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ORIGINAL ARTICLE

A small-scale experimental study of breast FNA consultation on the internet using Panoptiq

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Introduction To test the potential for cytopathology consultation using Panoptiq (ViewsIQ, Richmond, BC, Canada; this is a new type of whole-slide image that is made manually and incorporates video content), we investigated its application in the cytopathological diagnosis of cases that were difficult to diagnose by breast fine-needle aspiration (FNA).

Materials and methods Panoptiq files were created from liquid-based cytology slides prepared by the BD CytoRich Red (BD, Franklin Lakes, NJ) method. The slides were prepared from 23 consecutive samples of breast FNA that had been diagnosed as atypical or suspicious by the Hokkaido Cancer Center, Hokkaido, Japan. Nine volunteer reviewers, who were provided with the URL of the Panoptiq file, the

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original cytopathological diagnosis, and the clinical information, were asked to classify the cytopathological diagnosis of each case into 4 diagnostic categories (benign, atypical, suspicious, or malignant). We examined the consultation benefit (CB)—how much closer the reviewer's cytopathology diagnosis came to the final histopathological diagnosis than the original cytodiagnosis. The CB scoring system was decided in advance.

Results All 9 reviewers showed a positive total CB score and 2 reviewers showed a significantly higher CB score (Wilcoxon's signed rank test). The representative diagnosis (ie, the most frequently rendered diagnosis in each case) also showed a significant CB.

Conclusions Our small-scale experimental study, in which Panoptiq was used in the diagnosis of cases that were difficult to diagnose definitively by breast FNA, revealed a positive CB score by every reviewer and the representative diagnosis showed a significant CB. The study suggests that Panoptiq could be used for cytopathology consultation.

Introduction

Because of the small number of cytology slide glasses that can be prepared, it is difficult to develop innovative supplemental techniques that would increase its diagnostic accuracy—for example, immunocytochemistry. It is also difficult to perform cytopathology consultations. Cytopathologists have therefore focused on the potential of cytology image sharing using digital technology[1-4]; however, representation of the 3-dimensional structure of a cell or cell clusters on whole-slide images (WSIs) or still images has been considered difficult.[5,6] Recently, ViewsIQ (Richmond, BC, Canada) has developed a system, Panoptiq, in which WSI files are manually created with the incorporation of video.[7,8] In order to examine the potential application of Panoptiq in cytopathology consultation for breast FNA cases, we conducted an experimental study in which Panoptiq was applied in the cytopathological diagnosis of cases in which a definitive diagnosis was difficult to make. Volunteer reviewers participated in this study.

Materials and methods

The outline of research objects is as follows. Breast fine-needle aspiration (FNA) cytology samples submitted to the Division of Pathology of the Hokkaido Cancer Center,

Table 1 Detail of the cases.

Case	Age decade	Sex	Original CytoDx by HCC	Histopathological diagnosis	Benign or malignant
1	60s	F	Suspicious	Invasive ductal carcinoma of lt. breast	Malignant
2	60s	F	Atypical	c/w Fibroadenoma of rt. breast	Benign
3	70s	F	Suspicious	Ductal carcinoma in situ of rt. breast	Malignant
4	60s	F	Suspicious	Invasive ductal carcinoma of rt. breast	Malignant
5	70s	F	Atypical	Mastopathy	Benign
6	40s	F	Suspicious	Invasive ductal carcinoma of lt. breast	Malignant
7	80s	F	Atypical	Invasive ductal carcinoma of rt. breast	Malignant
8	70s	F	Atypical	Invasive ductal carcinoma of lt. breast	Malignant
9	60s	F	Atypical	Invasive ductal carcinoma of rt. breast	Malignant
10	50s	F	Suspicious	Invasive ductal carcinoma of lt. breast	Malignant
11	70s	F	Atypical	Ductal carcinoma in situ of rt. breast	Malignant
12	70s	F	Atypical	Intraductal papilloma of rt. breast	Benign
13	30s	F	Atypical	c/w Intraductal papilloma, lt. breast	Benign
14	70s	F	Atypical	Ductal carcinoma in situ of rt. breast	Malignant
15	60s	F	Atypical	Invasive ductal carcinoma of rt. breast	Malignant
16	80s	F	Atypical	Ductal carcinoma in situ of rt. breast	Malignant
17	40s	F	Atypical	No evidence of malignancy in lt. breast	Benign
18	80s	F	Suspicious	Apocrine carcinoma, lt. breast	Malignant
19	60s	F	Atypical	Invasive ductal carcinoma of rt. breast	Malignant
20	60s	F	Suspicious	Ductal carcinoma in situ, rt. breast	Malignant
21	60s	F	Atypical	Intracystic papillary lesion of rt. breast	Benign
22	40s	F	Suspicious	Mucinous carcinoma of lt. breast	Malignant
23	70s	F	Suspicious	c/w Apocrine carcinoma in situ of lt. breast	Malignant

