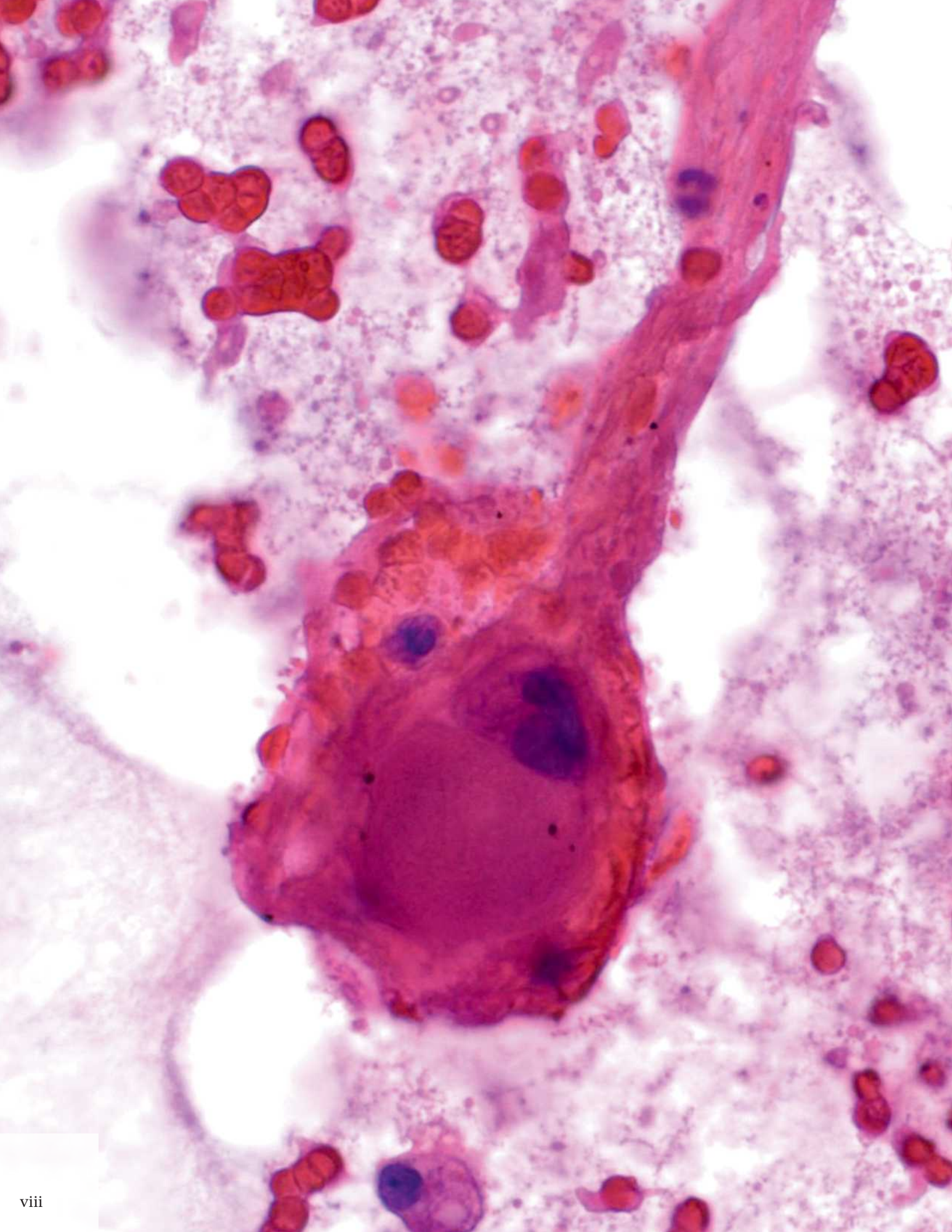

Preface

A very memorable event from my first year in residency was a frozen section. A young woman was under anesthesia being prepared to receive a kidney transplant. The surgeon unexpectedly discovered a firm nodule in the peritoneal cavity. If the diagnosis was cancer, the transplant would not be performed. If benign, she would receive the kidney. I was so impressed by the senior pathologist being able to quickly look at the frozen section and call back the surgeon to tell her the diagnosis was endometriosis and, therefore, the operation that would profoundly change this patient's life could proceed.

Pathology practice has changed in the ensuing years, but the critical importance of intraoperative consultation for patient care has not. In this second edition of *Diagnostic Pathology: Intraoperative Consultation*, the dedicated team of authors has taken the opportunity to extensively update and expand the information essential for pathologists to have available immediately when faced with a question from a surgeon during an operation. The easily accessible format of the first edition has been maintained. There are new chapters on lung wire localization biopsy, nipple margin evaluation, radioactive seed identification, and evaluation of specimens from patients with epilepsy. Essential techniques to rapidly preserve biomolecules for molecular assays are addressed. I am grateful to Dr. Lynette Sholl and Ms. Vivian M. Chan for allowing us to include a new technique recently developed by them to evaluate the staple margins of lung wedge resections. I am also grateful to Dr. Raphael Bueno and Dr. Ritu R. Gill for including the new technique of T-bar localization for lung biopsies.

