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An Evaluation of Frozen Section Biopsy in 4434 Cases

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Frozen section diagnosis is a highly useful method of diagnosis. There were 4434 frozen sections, 24 false positive diagnosis, 65 false negative diagnosis and 30 deferred diagnosis. This method achieves the highest accuracy when there is a cooperation between experienced surgeon and reliable and careful pathologist. It is wise to defer the diagnosis or consult to other pathologist in difficult situation.

Key Words: *Frozen section biopsy, cryopathology, accuracy*

INTRODUCTION

The frozen section technic for prompt diagnosis of surgical specimens has been used in hospitals throughout the country and has now reached a high level of accuracy.

This technic was first applied to clinical medicine by Welch in 1891 (Sparkman, 1962). When properly employed, it can help both clinicians and patients by sparing additional anesthesia, operation room fees, and anxiety associated with waiting for diagnosis (Jeong et al., 1985). However, there still are limitations compared for the paraffin section. Therefore, frozen section diagnosis should not be a method used routinely in every specimen removed at the operating table, but should be reserved for those instances in which an immediate therapeutic decision has to be made (Rosai, 1981 and Ackerman & Ramirez, 1959).

At Seoul National University Hospital we have applied frozen section diagnosis since early 1970's. However, it has not been everyday practice until early 1980's when the concept of cryopathology became quite popular.

Since the therapeutic impact of accurate diagnosis in frozen section is so important that we underwent a review of the cases and evaluate this procedure in detail.

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MATERIALS AND METHODS

4434 consecutive frozen section biopsies performed at Department of Pathology, Seoul National University Hospital from January, 1984 to December, 1986 were reviewed. The reports made at the time of frozen section were compared with the permanent paraffin section reports.

For frozen section, fresh tissue was sent from the operating room to the frozen section room in the operation unit and the blocks were cut on the cryostat followed by Hematoxylin-Eosin staining. Surgeons were immediately informed of frozen section diagnosis orally in the operation room or through the interphone. Frozen tissue as well as any remaining non frozen tissue not used for culture or election microscopy were then fixed in 10% formalin solution and processed for paraffin section.

When we reviewed the reports, the reports were classified as follows

1) When several frozen sections were performed

during one operation, these were counted as one case. Frozen sections from two operations on patient were counted as two cases.

2) When we classify the organs of the specimen, we applied the following rules; i) When more than two organs were frozen during one operation, this case was classified in according to the priority, e.g., if gastrointestinal margins were frozen with lymph nodes, liver, or pancreas during one operation, this case was classified as lymph node, liver, or pancreas. If main mass for identification and lymph node for metastasis were frozen during one operation, this case was classified as the organ having main mass. ii) The site of biopsy was classified according to the clinicopathological problem, e.g., the nasal skin sent by a dermatologist or plastic surgeon was counted as skin and the nasal skin sent by an otolaryngologist was counted as ENT.

3) The diagnosis were classified as i) false positive, when a benign lesion was diagnosed as malignant, ii) false negative, when a malignant lesion was diagnosed as benign, iii) deferred, when a definitive decision on benign or malignant nature of the lesion was not made at the time of frozen section, iv) grading error and incorrect histological typing, when the pathologists had correctly assessed the benign or malignant nature of the lesion, but errored in identifying the histological typing and grading. v) In the central nervous system, all gliomas were classified as a malignant lesion based on the clinical behavior. vi) In the colon biopsy for the diagnosis of aganglionosis, we classified as false positive when aganglionosis was erroneously diagnosed as presence of ganglion cells and vise versa.

The false negative and the false positive cases were selected and the original frozen section and permanent slides were reviewed by 3 pathologists.

RESULTS

The average accuracy over 3 years was 97.97%. We made 24 (0.54%) false positive, 65 (1.47%) false negative, and 30 (0.77%) deferred diagnosis and 96 (2.17%) grading error and incorrect histological typing (Table 1). After excluding 864 cases performed for gastrointestinal resection margins, the accuracy was slightly decreased (refer * at Table 1). The annual accuracy rate was not significantly changed over the three years.