Abbreviations: c/w, consistent with; CytoDx, cytodiagnosis; HCC, Hokkaido Cancer Center; lt., left; rt., right.

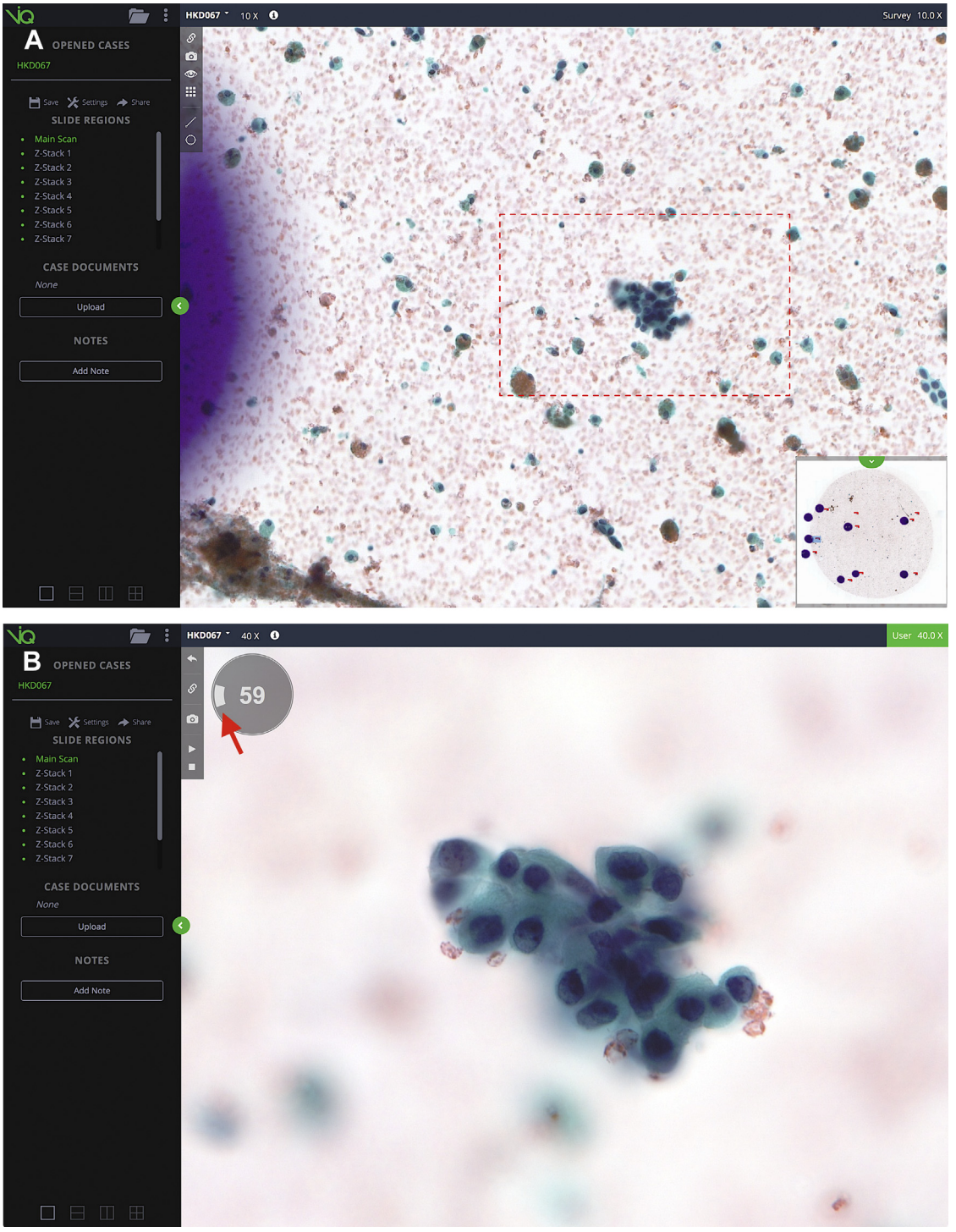

Figure 1 A, The Panoptiq screening window. The file was scanned manually using a 10x lens. Double-clicking on the red dashed rectangle transfers to the video window. B, The Panoptiq video window. The video was recorded using a 40x lens. The microscopic field was recorded with changing focus. The gray nob (red arrow) can change the focus. This makes it possible to grasp all of the features of the cells and cell clusters.

Hokkaido, Japan (HCC) from January 1, 2014, to December 31, 2015, were prepared by 2 methods: direct smear and liquid-based cytology (LBC) using BD CytoRich Red (BD, Franklin Lakes, NJ) intended for aspiration syringe content.[9,10] The original cytological diagnoses by the HCC were "atypical" or "suspicious"[11,12]; and the histopathological diagnoses were determined later. We finally obtained 23 LBC preparations in which the number of cells were

Table 2 Correspondence table showing the score of consultation benefit when 3 types of diagnoses are combined together.

Final histopathological diagnosis	Primary cytopathology diagnosis by HCC	Reviewer's cytopathology diagnosis			
		Benign	Atypical	Suspicious	Malignant
Benign	Atypical	1	0	−1	−2
	Suspicious	2	1	0	−1
Malignant	Atypical	−1	0	1	2
	Suspicious	−2	−1	0	1

Abbreviation: HCC, Hokkaido Cancer Center.

comparable to those in direct smears. The original cytological diagnoses included atypical (n = 14) and suspicious (n = 9). The details of the cases are shown in Table 1.