Preparing a book spanning so many topics requires the assistance of many people. Ms. Kristen K. Gill, Ms. Vivian M. Chan, and the other members of Brigham and Women's Hospital "Team Frozen" are treasured colleagues and collaborators. We also must thank and acknowledge our clinical colleagues, including Dr. Esther Rhei, Dr. Catherine S. Giess, Dr. Rajan Jain, Judyth O'Hara, RN and numerous others. We also thank Dr. Danielle Costigan, Dr. Alexander Christakis, Dr. Inga-Marie Schaefer, Dr. Christine E. Gruessner, Dr. David Hicks, Dr. Richard Owings, Dr. Richard H. Hewlett, Dr. William Welch, Dr. Joseph Corson, Dr. Martina Zink, Dr. Rolf Pfannl, Dr. Stefan Kraft, Ms. Alice Sedlak, Mr. Dennis Poliferno, Ms. Lucy Ross, Ms. Lindsey Cheney, and Ms. Deborah O'Leary.

This book would not have been completed without the outstanding assistance of the Elsevier staff. Our lead editor, Megg Morin, headed the project, kept us all on track, and provided invaluable help and enthusiasm all along the way. Lane Bennion, Rich Coombs, and Laura Wissler created excellent new graphic illustrations. Tom Olson designed a beautiful cover for the book. Lisa Steadman and Jeffrey Marmorstone thoroughly edited each image of every chapter. Rebecca Bluth, Angela Terry, and Emily Fassett saw the book to production. And Arthur Gelsinger, Nina Bennett, Terry Ferrell, Lisa Gervais, and Matt Hoecherl edited the book for months before it came to production.

We hope that, like the first edition, this is the book that every pathologist will want at his or her side the next time a page calls them to an intraoperative consultation.

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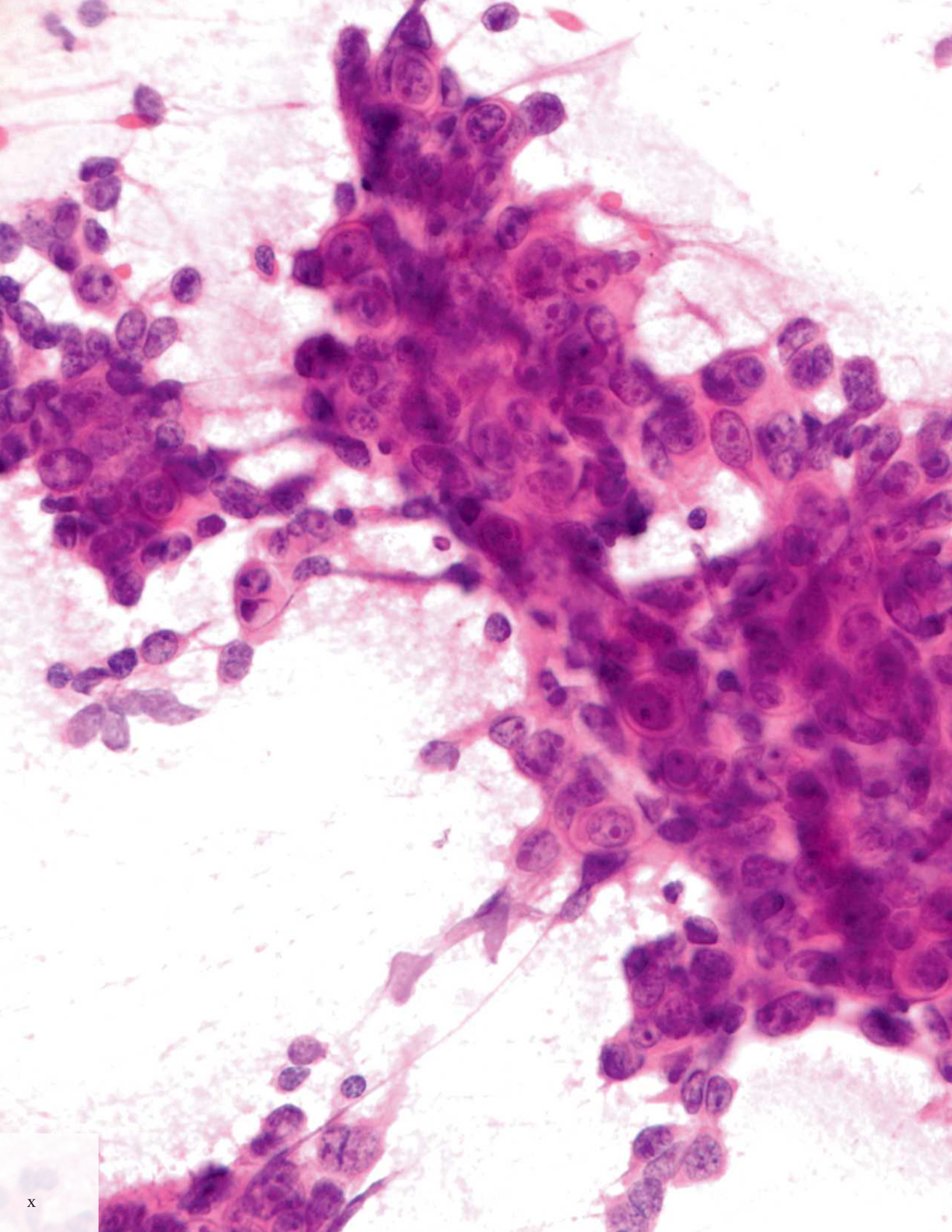

