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Telecytological Diagnosis of Space-Occupying Lesions of the Liver

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Key Words

Cytological patterns · Fine needle aspiration · Hepatocellular carcinoma · Liver · Space-occupying lesions · Telecytology · Telepathology

Abstract

Objective: In this study, the efficiency of telemedical consulting with regard to fine needle aspirates from space-occupying lesions (SOLs) of the liver is investigated for the first time. **Study Design:** The study includes fine needle aspirations from 62 patients, 33 with hepatocellular carcinoma (HCC) and 29 with non-hepatic tumors. Using the Internet-based iPath system, the initial pathologist submitted 1–8 images from smears and cell block sections. One consultant assessed the cytological and another one the histological images. Both made their diagnoses independent of each other. A final diagnosis was made by immunochemistry of cell block sections. The cytological images were analyzed retrospectively for the occurrence of the most typical HCC indicators. The number of these indicators was related to the initial diagnoses of the three pathologists, and possible reasons for diagnostic errors were analyzed based on this analysis. **Results:** The accuracy of the preliminary telemedical diagnoses regarding HCC was 82.0% for the cytological images and 87.7% for the histological images. Most of the false diagno-

ses occurred in tumors with unusual cytological and histological patterns. **Conclusions:** Telemedical consulting is a valuable tool to obtain a second opinion. However, for improvement of the diagnosis of HCC, supplementary immunochemical tests are necessary.

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Introduction

Several papers on telecytological evaluation of fine needle aspirations (FNAs) from various body sites have been published [1–4], but only few papers are available on specimens from one topographic region like the breast [5–7], thyroid gland [8, 9] or pancreas [10]. The results of these studies indicate that the accuracy of the telecytological diagnoses may considerably depend on the topographic origin of the specimen. The concordance was best for FNAs from the breast, moderate for smears from effusions and especially low for specimens from the urinary tract [11]. The main difficulty in examining FNAs from the breast is the differentiation between benign and malignant lesions. However, a broad spectrum of primary and metastatic tumors, some of which may perfectly mimic hepatocellular carcinoma (HCC) [12–14], is to be expected in FNAs from space-occupying lesions (SOLs)

Table 1. Antibodies used for IHC on cell block sections

Antibody	Cases, n
HepPar1	62
Glypican-3	58
AFP	1
TTF1	29
Cdx2	17
CK7	41
CK20	33
CK22 (Lu-5)	4
PSA	1
CD3	1
CD20	1
CD45	2
CD10	3
CD56	9
Synaptophysin	5
CD99	1
HMB45	1
PLAP	1

of the liver, similar to effusions. The phenotype of HCC is also extremely variable depending on the grade of malignancy – even an adenoid pattern may occur [15]. Moreover, analogous to urothelial lesions, the morphological differentiation between ‘dysplastic’ cells and HCC cells may be difficult [10] due to a sliding transition from reactive nuclear changes of cells in a cirrhotic liver to true cancerous atypia [16].

Therefore it seemed necessary to investigate the efficiency of telemedical consultation with regard to SOLs of the liver in more detail.

Materials and Methods

Patients

The study includes 62 patients with SOLs of the liver observed between 2008 and 2009 at two medical institutions (Anwara Medical Services and National Institute of Cancer Research and Hospital) in Dhaka, Bangladesh.

Fine Needle Technique

Each patient underwent an ultrasound-guided FNA procedure with one or two passes performed by the local pathologist (M.G.M.) using a 21-gauge needle. After each pass, the needle content was smeared on maximally three glass slides. The rest of the cells adhering to the needle and the connecting tube of the needle was washed out in saline and processed according to the cell block technique [17, 18]. The smears were fixed by immediate immersion in 95% denatured ethanol and stained with Papanicolaou stain. One cell block section was stained with hematoxylin and eosin (HE).

Telemedical Communication

For consultation with the foreign pathologists, the Internet-based iPath system was used, which had been developed at the Department of Pathology of the University of Basel, Switzerland [19]. Using a DP 20 camera[®] mounted on an Olympus BX41[®] microscope, the submitting pathologist in Dhaka (M.G.M.) captured one image at a magnification $\times 100$ –200 and one or more additional images at a magnification $\times 400$ or $\times 630$ from both the cytological and histological specimens of each patient, and uploaded them separately on the iPath server together with information on the patient’s gender and age. In a few cases, a CT or ultrasound image was also added. The images were in JPG format and image size was 400–800 pixels maximally.

Immunohistochemical Tests

The cell blocks were sent by DHL-Express to the Institute in Basel. After complete dehydration of the tissues, they were re-embedded into paraffin. Five-micrometer-thick sections were cut from the cell blocks and one section of each cell block was stained with HE; the others were kept for immunohistochemistry (IHC). The selection of antibody (table 1) for IHC depended on the initial cyto- and histological diagnoses made by the three pathologists. The evaluation of the staining results was done by estimation of the percentage of stained tumor cells and staining intensity (+/++/+++).

