

CRC

FROZEN SECTION
in
SURGICAL
PATHOLOGY:
AN ATLAS

Volume I
Joseph Kovi

CRC PRESS

Frozen Section In Surgical Pathology: An Atlas

Volume I

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CRC Press, Inc.
Boca Raton, Florida

Library of Congress Cataloging in Publication Data

Kovi, Joseph.

Frozen section in surgical pathology.

Bibliography.

Includes indexes.

I. Pathology, Surgical--Atlases. I. Duong, Hung Dinh. II. Title. [DNLM: 1. Microtomy--Atlases.

2. Diagnosis, Surgical--Atlases. 3. Biopsy--Atlases.

W0 517 K88f]

RD57.K68 1983 617'.0758 82-20765

ISBN 0-8493-5147-2 (v. 1)

ISBN 0-8493-5148-0 (v. 2)

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Direct all inquiries to CRC Press, Inc., 2000 Corporate Blvd., N.W., Boca Raton, Florida 33431.

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International Standard Book Number 0-8493-5147-2 (Volume I)

International Standard Book Number 0-8493-5148-0 (Volume II)

Library of Congress Card Number 82-20765

Printed in the United States

FOREWORD

Frozen section has assumed an indispensable role in the surgical management of the patient. Reserved entirely for the pathologist, the interpretation of the frozen section imposes a major responsibility on the pathologist: Is it malignant or benign? What type of malignancy is it? Is it completely removed? Are the lymph nodes negative or positive? These are some of the questions that a frozen section must answer.

For the proper interpretation of any biopsy, and most certainly the frozen section, during the examination of which there is no time to consult books, the pathologist must know the natural history of the suspected disease and the lesions that simulate it. However, information relative to interpretation of frozen sections is meager and it is dispersed. Dr. Kovi has effectively and successfully filled this gap. In this Atlas the discussion of equipment, technique, its nuances, and problems is followed by clinical and pathological presentations. Over 300 photomicrographs taken from actual frozen sections provide an extensive illustration of the subject and the reproductions are extremely good.

Dr. Kovi has not only produced a beautiful Atlas, he has done a great deal more. Supplementing his rich experience gained through many years of careful observation and meticulous collection with clinical and pathological discussion of the suspected lesion and its differential diagnosis, Dr. Kovi has, in fact, produced a richly illustrated textbook of surgical pathology.

The Atlas will be a most valuable guide to the newcomer to pathology and add immeasurably to the armamentarium of the practicing pathologist, providing them both with a much needed illustrative text for the interpretation of frozen sections. I congratulate Dr. Kovi on his highly successful accomplishment.

F. K. Mostofi, M.D.

INTRODUCTION

This illustrative Atlas is intended to be a ready reference guide for the pathologist and the surgeon in the interpretation of frozen section appearances. Frozen section technique is a procedure of great value to the surgeon. Biopsy diagnosis by frozen section significantly contributes to patient care, and often means one operation less. This leads to reduced bed occupancy and measurable cost-containment. In most hospitals in this country to date frozen sections are cut on a cryostat. In the past decade, cryostat became the standard equipment of virtually every surgical pathology laboratory. It is without question that frozen section diagnosis is vital in patient care because the decision to remove a breast, to resect a lung, to amputate a leg, or terminate the operative procedure depends upon the interpretation of frozen sections. With adequately trained personnel a frozen section report can be communicated to the surgeon within minutes.

The criteria of frozen section diagnosis are similar to those applied to paraffin sections, except that the interpretation must be made within seconds or minutes, and because the tissue has not been fixed, the morphologic appearance is somewhat different from the paraffin-embedded sections. Numerous atlases and textbooks of microscopic pathology have been published based on photomicrographs made from permanent paraffin sections. As far as it is known, no Atlas of biopsy diagnosis by frozen section has yet been published in the U.S. The only publication of relevance in the English literature is the monograph of Shivas and Fraser, *Frozen Section in Surgical Diagnosis*, published by Churchill Livingstone, Edinburgh, in 1971.

Most of the material for this Atlas has been obtained from the busy frozen section service of the Department of Pathology, Howard University Hospital, Washington, D.C. With the annual 8000 to 10,000 surgical accessions, about 500 to 800 frozen sections are prepared yearly. All photomicrographs have been taken by the author with the available Leitz automatic microphoto equipment. Each representative photomicrograph has a short description stressing the salient features of pathology and noting the important differential diagnostic possibilities.

The two volumes contain approximately 300 photomicrographs of actual frozen sections, a number of illustrative diagrams and charts, as well as tables for concise presentation of relevant data.

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Dr. Kovi received his M.D. degree from the College of Medicine University of Budapest, Hungary in 1953. After having completed his residency in pathology at Roswell Park Memorial Institute, Buffalo, N.Y., he became a Diplomate of the American Board of Pathology in 1967. Dr. Kovi has been on the faculty of Howard University College of Medicine since 1970. In 1979 he spent his sabbatical leave as a Visiting Professor in Virology at the Department of Molecular Carcinogenesis and Virology, M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

Dr. Kovi was a founder member of the College of Pathologists of Great Britain. He is presently a fellow of the Royal College of Pathologists, College of American Pathologists, American Society of Clinical Pathologists, and a member of the International Academy of Pathology and the Electron Microscopy Society of America.