The common sites sent for frozen section diagnosis were gastrointestinal tract (24.11%), lymph node (17.61%), breast (13.01%), and thyroid (7.91%) in descending order.

The thyroid had the lowest accuracy rate (95.30%) followed by soft tissue (95.80%) and lung and mediastinum (95.92%). The identification of nerve and ganglion during vegotomy or sympathectomy had 100% accuracy as with the male genital organs and adrenal gland (Table 2).

The gastrointestinal tract comprised 1069 cases and 111 cases out of them were malignant lesions, most of which were carcinomas. Almost all the cases classified as normal were resection margins of gastrointestinal malignancy.

Among 781 lymph node cases, 251 cases were metastatic cancers, 14 cases were lymphomas and the rest of these were benign lesions.

Among 577 breast cases, 148 cases were malignant lesions and infiltrating duct carcinoma being the most common one. Benign lesions comprised 427 cases, most of which were either fibrocystic diseases or fibroadenomas.

Among 319 thyroid cases, 84 cases were malignant lesions, most of which were papillary carcinomas. Benign lesions comprised 231 cases, adenomatous goiter being the most common one.

The frozen and the permanent diagnosis of the false positive cases were compared at table 3.

In the duodenum, the atypia of the villous adenoma was interpreted as a malignancy at the time of frozen section. The leiomyoma of the stomach was reported as leiomyosarcoma biased by the

Table 1. Frozen section diagnosis in 4434 cases

Year	Cases	False Pos. (%)	False Neg. (%)	Deferred (%)	Typing and grading error (%)	Accuracy (%)
1984	1403	0.43	1.71	0.57	2.42	97.86 (97.43)*
1985	1386	0.65	1.44	1.08	2.31	97.83 (97.37)*
1986	1645	0.55	1.28	0.67	1.82	98.17 (97.54)*
Total	4434	0.54 (0.69)*	1.47 (1.86)*	0.77	2.17	97.97 (97.45)*

• *Corrected errors and accuracy after excluding the resection margins of GI tract

Table 2. Types of tissues submitted for frozen section

Types of Tissues	No. of Cases (%)	False Pos. (%)	False Neg. (%)	Deferred (%)	Accuracy (%)
GI tract	1069 (24.11)	4 (0.37)	9 (0.84)	3 (0.28)	98.79
Lymph node	781 (17.61)	2 (0.26)	13 (1.66)	4 (0.52)	98.08
Breast	577 (13.01)	2 (0.35)	4 (0.70)	2 (0.34)	98.95
Thyroid gland	319 (7.19)	4 (1.25)	11 (3.45)	4 (1.25)	95.30
CNS	267 (6.02)	3 (1.12)	4 (1.50)	2 (0.74)	97.38
GYN	238 (5.37)	1 (0.42)	0 (0.00)	2 (0.84)	99.58
Soft tissue & Retroperitoneum	214 (4.83)	2 (0.83)	7 (3.27)	5 (2.34)	95.80
Liver & Biliary tract	212 (4.78)	0 (0.00)	2 (0.94)	2 (0.94)	99.06
Omentum & Peritoneum	127 (2.86)	0 (0.00)	4 (3.15)	3 (2.36)	96.85
ENT	124 (2.80)	1 (0.81)	3 (2.42)	1 (0.81)	96.77
Lung & Mediastinum	98 (2.21)	2 (2.04)	2 (2.04)	2 (2.04)	95.92
Salivary gland	79 (1.78)	0 (0.00)	2 (2.15)	0 (0.00)	97.47
Urinary tract	61 (1.38)	1 (1.64)	0 (0.00)	1 (1.64)	98.36
Bone	54 (1.22)	1 (1.85)	1 (1.85)	2 (3.70)	96.30
Pancreas	52 (1.17)	1 (1.92)	1 (1.92)	0 (0.00)	96.16
Skin	50 (1.13)	0 (0.00)	2 (4.00)	0 (0.00)	96.00
Nerve & Ganglion	29 (0.65)	0 (0.00)	0 (0.00)	0 (0.00)	100.00
Male genital organ	25 (0.56)	0 (0.00)	0 (0.00)	0 (0.00)	100.00
Adrenal gland	9 (0.20)	0 (0.00)	0 (0.00)	1 (11.1)	100.00
Others	49 (1.11)	0 (0.00)	0 (0.00)	0 (0.00)	100.00
Total	4434 (100.00)	24 (0.54)	65 (1.47)	34 (0.77)	97.97

large size and the clinical impression of leiomyosarcoma.