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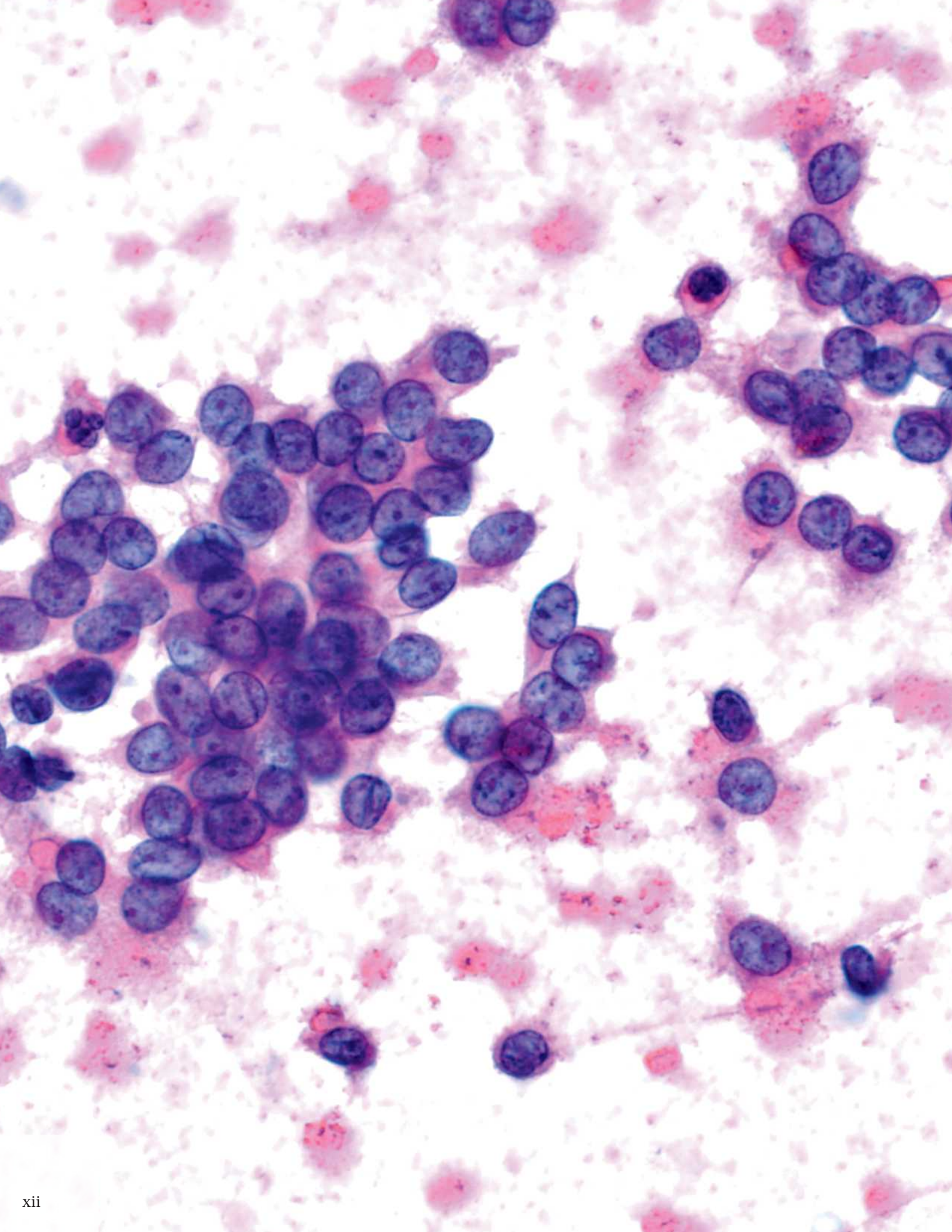