Dr. Kovi has published more than 70 research papers and has been the principal investigator or co-investigator of research grants from the National Cancer Institute.

ACKNOWLEDGMENT

I am deeply indebted to Mrs. Elizabeth Kovi for her silent but important contribution. The secretarial help of Mrs. Margaret R. Gonzales in preparing the manuscript is sincerely appreciated. Mr. Jeffrey Fearing was responsible for printing of negatives taken by the author. The line drawings were made by Mrs. Naida W. Page, medical artist. The photomicrographs, unless otherwise specified, were taken from the frozen sections prepared by the Surgical Pathology Laboratory of Howard University Hospital. The author is grateful to Dr. Marvin A. Jackson, former Chairman, Department of Pathology, for his encouragement and support. Special thanks are due to Mrs. Kathryn Berry, Supervisor, Surgical Pathology Laboratory and her assistants, Mrs. Rebecca Davis, Mrs. Gwendolyn Hargrow, and Mrs. Delores Thompson. The cooperation of Miss Sandy Pearlman, Managing Editor, Miss Anita Hetzler, Coordinating Editor, and the staff of the Photographic Department of CRC Press, Inc., is gratefully acknowledged.

J.K.

Dedicated to the uncounted millions of patients who have succumbed to cancer
because of late diagnosis and treatment

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Chapter 1

INTRODUCTION

I. FROZEN SECTION DIAGNOSIS

The earliest use of the frozen section technique is attributed to Welch of Johns Hopkins Hospital, who in 1891 performed the first frozen section on a benign breast tumor removed by Halstead. In 1895, Cullen described a rapid method of making permanent specimens from frozen sections by the use of formalin. In 1905, Wilson of the Mayo Clinic published his method of staining frozen sections with methylene blue for rapid intraoperative tissue diagnosis.¹ Today, in the two Mayo Clinic-affiliated hospitals, approximately 45,000 surgical pathology reports are generated annually. The material for all required microscopic sections is subjected to frozen section examination.²

In 1959, Ackerman and Ramirez³ in a review of 1269 consecutive frozen section diagnoses, specified the indications for and limitation of frozen section diagnosis. It was Shivas and Fraser⁴ who in 1971 published the first major illustrated monograph of frozen section diagnosis, entitled “Frozen Section in Surgical Diagnosis”, from Edinburgh, Scotland. One year later, Hermanek and Bunte⁵ from Erlangen, West Germany, reported on their experiences with the method in a book *Die intraoperative Schnellschnittuntersuchung. Methoden und Konsequenzen*, or *Intraoperative Frozen Section Examination. Methods and Results*.

As Shivas and Fraser⁴ noted, “the prime role of frozen section in surgical diagnosis is to spare the patient at most an operation, at least a period of distress and anxiety — often the most unpleasant feature of the entire illness — while a laboratory report is awaited. For the surgeon, anaesthetist and operating theatre staff, similarly, a diagnosis on frozen section often means one operation fewer.” Frozen section method is a reliable diagnostic procedure in trained hands. Spread of the tumor in the interval between the biopsy and the definitive surgery, e.g., mastectomy is avoided.⁶

A. Indications for Frozen Section Examination

- The need for the surgeon as Ackerman and Ramirez³ summed up, “to make a therapeutic decision.”
- To determine whether the lesion is benign or malignant.
- To make sure that the *margins* of the excision are free of tumor.
- In the case when no immediate diagnosis can be made from the biopsied specimen, to make sure that the removed tissue is representative, viable, and thereby a definitive diagnosis can be achieved by examination of the paraffin sections later.
- Identification of the tissue, e.g., parathyroid glands, vagus nerve, presence or absence of ganglion cells in Hirschsprung’s disease, etc.

B. Reliability of the Frozen Section Diagnosis

Application of the frozen section method for rapid tissue diagnosis during the course of surgical operations has become an essential part of the daily routine in hospitals throughout the U.S.¹

The overall accuracy of frozen section diagnosis in published frozen section series is presented in Table 1. In this composite series, the overall accuracy of the frozen section diagnosis of tissue biopsies was 98.5%. Among 36,698 tissue biopsies, there were 93 (0.3%) false positive diagnoses and 434 (1.2%) false negative diagnoses. A false positive diagnosis is made when a benign or non-neoplastic lesion is diagnosed as malignant. A false negative diagnosis is rendered when a malignant lesion is diagnosed as benign.

