Accuracy of Intraoperative Consultation of Central Nervous System Lesions in Siriraj Hospital

Pornsuk Cheunsuchon, M.D., Atthanisa Punyashthira, M.D., Jantima Tanboon, M.D., Tumtip Sangruchi, M.D.
Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To describe accuracy, identify diagnostic discordances and pitfalls of intraoperative neuropathology diagnosis in Siriraj Hospital.
Methods: All central nervous system lesions requested for rapid intraoperative consultation in Siriraj Hospital from 1998 to 2011 were reviewed. Accuracy rate and causes of diagnostic discrepancies were identified and discussed.
Results: Intraoperative neuropathology consultation was performed in 774 cases during the study period. Non-representative specimens (40 cases, 5.2%) and cases with deferred diagnosis (36 cases, 4.7%) were excluded from the study. Of 698 cases analysed, 85.5% were neoplastic and 14.5% were non-neoplastic. The overall accuracy rate was 89%. In the neoplastic category, the most common pitfall was tumor type misclassification (66.7%) especially misclassified astrocytic and oligodendroglial tumors as other tumors (23.8%). In non-neoplastic category, the most common error was misdiagnosis of non-tumor pathology as gliomas (64.3%).
Conclusion: Intraoperative neuropathology diagnosis has a crucial role in clinical management. Multidisciplinary and systematic approaches are required to overcome diagnostic limitations on small tissue samples and increase diagnostic accuracy.

Keywords: Central nervous system, intraoperative, frozen section, accuracy

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INTRODUCTION

Intraoperative neuropathology consultation plays a crucial role in neurosurgical management. It can be used as a tool to assess specimen adequacy for further laboratory tests during a stereotactic or endoscopic biopsy or to determine the extent of resection during open surgery. However, the pathology of a central nervous system (CNS) lesion is diverse and certain lesions require special technical assistance and experience to make accurate diagnoses during rapid intraoperative consultation (IC). This study assessed the diagnostic accuracy and pitfalls of IC of CNS lesions performed in Siriraj Hospital from 1998 to 2011.

MATERIALS AND METHODS

All IC cases of CNS lesions performed in Siriraj Hospital from 1998 to 2011 were retrieved from the Department of Pathology computer database. Squash smear and frozen

Correspondence to: Pornsuk Cheunsuchon
E-mail: pornsuk.che@mahidol.ac.th
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section (FS) were performed in all cases except for the cases with tiny samples in which smears were solely performed. Results of intraoperative diagnosis were compared to final diagnoses based on formalin-fixed permanent sections which included defrosted and remaining tissues from FS and additional specimen sent for examination after the operation. Accuracy rates were calculated and types of diagnostic discrepancy were recorded. Discrepant cases were reviewed and causes of diagnostic disagreements were identified and discussed. The study was approved by institutional review board, approval number 740/2553(EC1).

RESULTS

A total number of 774 cases of CNS lesions were requested for IC during the study period. There were 359 females and 415 males (mean age 40.7 years, ranged 0-90 years). Non-representative specimens were found in 40 cases (5.2%). In thirty six cases (4.7%), specific diagnoses were not rendered during FS and the diagnoses were deferred to permanent sections. These two groups were excluded from the study. In 698 cases analysed, 597 cases (85.5%) were neoplastic predominantly astrocytic and oligodendroglial neoplasms (39.5%, Table 1). We compared the IC and final diagnoses. The overall accuracy rate was 89%. In neoplastic and non-neoplastic lesions, the accuracy rates were 89.4% and 86.1%, respectively (Table 1).