In the breast, the papillary projection of the lactiferous ducts in the fibrocystic disease was interpreted as suggestive of malignancy and chronic granulomatous inflammation with inflammatory cell infiltrate in the stroma was reported once as carcinoma. When we reviewed these frozen slides retrospectively, we agreed that it was really difficult to make a definitive diagnosis.

Three cases of adenomatous goiter were difficult to differentiate from papillary carcinoma, even retrospectively, however, in one case, the papillary infoldings of adenomatous goiter was misinterpreted as papillary carcinoma and in other case, small abortive follicles in adenomatous goiter was misinterpreted as follicular carcinoma.

In the central nervous system, one neurofibroma and one glial hamartoma were reported as astrocytomas, and one meningioma was reported as malignant intracranial tumor possibly lymphoma.

Ganglioneurofibroma and paraganglioma of the soft tissue were difficult to make a definite nature of the lesion especially with the poor quality of the slides.

Angiomyolipoma of the kidney was one of the rare tumors and might appear pleomorphic on frozen section. It might have been really difficult unless the pathologists were familiar with this entity.

False negative cases far outnumbered the false positive cases. The frozen and the permanent diagnosis of the false negative cases were compared at Table 4. Four metastatic poorly differentiated adenocarcinomas in lymph nodes (three mesenteric, one portal area) and one papillary carcinoma in thyroid were overlooked largely due to poor quality of the slides.

In two lymph nodes, one thyroid, one resection margin of stomach, and one resection margin of the skin, the malignant tumor cells were not present on

Table 3. Comparison of frozen and final diagnoses in false positive cases

Site	Frozen Diagnosis	Final Diagnosis
GI tract (4)		
Colon	Presence of ganglion cells (2)	Absence of ganglion cells
Duodenum	Adenocarcinoma	Villous adenoma
Stomach	Leiomyosarcoma	Leiomyoma
Lymph node (2)		
Cervical	Metastatic sq. cell ca.	No tumor
Mesenteric	Positive for tumor	No tumor
Breast (2)	Suggestive of Malignancy	Fibrocystic disease
	Carcinoma	Chronic granulomatous inflammation
Thyroid (5)		
	Papillary carcinoma (3)	Adenomatous goiter
	Probable papillary carcinoma	Adenomatous goiter
	Follicular tumor highly suggestive of carcinoma	Adenomatous goiter
CNS (3)		
Conus medullaris	Astrocytoma	Neurofibroma
Suprasellar	Astrocytoma	Neuroglial hamartoma
Occipital	Malignant intracranial tumor possibly lymphoma	Meningioma
GYN (1)		
Uterine serosa	Malignancy	Papillary serous cystadenoma
Soft tissue & Retroperitoneum (2)		
Cheek	Liposarcoma, low grade	Ganglioneurofibroma
RLQ	Malignant nonepithelial tumor	Paraganglioma
ENT (1)		
Tonsil	Squamous cell carcinoma	No tumor
Kidney (1)	Sarcoma, most likely liposarcoma	Angiomyolipoma
Bone (1)		
Femur head	Possible malignancy	Benign lesion
Pancreas (1)	Sarcoma	Epithelial leiomyoma
Lung & Mediastinum (2)		
Mediastinum	Malignant tumor	Thymoma
Mediastinum	Highly suggestive of lymphoma	Thymoma lymphocyte predominant

the original frozen section slides, but present on permanent slides of the remained tissue submitted for frozen section.

When we reviewed retrospectively, we agreed that diagnosis of malignant lymphoma, Hodgkin's disease, papillary carcinoma of the breast, follicular variant of papillary carcinoma of thyroid, all four central nervous system lesions (germ cell tumor, chondrosarcoma, oligodendroglioma, and metastatic squamous cell carcinoma), embryonal rhabdomyosarcoma of the chest wall, chondrosarcoma of the inguinal area, and biliary cystadenocarcinoma of the liver were difficult lesions to make a definitive diagnosis at the time of frozen section.