Sections

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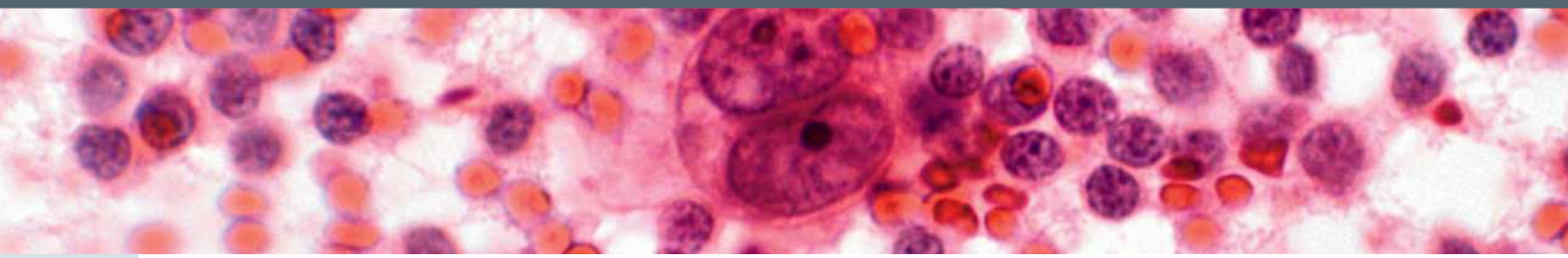

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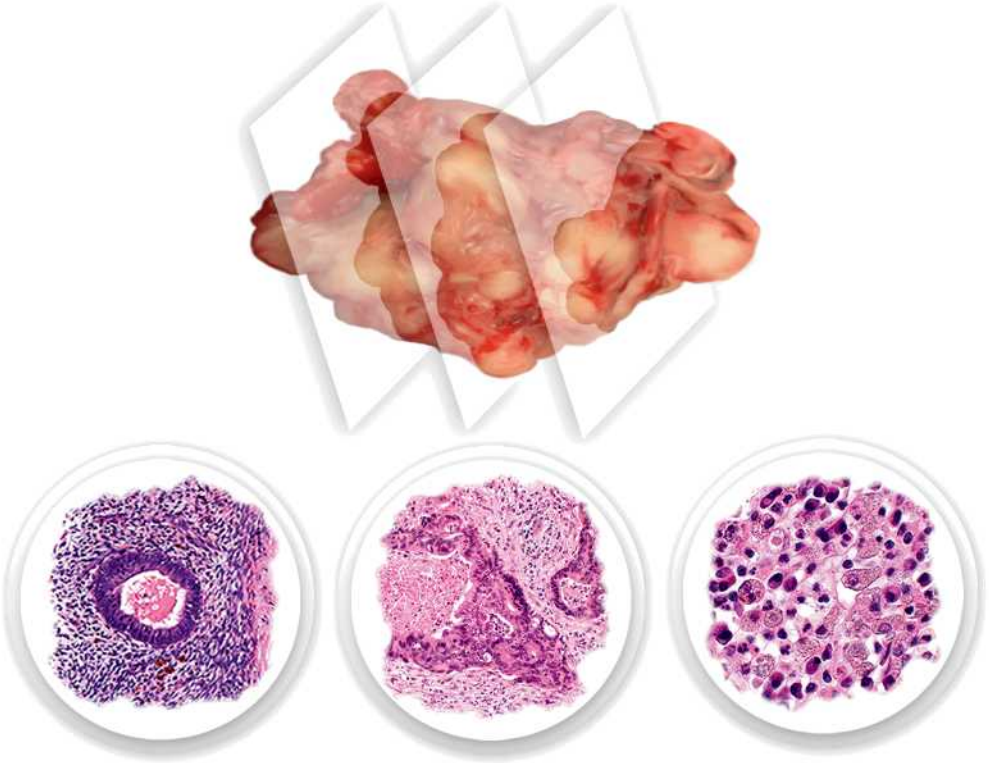

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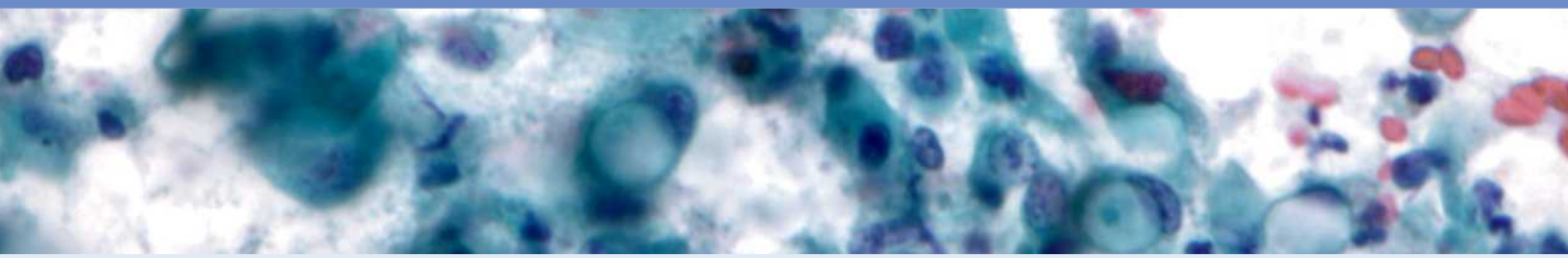
SECTION 1