In the neoplastic category, tumor type misclassification was the most common discrepancy (42 cases, 66.7%) followed by deviation of tumor grading (17 cases, 27%) and misdiagnosis of tumor to non-tumor condition (4 cases, 6.3%, Table 3). Discrepancies involved astrocytic, oligodendroglial neoplasms, meningioma, embryonal tumor, ependymal tumor, hematologic malignancy, and pituitary adenoma in descending orders (Table 1). Of 17 cases with grading mismatch, undergrading was found in 15 cases (12 astrocytic and oligodendroglial tumors, 2 meningiomas and 1 ependymoma) and overgrading was found in 2 cases (1 astrocytoma and 1 ependymoma). Four cases of misinterpretation of tumor to non-tumor pathology consisted of 1 lymphoplasmacyte-rich meningioma diagnosed as chronic inflammation, 1 lymphoma diagnosed

TABLE 1. Spectrum and number of discrepancy in neoplastic category.

Tumor types	Number of cases	Number of discrepant cases
Astrocytic and oligodendroglial tumors	236	23
Meningioma	65	8
Hematologic malignancy	63	5
Metastatic carcinoma	62	1
Ependymal tumor	40	5
Embryonal tumor	39	6
Germ cell tumor	32	3
Schwannoma	16	1
Glioneuronal tumor	12	2
Mesenchymal/vascular tumor	11	1
Pituitary adenoma	8	4
Choroid plexus tumor	5	1
Craniopharyngioma	5	-
Olfactory neuroblastoma	1	1
Pineal region tumor	1	1
Melanocytic tumor	1	1
Total	597	63

TABLE 2. Spectrum and number of discrepancy in non-neoplastic category.

Category	Number of cases	Number of discrepant cases
Infection/inflammation	41	6
Biopsy of normal/non-lesional tissue	24	1
Reactive change	14	-
Hemorrhage	6	-
Demyelination	5	3
Vascular lesion	5	1
Infarct/ischemic lesion	3	2
Malformation/hamartoma	3	1
Total	101	14

as chronic inflammation, 1 hemangioblastoma diagnosed as dilated vessel, and 1 pituitary adenoma diagnosed as normal pituitary tissue. In the non-neoplastic category, infection/inflammatory conditions were commonly requested for IC and had the highest number of diagnostic disagreements (Table 2). The most common pitfall in the non-tumor group was misdiagnoses of these lesions as low grade glioma during IC (64.3%, Table 4).

DISCUSSION

Rapid intraoperative neuropathology consultation contributes useful information in neurosurgical managements. However, making an intraoperative diagnosis can be difficult due to a wide variety of CNS pathology and limitation of time and sample size during IC. In this study, we demonstrated an 89% accuracy of intraoperative neuropathology service in Siriraj Hospital which was comparable to the range of 84-97% reported by others[1-9] and the accuracy for interpretation of neoplastic lesions was higher than non-neoplastic diseases.

In the neoplastic category, misinterpretation of tumor type was the most common problem and gliomas had the highest number of discrepant cases. High grade gliomas were often misinterpreted as metastatic carcinoma (Table 3). This pitfall was also mentioned by others.[2,5-7] Generally, cytologic smears may be superior to FS for diagnosis of glioma as the thick, coarse neoplastic glial fibrils are better demonstrated while carcinoma has sharp cell borders with no cellular process and displays a cohesive cluster (Fig 1A, B).[1,7,10,11] Although glial fibrils are important characteristics of gliomas, their distribution can vary from tumor to tumor or within the same tumor. Moreover, they might not be well developed in high grade gliomas which leads to misinterpretation as carcinoma on cytologic smears.[11] In this circumstance, palisading necrosis and/or microvascular proliferation which are characteristics of high grade gliomas, if present, are helpful. These features are better observed on FS than cytologic preparation. Other pitfalls in tumor classification in the present study were misdiagnoses between meningioma, carcinoma and glioma (Table 3). Meningioma is a non-neuroepithelial CNS tumor derived from arachnoidal cells and has complex interdigitating cell processes.[11,12] The most common diagnostic characteristic of meningiomas is whorl formation. However, meningiomas have varied growth patterns and whorl formation can be absent. On cytologic preparation, meningiomas often show clustering and cohesiveness mimicking metastatic carcinoma. The presence of pink wispy cytoplasm, ill-defined syncytial cellular border, delicate, bland-looking nuclear chromatin, and intranuclear pseudoinclusion are diagnostic clues for meningiomas (Fig 2A).[11,13] To differentiate meningiomas from gliomas, careful observation of the cytoplasmic

TABLE 3. Pitfalls of intraoperative diagnosis in tumor type classification.