Table 4. Comparison of frozen and final diagnoses of false negative cases

Site	Frozen Diagnosis	Final Diagnosis
GI tract (9)		
Colon	Absence of ganglion cells (3)	Presence of ganglion cells
Stomach	No tumor (4)	Positive for tumor
Stomach	Benign spindle cell tumor	Leiomyosarcoma
Colon	Benign	Polyp with adenocarcinoma
Lymph node (13)		
Mediastinal	Granuloma	Hodgkin's disease with granuloma
Cervical	Chronic inflammation (2)	Metastatic squamous cell carcinoma
	Chronic inflammation	Hodgkin's disease
Submandibular	Benign	Malignant lymphoma
Paratracheal	No tumor	Metastatic squamous cell carcinoma
Portal area	No tumor (2)	Adenocarcinoma
Mesenteric	No tumor (5)	Metastatic adenocarcinoma
Breast (4)	Papillary lesion, probably benign	Papillary adenocarcinoma
	Atypical cell clusters	Intraductal papillary carcinoma
	Inflammation	Medullary carcinoma
	Probably benign papillomatosis	Intraductal carcinoma
Thyroid (11)	Hashimoto's thyroiditis (2)	Malignant lymphoma
	Benign or goiter (7)	Follicular variant of papillary carcinoma
	Follicular adenoma (2)	Follicular carcinoma
CNS (4)		
Basal ganglia	Glial tumor, probably benign	Germ cell tumor
Cerebellum	Hemangioblastoma	Oligodendroglioma, P-D
Frontal	Chordoma	Chondrosarcoma
Frontal	Meningioma	Metastatic squamous cell carcinoma
Soft tissue & Retroperitoneum (7)		
Retroperitoneum	Lipoma	Liposarcoma
Abdominal wall	No tumor	Metastatic adenocarcinoma
Abdominal wall	Neurogenic tumor, probably neurofibroma	Malignant schwanoma
Abdominal wall	Benign, probably neurogenic tumor	Spindle cell sarcoma, probably malignant schwanoma
Elbow	Hemangioendothelioma	Spindle cell sarcoma, probably synovial sarcoma
Chest wall	Benign fibrous tissue	Small round cell sarcoma, suggestive of embryonal rhabdomyosarcoma
Inguinal	Benign chondroid tumor	Chondrosarcoma
Liver & Biliary (2)		
Liver (resection margin)	No tumor	Positive for tumor
Liver	Fibrocollagenous tissue without lining epithelium	Biliary cystadenocarcinoma of low grade malignancy
Omentum, Mesentery etc. (4)		
Mesentery	No tumor	Adenocarcinoma
Mesenteric mass	Low grade spindle cell lesion	Malignant schwanoma
Omental cyst	Inflammatory pseudocyst	Pleomorphic sarcoma
Peritoneal wall	No tumor	Adenocarcinoma

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ENT (3)		
Ear	No tumor	Superficial basal cell carcinoma
Neck	Branchial cyst	Papillary carcinoma
Vocal cord biopsy	Probably benign	Squamous cell carcinoma
Bone (1)		
Humerus	Benign	Metastatic carcinoma
Pancreas (1)	Benign pseudocyst	Epithelial tumor of low grade malignancy
Skin (2)		
Scalp	Neurofibroma	Malignant schwanoma
Nose (RM)	No tumor	Trichoepithelioma
Lung & Mediastinum (2)		
Pleura	Atypical mesothelial hyperplasia	Epithelioid mesothelioma
Mediastinum	Thymoma	Hodgkin's disease
Salivary gland (1)	Pleomorphic adenoma	Mucoepidermoid carcinoma

Table 5. Major causes of erroneous diagnosis

Causes	False Pos.	False Neg.
Unavoidable error	11	18
Misinterpretation	5	13
Poor section	0	5
Incorrect clinical inform.	1	0
Sampling error	0	5

DISCUSSION

The frozen section technic is a useful and convenient method for prompt diagnosis, which enables surgeons to decide the next appropriate therapeutic steps. However, as previously mentioned there is certain limitations, the most critical fact of which is the accuracy of the diagnosis.