General



THE ART OF INTRAOPERATIVE CONSULTATION

More Than Pathology at High Speed

- Intraoperative consultation (IOC) has significant differences compared to general pathology practice
  - Major purpose is to answer a specific question required for directing surgery
    - Diagnosis has immediate impact on care of patient
  - Definitive diagnosis generally not necessary or optimal
    - Information should be limited to that essential for immediate management of patient
    - Majority of special studies not available; diagnosis based almost exclusively on H&E slides
    - Only limited sampling of large specimens possible within time limits
  - Judicious interpretation of findings often necessary given limitation of frozen sections
    - Conservative approach, but not too conservative, is appropriate
    - Degrees of uncertainty when a definitive diagnosis is not possible may need to be shared with surgeon
  - Time-limited consultation
    - Ideally, an answer is available to surgeon within 20 minutes
    - Takes precedence over all other activities
    - In most institutions, a pathologist is available on call for consultation at all times
  - Direct interaction between pathologist and surgeon is preferred
    - Precise oral and written communication is essential
  - Often occurs at a site distant from pathology department
    - Pathologists typically prefer using their own microscope in their own workspace
  - Does not occur at predetermined time
    - May be requested at times outside normal working hours (e.g., nights and weekends)
  - Reference material may be limited or difficult to access (e.g., books and journals)
  - Consultation with colleagues often not possible
  - Not subspecialized; pathologists may see specimens outside their areas of expertise
- Pathologist plays important role in advocating for patient during IOC
  - Should only comply with requests for frozen section when they are in best interest of patient
  - Should request additional biopsies when received material is not sufficient for diagnosis
  - Must ensure that tissue is used 1st for diagnosis and clinical care and only 2nd for investigational studies and other uses
- Pearls of knowledge are suggestions and advice
  - Pearls start as grain of sand but gain value over time
  - Knowledge is gained after long years of experience with IOC, many close calls, and a few errors
  - Learning from errors is an excellent method to improve practice (especially when errors are not yours)

Goals of Intraoperative Consultation

- There are 3 principal reasons for immediate microscopic evaluation of specimens
  - **Diagnosis to guide intra- or perioperative patient management**
    - Identification or confirmation of pathologic process
    - Evaluation of margins for known malignancy
  - **Confirm sufficient lesional tissue is present for diagnosis on permanent sections &/or after special studies**
    - Definitive diagnosis is not necessary intraoperative
    - Pathologist confirms to surgeon there is no need to remove additional tissue, resulting in possible additional morbidity
  - **Optimally process tissue for ancillary studies to be used for diagnosis, treatment, or research**
    - Lymphomas
    - Sarcomas
    - Pediatric tumors
    - Other tumors requiring special handling

Intraoperative Consultation: Gross Findings

Intraoperative Consultation: Microscopic Findings

(Left) *Close cooperation and communication between surgical and pathology teams (preferably in person) is imperative to making sure the patient receives the optimal treatment in the operating room. [Courtesy L. Cheney, PA (ASCP)cm, and E. Rhei, MD.]* **(Right)** *Intraoperative consultation has features that set it apart from general pathology practice in many ways and requires a specialized skill set and diagnostic acumen in a challenging and time-limited professional setting. (Courtesy W. Welch, MD.)*

Most Common Diagnostic Questions

- **Diagnosis of primary lesion (~ 20%)**
  - In many cases, preoperative diagnosis is possible using needle or endoscopic biopsies
    - In some cases, prior attempt to diagnose may have been unsuccessful or contraindicated due to location or type of lesion
  - Definitive diagnosis need only be provided when relevant to immediate patient management
    - Often benign vs. malignant is sufficient for intraoperative management
    - Provisional diagnosis can aid in allocation of tissue for ancillary studies
    - In many cases (e.g., lymphomas, small round blue cell tumors, and soft tissue tumors), ancillary studies are often critical; definitive diagnosis at time of IOC is unnecessary
- **Evaluation of margins for known malignant tumor (~ 40%)**
  - Additional tissue may be taken to achieve negative margins in a single procedure
  - Accuracy is generally very high
- **Identification of lymph node metastasis (~ 20%)**
  - Resection with curative intent may be canceled if metastatic disease is identified
    - Additional nodes may not need to be sampled
    - Patients may be treated with systemic therapy prior to definitive resection
  - If a positive sentinel node is identified, additional nodes may be excised
- **Adequacy of tissue for future diagnosis (~ 5%)**
  - Presurgical treatment is becoming more widely used to reduce tumor burden and as a measure of tumor response
  - Tumors must be diagnosed with certainty prior to treatment
    - Fresh tissue may also be desirable for ancillary studies to identify cellular constituents vulnerable to targeted therapy
    - Patients may also consent to have tissue taken for tumor banks
  - Pathologist must request additional tissue when appropriate
- **Evaluation of organ prior to transplant (< 5%)**
  - Scarcity of organs has resulted in donor pool being expanded to include donors with possibly marginally functional organs
  - Intraoperative assessment is important to avoid transplantation of organs with high likelihood of failure