Two cytotechnologists who had not been involved in the original cytological diagnosis created the Panoptiq files independently. They were provided with the comments on the cytology finding and diagnosis by the HCC in each case, the clinical information, and the LBC preparation with the original markings for cells of interest. Using a 10x lens, the WSI file was created through the manual scanning of the circular area on which the cells were exclusively laid. The file creators were asked to record several videos (up to 10) mainly of the marked cells using a 40x lens. The videos included a microscopic field with a changing focus. Forty-six files were uploaded onto a cloud server (Fig. 1A, B).

After the files were uploaded on the cloud server, we recruited volunteer reviewers and launched the experiment. The selection was never limited to breast FNA specialists and reviewers were not asked for abundant experience. Cytologists, who of course do not finalize the diagnosis, are deeply involved in nongynecologic cytopathology including diagnosis, and we decided to adopt them as reviewers. The

Table 3 Nine reviewers' cytodiagnoses in each case.

Case	Original CytoDx	Histology	Reviewer's CytoDx				Representative CytoDx
			Benign	Atypical	Suspicious	Malignant	
1	Suspicious	Malignant	1	0	4	4	Suspicious
2	Atypical	Benign	5	4	0	0	Benign
3	Suspicious	Malignant	1	1	4	3	Suspicious
4	Suspicious	Malignant	0	0	1	8	Malignant
5	Atypical	Benign	3	5	1	0	Atypical
6	Suspicious	Malignant	0	5	1	3	Atypical
7	Atypical	Malignant	0	2	4	3	Suspicious
8	Atypical	Malignant	2	4	1	2	Atypical
9	Atypical	Malignant	0	2	4	3	Suspicious
10	Suspicious	Malignant	0	1	6	2	Suspicious
11	Atypical	Malignant	2	4	2	1	Atypical
12	Atypical	Benign	2	5	0	2	Atypical
13	Atypical	Benign	1	6	1	1	Atypical
14	Atypical	Malignant	0	4	3	2	Atypical
15	Atypical	Malignant	3	4	2	0	Atypical
16	Atypical	Malignant	0	3	4	2	Suspicious
17	Atypical	Benign	3	2	2	2	Benign
18	Suspicious	Malignant	1	1	5	2	Suspicious
19	Atypical	Malignant	0	7	2	0	Atypical
20	Suspicious	Malignant	0	0	3	6	Malignant
21	Atypical	Benign	5	3	1	0	Benign
22	Suspicious	Malignant	0	2	3	4	Malignant
23	Suspicious	Malignant	0	1	4	4	Suspicious