Final diagnosis	Intraoperative diagnosis	Number
Glioblastoma	Metastatic carcinoma	2
	Atypical meningioma	1
Anaplastic astrocytoma	Metastatic carcinoma	1
Anaplastic oligoastrocytoma	Metastatic carcinoma	1
Anaplastic oligodendroglioma	Malignant lymphoma	1
Diffuse astrocytoma	Ependymoma	1
	Non-neuroepithelial tumor	1
Oligodendroglioma	Low grade astrocytoma	1
	High grade astrocytoma	1
Ependymoma	Low grade astrocytoma	1
	Meningioma	2
Ganglioglioma	High grade glioma	1
	Low grade spindle cell tumor	1
Meningioma	Schwannoma	2
	Metastatic carcinoma	1
	High grade glioma	1
	Low grade glioma	1
Schwannoma	Low grade glioma	1
CNS primitive neuroectodermal tumor	Germinoma	3
	Malignant lymphoma	1
	Metastatic small cell carcinoma	1
Atypical teratoid/rhabdoid tumor	High grade glioma	1
Malignant lymphoma	High grade glioma/glioblastoma	2
	Low grade glioma	1
	Germinoma	1
Germinoma	High grade glioma	1
	Malignant lymphoma	1
Endodermal sinus tumor	Teratoma and mixed germ cell tumor	1
Pituitary adenoma	Germinoma	1
	Malignant lymphoma	1
	Neuronal tumor	1
Papillary tumor of pineal region	Germinoma	1
Olfactoryneuroblastoma	High grade glioma	1
Malignant melanoma	Meningioma	1
Choroid plexus carcinoma	Embryonal tumor	1
Metastatic small cell carcinoma	Malignant lymphoma, small cell type	1

processes and nuclear details of tumor cells can hint at the diagnosis. In addition, imaging information of tumor location can be helpful since meningiomas are often located extra-axially while gliomas are mostly intra-axial tumors.

Misdiagnosis of tumor type during IC can have an effect on clinical management in certain types of tumors in which surgery is not a primary role of treatment, for example, hematologic malignancy and germinomas. In our report, malignant lymphomas were often interpreted as gliomas or germinomas and vice versa. Cytologically, lymphoma cells are discohesive on smears. They possess large, coarse

TABLE 4. Pitfalls of intraoperative diagnosis in non-neoplastic category.

Final diagnosis	Intraoperative diagnosis	Number
Inflammation/infection	Low grade glioma	5
	Malignant lymphoma	1
Demyelination	Reactive gliosis	2
	Low grade glioma	1
Ischemia/infarct	Low grade glioma	2
Hemorrhage	Low grade glioma	1
Papillary endothelial hyperplasia	Spindle cell neoplasm	1
Normal pituitary tissue	Meningioma	1

chromatic nuclei with irregular and convoluted nuclear borders (Fig 1C). Moreover, lymphoma cells infiltrate into surrounding brain tissue and can induce reactive gliosis. If tissue sent for IC is taken from the gliotic area, lymphoma cells may be enmeshed in the glial network and hence lead to diagnosis of glioma (Fig 1D).[11] To avoid this pitfall, interpretation of such a case should be taken in an area that lymphoma cells spread away from the gliotic background where typical cytologic details of lymphoma cells are discernable. Other clues that might be helpful are location and pattern of tumor involvement. Multiple deep seated tumor masses situated close to the lateral ventricles are more common in lymphomas.[14] Characteristically, germinomas are biphasic and composed of