Changes in Intraoperative Consultation Over Time

- Need for IOC changes as treatment of patients changes
- **Consultations becoming more common**
  - Evaluation of lung lesions detected by screening
    - United States Preventative Services Task Force issued recommendations for screening for lung cancer using annual low-dose computed tomography for individuals between the ages of 55-80 with 30-year history of smoking and who currently smoke or have quit smoking within last 15 years
    - Lesions detected by screening are typically small or of low density (ground glass)
    - Lesions can be difficult or impossible for surgeon to palpate
      - Special localization techniques may be required
    - More limited surgery may be considered for adenocarcinoma in situ or minimally invasive adenocarcinoma
  - Evaluation of margins of partial nephrectomies
    - Small renal tumors are detected by imaging
    - Increased effort is being made to preserve renal function to avoid need for dialysis
  - Radioactive seed retrieval
    - The use of radioactive seeds rather than wires to mark breast lesions has many advantages for patients and surgeons
    - Retrieval of the seed in the IOC room may be preferred to ensure all seeds are identified, documented, and stored until they can be disposed of safely
  - Nipple margin of mastectomies
    - Nipple- and skin-sparing mastectomies offer cosmetically superior procedure for carefully selected women
    - The base of the nipple may be examined intraoperatively with removal of nipple when carcinoma is detected
  - Evaluation of organs prior to transplant
  - Evaluation of small biopsies for adequacy
- **Consultations currently rarely performed**
  - Identification of parathyroid adenomas
    - Intraoperative measurement of parathyroid hormone level is a useful functional assay that is used to guide surgery
  - Sentinel node evaluation for breast carcinoma
    - Studies have shown good outcomes for carefully selected women with positive sentinel nodes without axillary dissection
    - The need to determine if metastatic carcinoma is in sentinel node intraoperatively has diminished
  - Primary diagnosis of breast lesions
    - Core needle biopsies are highly accurate and allow decisions to be made concerning choice of surgery and systemic therapy (neoadjuvant or adjuvant)
    - Definitive surgery can be planned based on the core needle biopsy diagnosis

Limitations

- Frozen sections are not equivalent to evaluation of specimens on permanent sections
  - Diagnoses on frozen section should be limited to information needed for intraoperative management of patient
- **Sampling**
  - Tissue sections must be small to freeze well and quickly
  - Amount of tissue examined is less than that examined by permanent sections
  - **Pearl of knowledge**: The pathologist evaluating microscopic slides should always perform, or be aware of, the gross findings
    - If macroscopic and microscopic findings are not compatible, pathologist should suspect error

        - A good gross examination is often more accurate than a suboptimal microscopic section
        - Ink can often leak into specimens or smear, making it difficult to identify true margin
- **Ice crystal artifact**
    - Freezing introduces permanent changes in tissues by disrupting cell membranes and other structures
    - Although artifact can be minimized by rapid freezing of small samples, it is usually present
    - Artifacts can make diagnosis difficult or even impossible in extreme cases
        - Nuclei can look larger and more variable in size and shape
        - Holes in tissue can mimic intracellular vacuoles or fat
    - Tissue should only be frozen if benefit to patient outweighs risk of compromising eventual diagnosis
    - **Pearl of knowledge**: Nonpathologists often do not understand that patients can be harmed by inappropriate freezing of tissue due to artifacts permanently introduced
        - This fact can be helpful as part of explanation as to why frozen section should not be performed
- **Technical issues**
    - Some tissues (e.g., adipose tissue) do not freeze well
    - Tissues may be cut thickly
    - Tissue folds can complicate interpretation
- **Absence of special studies**
    - Histochemical and immunohistochemical studies are generally not available
    - Some diagnoses require additional studies