Abbreviation: CytoDx, cytodiagnosis.
Number provided is number of diagnostic categories by reviewers.
Representative diagnoses were decided according to the following rules:
1. The most frequently rendered diagnosis is chosen.
2. If there are multiple frequently rendered diagnoses with the same number, the diagnosis matching the original cytodiagnosis of the HCC is adopted.
3. Situations other than those above are excluded from the study object.

reviewers were given a URL to access the file, the original cytopathological diagnosis, the original comments on the cytological findings, and clinical information about each case. In addition to describing the comments on the cytological findings, the reviewers were asked to classify the cytopathological diagnosis of each case into 4 diagnostic categories (benign, atypical, suspicious, and malignant[11,12]) which were defined according to the probability of malignancy; these definitions were presented to the reviewers in advance. A manual on viewing Panoptiq files was provided. No specific browser applications were designated for reviewers to view the files, and the computer and Internet environment were decided by the reviewer.

The primary endpoint of the experiment was whether cytopathology consultation using Panoptiq could be performed. In particular, if the reviewer's diagnosis was adopted, how much closer would it be to the histopathological diagnosis? Thus, we decided to evaluate the consultation benefit (CB) through a scoring system based on a correspondence table that combined 3 diagnoses: the final histopathological diagnosis, the original cytopathological diagnosis, and the reviewer's diagnosis (Table 2). The Wilcoxon's signed rank test was performed to examine the increase in the reviewer's CB score (the score of the original diagnosis was considered to be 0). As the reviewers can take into account the thinking process of original diagnostician, the diagnostic accuracy of reviewer is expected to be higher than the original if they are able to correctly interpret the cytological findings obtained from Panoptiq images similar to microscopic observation. The study is thus considered as a superiority test.

The study was approved by the ethics committee of the HCC in September 2016. The committee concluded that informed consent was not needed from the patients because the study never involved the handling of personal information and simply included an uncomplicated statistical analysis of experimental diagnoses.

Results

Nine volunteers (A to I), including 2 cytopathologists and 7 cytotechnologists, joined the experiment as reviewers. The

Table 4 Evaluation of consultation benefit in each case.

Case	Reviewer									Representative
	A	B	C	D	E	F	G	H	I	
1	1	0	1	0	0	0	1	−2	1	0
2	1	0	0	1	1	0	1	1	0	1
3	0	−1	1	0	1	0	0	−2	1	0
4	1	0	1	1	1	1	1	1	1	1
5	0	1	1	1	0	0	0	−1	0	0
6	1	−1	−1	−1	0	−1	−1	1	1	−1
7	2	1	2	1	1	0	1	0	2	1
8	−1	0	1	0	−1	0	2	0	2	0
9	2	1	1	0	1	0	2	1	2	1
10	1	0	0	0	0	0	1	−1	0	0
11	0	1	1	0	−1	0	−1	0	2	0
12	0	1	0	0	0	0	−2	1	−2	0
13	0	−1	0	0	0	0	1	0	−2	0
14	2	0	1	1	1	0	0	0	2	0
15	−1	0	0	0	−1	1	−1	0	1	0
16	1	1	1	0	1	0	2	0	2	1
17	−2	−2	−1	1	0	0	1	1	−1	1
18	0	0	1	−1	0	0	−2	0	1	0
19	0	0	0	0	0	0	0	1	1	0
20	0	1	1	0	0	1	1	1	1	1
21	0	1	0	1	1	−1	1	1	0	1
22	0	1	1	−1	0	0	1	−1	1	1
23	0	0	1	−1	0	0	1	1	1	0
Score sum	8	4	13	3	5	1	10	3	17	8
Number of −2	1	1	0	0	0	0	2	2	2	0
Wilcoxon's signed rank test	0.131	0.375	0.0074	0.4354	0.1902	NA	0.1236	0.5823	0.0203	0.0264

Abbreviation: NA, not applicable.