Authors reviewed and classified the erroneous diagnosis in according to the underlying cause (Table 5). We had 18 misinterpretations which we believe that should have been avoided, if the pathologists were more careful or he/she consulted the senior pathologists. We made 5 false negative diagnosis which might have been avoidable, if the pathologist made an effort to make decent sections. However, tissues which are friable, mucoid, hemorrhagic, and full of adipose tissue are not always easy to make nice sections. We made one false positive diagnosis influenced by wrong clinical judgement. We made 5 false negative diagnosis due to sampling error by the pathologist. We did not include surgeon's sampling error in our study, however, there were several sampling errors made by surgeons.

Authors agreed that 29 cases were really difficult to make a definitive diagnosis at the time of frozen section and classified this catagory as an unavoidable error, however, we felt that we could have avoided making errors even by deferring the diagnosis. Diagnosis of malignant lymphoma and Hodgkin's disease on the frozen section slides are the greatest difficulty and are often impossibe mainly due to frozen artifact, cellular swelling, and the inability to get thin sections. The routine paraffin section slides are often inadequate to make an accurate diagnosis, and the special technics including early fixation after making thin slices of tissue, special fixatives, very thin sections and sometimes immunoperoxidase staining and electron microscopy technic are required. Diagnosis of papillary carcinoma of the breast is one of the greatest difficulty in the frozen section diagnosis as emphasized by Ackerman and Ramirez, 1959. Papillary carcinoma often gives pathologists a great problem even with a permanent paraffin section slides. It is not surprising that the pathologists have difficulty at the time of frozen section biopsy since the frozen section slides usually lack the cytological and the structural details

compared to the permant slides. Helpful diagnostic features of papillary carcinoma of the thyroid are papillary structures containing fibrovascular stroma, ground-glass appearance of the nuclei, psammoma bodies, and intranuclear cytoplasmic invasination. The ground glass appearance of the nuclei is understood as an artifact produced during fixation, therefore, it is not present on the frozen section slides. Papillary structures may not be seen in the follicular variant of papillary carcinoma, especially on small limited biopsy specimen. Psammoma bodies and intranuclear cytoplasmic inclusions are really helpful and diagnostic features, but not frequently seen. Germ cell tumor and chondrosarcoma are very rarely seen in the central nervous system and poorly differentiated oligodendroglioma and metastatic squamous cell carcinoma are not very common. All above lesions were difficult to interprete mainly due to small size and fragmentation of the specimen, frozen artifact and comparative less incidence. In embryonal rhabdomyosarcma of the chest, only few rather poorly preserved tumor cells were present on the edge of the specimen. Differential diagnosis of well differentiated chondrosarcoma and benigh chondroma is always a problem for the pathologists. Clinical information (age of the patient, location of the lesion, size of the tumor and radiological findings) and gross appearance of the tumor should always be cosidered. Biliary cystadenocarcinoma is another very difficult entity and it is almost impossible to make a definitive diagnosis on small frozen biopsy specimen. Even the malignant or benign nature of the lesion can not be assessed if the pathologists received an area mainly composed of dilated cystic spaces without lining cells.

The accuracy of frozen section diagnosis varied from 93.4 to 99.77% depending on the authors and the type of tissues (Ackerman & Ramirez, 1959, Winship & Rosvoll, 1959, Jeong et al., 1985, Nakazawa et al., 1968, Preston & Bale, 1985, Rosen, 1978, Silverberg, 1983, Sparkman, 1962). The deferred rate also varied from 0.3 to 5.7% and the frequency of false positive diagnosis is inversely related to that of deferred diagnosis, so the attempt to "force" a diagnosis in a difficult situation is likely to lead the feared result of false positive interpretation (Silverberg, 1983).

In conclusion, there are certain limitations in the frozen section biopsy technic and the pathologists should make an effort to avoid errors by careful handling of the specimen, intimate cooperation with the surgeons, and even by deferring the diagnosis.

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