Inappropriate Intraoperative Consultations

- If IOC is requested but the information is not needed for intraoperative or immediate perioperative patient management, the request may be inappropriate
    - Inappropriate IOC can squander valuable resources and time
        - Could delay appropriate IOC for other patients
        - Generates unnecessary medical cost
    - May compromise ultimate diagnosis
- **Unnecessary and potentially harmful to patient**
    - Completely freezing any lesion may preclude ultimate definitive diagnosis
        - Freezing artifact can obscure diagnostic features
        - Tissue loss can occur during sectioning in cryostat
    - Pigmented lesions of skin and small breast lesions should not be entirely frozen
        - These lesions should be diagnosed and features evaluated on optimal permanent sections
        - Freezing artifact and potential loss of tissue can preclude making a definitive diagnosis
    - Pathologist must be advocate for patient
        - Surgeon must be informed as to why freezing entire lesion could be harmful to patient
        - Alternatives can be discussed, such as expedited processing of permanent sections
    - **Pearl of knowledge**: There are rare occasions in which unusual requests for frozen section examination are appropriate
        - Rather than refusing to perform examination, it can be more helpful to ask surgeon how examination will benefit patient
        - Pathologist and surgeon can reach an agreement about best course of action
        - Ultimately, pathologist must act in the best interest of patient
- **Unnecessary but not harmful to patient**
    - There is usually no need for frozen section diagnosis on large tumor that has been completely excised
        - However, performing a frozen section on a small portion of tumor will not interfere with eventual diagnosis
        - Surgeon may request IOC to provide information to the patient or family
    - Request should be discussed with surgeon to determine how intraoperative or immediate postoperative management would be changed by diagnosis
        - If there would be no change, then discuss why frozen section is unnecessary
        - In some cases, there may be clinical indications for diagnosis of which the pathologist is not aware
    - **Pearl of knowledge**: It can be difficult to discuss departmental policy with a surgeon while the patient is under anesthesia
        - If inappropriate requests are recurring problem, departmental and institutional policies should be developed by surgeons and pathologists and discussed in a multidisciplinary setting
- **IOCs known to have low sensitivity or specificity**
    - Value of performing frozen section may be very low in some situations
        - Evaluation of follicular thyroid lesions for capsular invasion
        - Evaluation of margins of large breast excisions
    - Surgeon should be aware of likelihood of a change in diagnosis on permanent sections
    - Departmental and institutional policies should be developed for evaluating these types of specimens

PATIENT HISTORY

Prior to Intraoperative Consultation

- Knowledge about clinical setting helps establish a safety net for patient
    - Substantial number of errors occur because pathologist interprets specimen without adequate information (e.g., not knowing patient has received radiation or chemotherapy)
    - Especially helpful in some situations
        - Biopsies of mediastinal lymph nodes (important to know if for tumor staging or to evaluate lymphadenopathy)
            - Determines if entire specimen should be frozen or only a representative portion
        - Resections after neoadjuvant chemotherapy or radiation therapy
            - Changes in normal cells due to treatment can be mistaken for malignancy
        - Rare tumor types

    - Tumors for which imaging appearance is critical for final diagnosis (central nervous system tumors, bone tumors)
  - **Pearl of knowledge**: Reviewing clinical histories prior to IOC leads to faster and more confident diagnoses and considerably less anxiety
    - Some people believe that pathologists should be able to divine all clinical information from surgical specimens as the haruspices in ancient Rome were able to divine information from examining organs—this is not true
- IOC requiring the allocation of tissue for purposes beyond diagnosis must be identified
  - Tissue required for patient treatment should be distinguished from tissue requested for research
    - Patients may require tissue sampling to be eligible for clinical trials
  - Special procedures may be required
    - Sterile tissue is necessary for cell cultures (e.g., vaccine studies)
    - Warm ischemia time (in operating room) and cold ischemia time (until tissue is frozen or placed in fixative should be minimized)
  - Patient care must always take precedence over use of tissue for research that does not directly impact patient
- Obtaining information prior to IOC is preferable, when possible
  - Does not extend the time of the IOC while patient is under anesthesia
  - Allows time to review prior pathology or imaging studies when available
- Well-designed electronic medical records can facilitate obtaining key information prior to the operation

Important Information for Pathologic Interpretation

- Age: Likelihood of diagnosis can be highly dependent on age
- Gender: Some tumors have gender-specific frequencies
- Prior history of malignancy
  - Metastatic disease must always be considered
  - Type of malignancy, stage, and prior treatment are all important factors
  - Treatment-related changes can be mistaken for malignancy
  - Tumors with treatment effect may be difficult to recognize
- Prior history of surgery
  - Surgical changes can be mistaken for malignancy
- Drug use or therapy
  - Drug use can cause changes (e.g., increased mitoses) that can be mistaken for malignancy
- Current pregnancy or lactation
  - Benign breast lesions can have increased mitotic rate &/or necrosis
    - These changes can mimic malignancy
- Known or suspected infection
  - Some diseases may require modifications to protect pathology personnel
    - Special respiratory masks are required to protect from *Mycobacterium tuberculosis*
    - Specimens from patients with suspected Creutzfeldt-Jakob disease should not be examined
  - Specimens should be kept sterile in order to obtain cultures
- Imaging findings
  - In some settings, appearance on imaging is critical
    - Essential to develop differential diagnosis
    - Particularly important for brain lesions, bone tumors, and lung lesions
    - May be necessary to locate lesion in large resections