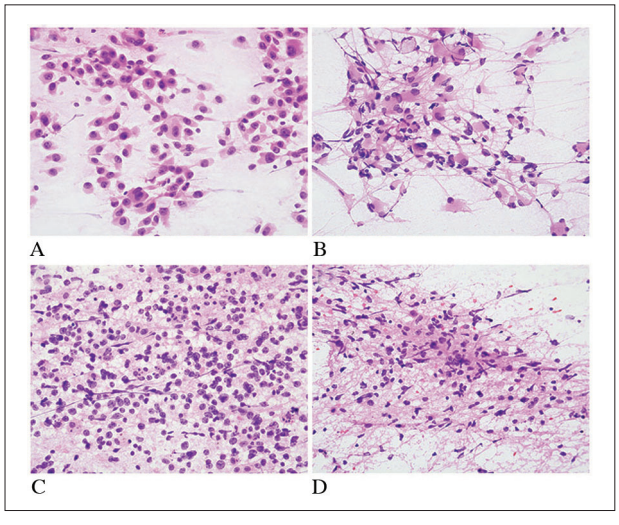

Fig 1. (Hematoxylin and eosin, x400) (A) Smear from metastatic carcinoma, tumor cells arrange in cohesive cluster and display sharp cytoplasmic border. (B) Smear from glioblastoma shows thick and coarse fibrillary processes characteristic of glioma. (C) Malignant lymphoma in well-spread area displays discohesive cells with hyperchromatic nuclei, conspicuous nucleoli and scant cytoplasm. (D) Area of lymphoma infiltrating brain tissue shows glial background and may lead to diagnosis of glioma. Interpretation should be avoided in this area.

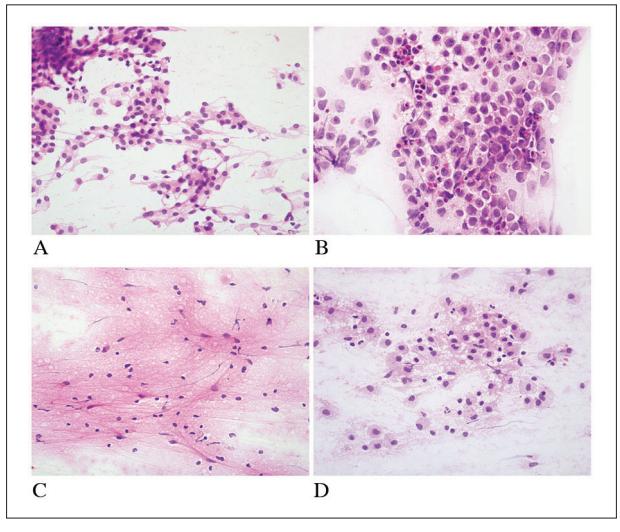

Fig 2. (Hematoxylin and eosin, x400) (A) Smear from meningioma shows monotonous tumor cells with syncytial sheet, delicate nuclear chromatin and broad non-fibrillary cellular processes. (B) Germinoma shows large, round neoplastic cells with prominent nucleoli and abundant cytoplasm. Small reactive lym phocytes are noted. (C) Reactive astrocytes have radiating, fine glial fibrils, small nuclei, and fine nuclear chromatin. (D) Foamy histiocytes usually found in non-neoplastic lesions show sharply defined cell borders, granular cytoplasmic content and small bland nuclei.