Table 1
OVERALL ACCURACY OF DIAGNOSIS IN PUBLISHED
FROZEN SECTION SERIES

Author, date, and location	Total no. of cases	False positive cases	%	False negative cases	%	Accuracy (%)
Winship and Rosvoll ⁷ Washington, D.C., 1959	1,810	3	0.2	18	1.0	98.8
Ackerman and Ramirez ³ St. Louis, 1959	1,269	4	0.3	22	1.7	98
Khoo ⁸ Singapore, 1965	443	3	0.7	10	2.3	97
Funkhouser et al. ⁹ Dayton, 1966	1,176	2	0.2	20	1.7	98.1
Elsner ¹⁰ St. Louis, 1968	2,240	5	0.2	13	0.6	99.2
Nakazawa et al. ¹¹ New York, 1968	3,000	8	0.3	35	1.2	98.5
Funkhouser et al. ¹² Dayton, 1970	3,986	8	0.2	61	1.5	98.3
Bredahl and Simonsen ¹³ Copenhagen, 1970	1,964	12	0.6	17	0.9	98.5
Hermanek and Bunte ⁵ Erlangen, 1972	2,000	3	0.2	48	2.4	97.4
Saltzstein and Nahum ¹⁴ San Diego, 1973	2,665	4	0.2	43	1.6	98.2
Holaday and Assor ¹⁵ Columbus, 1974	10,000	15	0.2	88	0.9	98.9
Lessells and Simpson ¹⁶ Aberdeen, 1976	3,556	6	0.2	13	0.4	99.4
Iri ¹⁷ Tokyo, 1977	760	5	0.7	22	2.9	96.4
Dehner and Rosai ¹⁸ Minnesota, 1977	778	0	0.0	11	1.4	98.6
Dalal et al. ¹⁹ Chandigarh, 1979	1,051	15	1.4	13	1.2	97.4
Total	36,698	93	0.3	434	1.2	98.5

A *false negative* diagnosis of cancer is *not* an incorrigible mistake. A *false positive* diagnosis, on the other hand, is a *most serious error* and may result in unjustifiable surgery, an unnecessary mastectomy, or an unwarranted resection of a portion of the pancreas, etc. As noted, among 36,698 biopsies diagnosed on frozen section, only 93 false positive diagnoses were made. Sparkman¹ pointed out that diagnostic errors occur also when the diagnosis is rendered from paraffin sections.

The relative frequency of *deferred diagnoses* of surgical biopsies in published frozen section series is documented in Table 2. In this composite series of a total of 26,493 biopsies the diagnosis was deferred only in 315 cases, that is, in 1.2% of the patients. When the pathologist defers the diagnosis the surgeon must wait 12 to 24 hr until the paraffin sections are available and a definitive diagnosis can be rendered. There has been no report on any harmful effect to the patient because of this brief waiting period.

The frozen section method must be considered as a highly reliable diagnostic procedure until the pathologist follows the principles foreset by Ackerman²⁰ in 1953; only three possible frozen section diagnoses can be rendered, (1) positive for cancer, (2) negative for cancer, and (3) deferred.

Table 2
RELATIVE FREQUENCY OF
DEFERRED DIAGNOSES IN
PUBLISHED FROZEN SECTION
SERIES

Author, date, and location	Total no. of cases	Deferred diagnosis	
		No.	%
Khoo ⁸ Singapore, 1965	443	11	2.5
Elsner ¹⁰ St. Louis, 1968	2,240	38	1.7
Nakazawa et al. ¹¹ New York, 1968	3,000	37	1.2
Hermanek and Bunte ⁵ Erlangen, 1972	2,000	66	3.3
Saltzstein and Nahum ¹⁴ San Diego, 1973	2,665	46	1.7
Holaday and Assor ¹⁵ Columbus, 1974	10,000	50	0.5
Lessells and Simpson ¹⁶ Aberdeen, 1976	3,556	7	0.2
Iri ¹⁷ Tokyo, 1977	760	7	0.9
Dehner and Rosai ¹⁸ Minnesota, 1977	778	32	4.1
Dalal et al. ¹⁹ Chandigarh, 1979	1,051	21	2.0
Total	26,493	315	1.2

C. Limitations of the Frozen Section Method

Since the first utilization of the frozen section procedure by Welch at Johns Hopkins in 1891, it has been conceded that one of the major limitations of the use of the frozen section method in surgical pathology is the imperfections of the technique.⁹ Many prominent pathologists in the period 1920 to 1940, such as Ewing, Warthin, Breuer, and Simpson were quite skeptical about the procedure.¹² The introduction of the cryostat in surgical pathology by Ibanez et al.,²¹ Chang et al.,²² and Russell et al.,²³ in 1960 to 1961 contributed immensely to the gradual acceptance of the technique. As Funkhouser et al.¹² noted, the quality of cryostat frozen section is in most instances equal to or only slightly different from the quality of the paraffin sections.

Implantation of tumor at the time of the biopsy is a distinct possibility, especially in the thyroid gland and in the lung. Ackerman and Ramirez³ pointed out that when the tumor is excised with an ample margin of normal tissue the risk can be completely avoided.

The technique is not suitable for the study of bone, teeth, and fat tissue.²⁴

II. SOURCES OF ERROR

A. The Role of the Surgeon

1. *Sampling error.* The surgeon may submit to the pathologist tissue which does not contain the lesion. Foraker (as quoted by Sparkman¹) noted that pathologists have not yet learned to make tumor diagnoses from tissue taken *near* the lesion.