Information Provided at Time of Intraoperative Consultation

- **Requisition form**
  - Patient identification, surgeon name, operating room number (including phone number) are all essential information
    - Known or suspected infectious diseases should be specified
  - Type of specimen submitted
    - Location
    - Biopsy or complete excision
    - Orientation
  - Purpose of consultation
    - In many cases, will be clear from type of specimen submitted and operative procedure
    - If purpose is not clear, pathologist should discuss with surgeon
    - **Pearl of knowledge**: If the reason for examining specimen is not immediately clear, it is an unusual case and best course of action is to contact surgeon
- **Information obtained during IOC**
  - If information is obtained from surgeon that is helpful for interpretation of frozen section, this will also be helpful for final diagnosis
  - Information should be recorded on requisition form and available to pathologist reviewing case for final sign out
- **Information obtained in operating room**
  - In some institutions, it may be possible for the pathologist to directly observe operative field and to discuss the case face to face with the surgeon

REPORTING RESULTS

Written Report

- Diagnosis is written and signed by attending pathologist
  - Most laboratories have a specific form for this purpose
  - Form should be labeled with patient name, medical record number, and surgical pathology number
  - Specific specimen and subdesignation for frozen section are included
- The diagnosis should directly address the question posed by the surgeon to successfully complete the operation
  - **Pearl of knowledge**: Diagnoses should be brief and include only the information necessary (e.g., "no tumor present" or "metastatic cancer present")
    - Long and wordy reports are difficult to communicate orally and more likely to be misunderstood
  - Avoid using abbreviations
    - An abbreviation saves time for 1 person and aggravates everyone else

History of Intraoperative Consultations

Era	Clinical Setting	Surgery	Pathology
Pre-1800s	Cancer less common as patients often die due to other diseases at early ages	Usually, rapid brutal procedures performed late in course of disease; does not change ultimate outcome	Capacity to evaluate tumors by microscopic examination not available
1800s	Patients come to medical attention late in disease when cancers are locally advanced	Anesthesia and aseptic technique allow earlier surgery and better outcomes; malignant tumors easily identified by gross features; radical surgical procedures performed	Advances in microscopy, microtomes, formalin, and tissue dyes allow identification and classification of tumors
1891	First recorded intraoperative consultation	William S. Halsted requests intraoperative consultation on mastectomy specimen	William H. Welch performs frozen section, but procedure requires an hour and results are not available until after operation has been completed
Early 1900s	Awareness of utility of early diagnosis and new imaging techniques results in patients presenting with smaller tumors	Gross examination not sufficient to identify smaller tumors as benign or malignant; growing impetus for more limited surgery; "When cancer becomes a microscopic disease, there must be tissue diagnosis in the operating room" (Joseph Colt Bloodgood, 1927)	In 1905, Louis B. Wilson publishes frozen section technique that can be performed in a few minutes
Current	Screening and modern imaging modalities detect many cancers at early stage; cancer is truly microscopic disease for many patients	Modern surgery minimizes tissue removed to maintain function and optimize cosmesis	Intraoperative diagnosis plays important role in providing information surgeon needs to ensure tumors have been removed and margins are clear

    - Abbreviations may vary among specialties and may be misunderstood
        - For example, pathologists understand "c/w" to mean "consistent with," whereas radiologists understand "c/w" to mean "compared with"
    - Superfluous information (typically histologic type or grade) is unnecessary and can create potential discrepancies with the final diagnosis
    - **Pearl of knowledge**: It is critical to know the consequences of a diagnosis (e.g. surgery for potential cure terminated or continued) when making diagnostic judgement calls when a definitive diagnosis is not obvious
        - The harm of a false-negative vs. a false-positive diagnosis for a patient is often not equivalent
- Copy of report is made and provided for patient's medical record
- Written reports of IOC may not be available to patient's caregivers for hours to days
    - When possible, documentation of IOC in manner that is available in patient's record is preferable
    - In electronic medical records, this may be possible using hold note

Oral Report

- Final diagnosis is called back to operating room
    - It is preferable to read written report exactly
- When possible, information should be relayed directly to surgeon
    - **Pearl of knowledge**: Complex or unusual diagnoses are best communicated directly between pathologist and surgeon
        - There is high rate of miscommunication when diagnosis is other than "benign" or "malignant"
        - Reports including terms indicating degrees of certainty ("suspicious for," "cannot exclude," "atypical") can be interpreted differently by pathologist and surgeon
        - Similar terms (e.g., "carcinoid" and "carcinoma") must be clearly distinguished
- The person receiving information should write down information and read diagnosis back to pathologist
    - This is requirement of The Joint Commission (TJC), formerly, The Joint Commission on Accreditation of Healthcare Organizations (JCAHO)

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