moderately large tumor cells and small reactive lymphocytes. In contrast to lymphomas, germinoma cells possess discrete cell membranes, relatively abundant cytoplasm, and prominent eosinophilic nucleoli (Fig 2B). Lymphoid cells in germinoma are non-neoplastic mature small lymphocytes. However, distinguishing between germinoma and lymphoma can be frustrating as some subtypes of lymphoma can contain highly anaplastic cells and lymphoplasmacytic reaction in germinoma can be florid which obscures germinoma cells. In this circumstance, clinical information including patient's age and tumor location may be helpful. Most germinomas affect individuals younger than 25 years of age while CNS lymphomas mostly occur during 6^{th}-7^{th} decades except for immunocompromised individuals in which lymphomas can occur at younger ages.[12,13] Common locations for germinomas include third ventricle, pineal gland and suprasellar region while 60% of lymphomas involve supratentorial location with predominant hemispheric involvement. Approximately 25-70% of lymphomas are multiple.[12,14] If the diagnosis between these two entities is still uncertain, communication to the neurosurgeon is encouraged. Generally, both tumors are treated by chemotherapy and/or radiation. Surgical procedure is usually performed to obtain tissue diagnosis, but not for tumor removal. In this situation, the pathologist should ensure that other tumors requiring surgical removal e.g. gliomas or metastatic carcinomas are excluded.

The second most common error in IC of neoplastic lesions was deviation of tumor grading and most of them were undergrading of gliomas. Grading of infiltrative gliomas was based on WHO criteria.[12,15,16] Astrocytic tumor nuclei are larger, darker and more pleomorphic than those seen in reactive astrocytes. Low grade or WHO grade II gliomas show moderately increased cellularity compared to normal brain. Mitosis is rare. Necrosis and microvascular proliferation are absent. As this tumor progresses to higher grade, cell density, degree of pleomorphism and mitotic rate are increased. Necrosis and endothelial proliferation are present. In small tissue samples such as samples received during IC, the presence of single mitosis along with increased cellularity is considered sufficient for the diagnosis of high grade glioma according to the current WHO classification.[12] Upon carefully review of those undergrading cases, high grade features were recognized either on smear or FS. In 11 out of 12 undergrading gliomas, increased cellularity with presence of mitosis was identified. One case of glioblastoma which was diagnosed a slow grade glioma during IC, was later identified as microvascular proliferation on FS. Some studies suggested that in this circumstance FS is superior to smear in order to demonstrate palisading necrosis and microvascular proliferation due to better architectural preservation.[7] Two cases of undergrading meningiomas were papillary meningiomas. Papillary meningioma is a rare subtype of high grade meningiomas.[12,15,16] Making the diagnosis of papillary meningioma requires the presence of papillary configuration in more than 50% of the whole lesion. Its cytomorphology is usually low grade, but it has aggressive behaviour corresponding to WHO grade III.[12,16] Both cases were diagnosed as low grade papillary neoplasm on IC due to its histology.

In our study, the accuracy of IC of non-neoplastic lesions was lower than that of neoplastic lesions, similar to the report from Plesec et al.[3] The most common error was misdiagnosis of non-neoplastic lesions as neoplasms, especially gliomas. These lesions included inflammation/infection, demyelination, ischemic, and hemorrhagic strokes (Table 4). These lesions are usually accompanied by reactive gliosis which is a common CNS response to various stimuli. Astrocytes proliferate and are responsible for this reaction. The degree of astrocytic proliferation in reactive gliosis can be similar to low grade gliomas, or sometimes even as high as high grade gliomas. Presence of fine, numerous radiating and tapering glial processes favors a reactive rather than neoplastic condition (Fig 2C). In contrast to the large, hyperchromatic and irregular nuclei

of neoplastic glial cells, reactive astrocytes often show small, smooth nuclear border and relatively fine chromatin.[11,12] Furthermore, the presence of foamy histiocytes which can be found in several non-neoplastic conditions such as infarct, demyelination and inflammation should raise consideration of a non-neoplastic diagnosis (Fig 2D).[9,11,13,17]

In conclusion, reasonable accuracy of our intraoperative neuropathology service was found. Frequent discordant diagnoses in both neoplastic and non-neoplastic lesions were similar to other studies. Identifying areas of diagnostic errors can help pathologists improve their intraoperative diagnostic skills. When lesions are encountered that often cause an error, knowing their common pitfalls will help pathologists in differential diagnoses to avoid mistakes. More importantly, multidisciplinary and systematic approaches are required to overcome diagnostic limitations on small tissue samples and increase diagnostic accuracy.

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