Consultation benefits were scored according to Table 2. Scores were sorted by each reviewer and each case. When the score of the original cytodiagnosis by the HCC was considered as 0, the score of the HCC and that of the individual reviewer were compared in each case by Wilcoxon's signed rank test. The results were examined by a 2-tailed test.

diagnostic results are shown in Table 3. The distribution of the diagnostic categories is shown for each case. In 6 cases the reviewer's diagnosis was classified into 4 diagnostic categories, in 13 cases they were classified into 3 categories, and in 4 cases they were classified into 2 categories. The "representative diagnosis" was defined as the most frequently rendered diagnostic category; in the event of a tie, the same category as the original made by the HCC was adopted.

Table 4 shows the CB scores of the reviewers according to the scoring system (defined according to the combination of the 3 types of diagnosis in Table 2). All of the reviewers had a positive total score, with scores ranging from 1 to 17. Diagnoses from 2 categories that deviated toward a misdiagnosis are indicated with −2 in the table; 5 reviewers had a score of −2 in 6 cases. However, none of the representative diagnoses had a score of −2.

In comparison to the original diagnosis, the diagnoses of 2 reviewers showed significantly higher CB scores (Wilcoxon's signed rank test). The scores of the representative diagnosis were also significantly high.

Discussion

Although consultation by a highly experienced cytopathologist is expected to improve the diagnostic accuracy, there are few reports on the benefits of cytology consultation. Although the practice of referring a patient to a hospital that provides patient care and a second-opinion diagnosis has become widely established,[13-16] it is suspected that many cytopathologists still hesitate to ask for inter-institutional consultation via the exchange of glass slides for fear of losing them due to an accident.

Therefore, some cytopathologists have focused on the potential application of digital technology in cytopathology consultation. The observation objects have a 3-dimensional depth, however, that sometimes exceeds several dozen micrometers; thus, it is difficult to use conventional technologies (ie, static imaging and WSI).[5,6] On the other hand, Z-axis video for cytology (Zavic),[17,18] which uses video recording of microscopic views with changing focus, has recently been proposed. This technology makes it possible to grasp all of the features of cells and cell clusters in a way similar to "focusing through observation". A newer technology, Panoptiq, which enables the manual creation of combined WSI and Zavic files, has recently been brought to market.[7,8]

We performed an experimental study of the application of Panoptiq in cytopathology consultation. Our study design incorporated several important features: 1) the objects were cases that were difficult to definitively diagnose by breast FNA; 2) BD LBC preparations using CytoRich Red maintain 3-D cellular structures very well, which require cytologists to perform focusing through observation; 3) reviewers were provided with the original cytological diagnosis and the original comments on the cytology findings in addition to the clinical information; and 4) reviewers were widely recruited (the selection was not limited to breast FNA specialists).

In comparison to the original diagnosis by the HCC, all 9 reviewers showed positive total CB scores (although the scores varied widely) and 2 showed significantly higher CB scores (Wilcoxon's signed rank test). However, 5 of the 9 reviewers presented diagnoses that deviated toward misdiagnosis in 2 categories, and 3 reviewers showed 2 such cases. If the histological diagnosis were benign, it could result in serious consequences for the patient. Accordingly, consultants should pay careful attention to consultation in the clinical setting.

The greatest advantage of cytopathology consultation using digital technology is to collect opinions from multiple consultants in the shortest amount of time. On this occasion, we should assume that the consultants will not always be in agreement and should determine countermeasures for such cases in advance. In the present study we adopted a representative diagnosis in each case in order to exclude extreme opinions. In this experiment, none of the representative diagnoses had a score of −2; furthermore, a significant increase in the diagnostic accuracy was still observed. Therefore we conclude that Panoptiq showed its potential to perform the cytopathology consultation safely via the Internet.

Although the variation in the comments on cytological findings between the HCC and reviewers should have been studied, we decided not to do so because the comments were not systematically collected for analysis.

Of course, we have no intention of insisting that the representative diagnosis should replace the client's diagnosis in an automatic manner in future consultations. The former is just 1 example of an important opinion and the final cytological diagnosis should be decided by the client cytopathologist. But then, if all the consultants are experts in breast FNA, the representative diagnosis may be widely accepted.

Because of the small scale of our study, our hypothesis might not have been validated in the true sense. Nevertheless, it is true that our experimental study of consultation using Panoptiq in the cases that were difficult to diagnose by breast FNA yielded a positive CB score and that the representative diagnosis showed a significantly high CB. We believe that additional studies are required to validate the application of Panoptiq to remote cytopathology consultation in the near future.

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