Diagnostic Procedure

For each case, the submitting pathologist (M.G.M.) made his diagnosis combining his observations on both the original smears and cell block specimens. One of the two consultants (D.K.) evaluated the images from cell block sections, the other (P.D.) evaluated the images from the smears. Both reviewers made their diagnoses independent of each other. In some cases, the initial diagnosis made by a pathologist consisted of a spectrum of differential diagnoses. One diagnosis marked as ‘most favored’ was regarded relevant for this study. Final diagnoses were reached by IHC tests confirming the results or if the three pathologists agreed on the diagnosis of non-HCC (N-HCC). Only the initial diagnoses of the consultants made within 24–48 h after the images were set on the iPath had some clinical relevance. The definite diagnoses were made with considerable delay and did therefore not influence the clinical procedures.

Assessment of the Number and Quality of the Digital Images

To identify possible reasons for misdiagnosis, one author (P.D.) checked (a) the number of images per case and (b) the image quality with respect to photographic quality, cellularity (3 = high, 2 = moderate and 1 = low) and staining quality irrespective of the comments offered by the consultants. Based on these parameters, the quality of both kinds of images was classified separately into 3 categories. For cytological images: *adequate* = nuclear chromatin structure and nucleoli are well represented; *sufficient* = nuclei are overstained, cytoplasm is preserved, the form of sheets is recognizable, and *insufficient* = cytological details are insufficiently represented, with low cellularity. For histological images: *adequate* = plenty of well-preserved tissue; *sufficient* = extensive necrosis, but enough well-preserved material, and *insufficient* = not enough or no intact tissue, lacking tumor tissue, overstaining or section too thick to enable a diagnosis.

Fig. 1. Nuclear chromatin pattern. **a** Monolayer sheet of normal hepatocytes. **b** Moderately differentiated HCC, prominent nucleoli, porous chromatin, intranuclear vacuoles (probably artifacts); porous chromatin and prominent nucleoli in HCC. **c** Well-differentiated HCC and trabeculae enwrapped by endothelial cells (best seen on the upper left margin). **d** Poorly differentiated HCC, 'lymphoid' cells, high cellularity and debris in the background. Papanicolaou. **a, b** Additionally magnified clippings from $\times 400$ images. **c** $\times 200$. **d** $\times 400$.

Detailed Analysis of Cytological Patterns

After completion of the case series, the cytological patterns represented by the cytological images were analyzed by the cytopathologist (P.D.) irrespective of the prior diagnosis for presence (yes/no) and grade of expression ($\emptyset$, +, ++, +++) of the following criteria, which are thought to be important for the differential diagnosis between HCC and N-HCC [20–25]: (1) tumor cell cohesion (trabeculae/clusters/dis-cohesiveness); (2) endothelial cells wrapping the trabeculae; (3) form of the atypical cells (polygonal, cuboidal, cylindrical); (4) nuclear pleomorphism (low, moderate, high); (5) size of nucleoli; (6) nuclear chromatin structure (porous, coarse, fine); (7) striped nuclei; (8) structure of the cytoplasm (granular/homogeneous); (9) nuclear/cytoplasmic ratio $>/>/>/>$; (10) giant cells; (11) pigmentation; (12) nuclear vacuoles, and (13) cytoplasmic vacuoles.

Assessment of Diagnostic Accuracy

First, the seven most relevant HCC indicators present in each of the cytological images were evaluated: (1) trabecular cell aggregations; (2) endothelial cells; (3) macronucleoli; (4) porous chromatin pattern; (5) polygonal cell form; (6) a low or moderate nuclear/cytoplasmic ratio, and (7) stripped nuclei. It was tested to what extent the preliminary diagnoses of the three pathologists were related to the occurrence of the cytological criteria to uncover the reasons for their diagnostic decisions. Finally, the accuracy of the preliminary diagnoses in relation to the final diagnoses was established. For statistical analyses, the diagnosis regarding HCC and N-HCC was regarded as true positive or true negative, and as false positive or false negative. From these data, sensitivity and specificity of the telecytological diagnoses were calculated. The χ^2 test was used to test frequency differences between groups.

Results

Forty-one of the 62 patients were male and 21 were female. Their mean age was 54.4 years (range 26–80, median 55 years). Fifteen patients were younger than 40 years.

Immunohistochemical Results

HepPar1 could be tested in 64 and Glypican-3 in 59 cases. As expected, HepPar1 was regularly expressed by well- or moderately differentiated HCC, and Glypican-3 was also expressed by poorly differentiated HCC. HCC was confirmed by IHC in a total of 33 cases. One case showing 70% positivity for Glypican-3 and few single cells positive for CK7 was attributed to the HCC group. CD10 was only tested in 2 cases, and 1 of them showed the typical canalicular staining pattern.

In 8 cases, the tests with CK7 and CK20 suggested the diagnosis of metastasizing adenocarcinoma. In 2 of 9 cases, the primary was suspected in the colon – one by Cdx2 positivity and the other by CK7 negativity but clear CK20 positivity.

Of the 14 cases tested for TTF1, 6 were positive and diagnosed as neuroendocrine small cell carcinomas, but in 3 of the 6 cases tested for CD56 only 1 was clearly positive. Another case was strongly positive for synaptophysin and CD99. Strong cytoplasmic staining for TTF1

Fig. 2. Special features of N-HCC. Papanicolaou. **a** Fine pepper-and-salt structure and discrete chromocenters/nucleoli in a poorly differentiated adenocarcinoma ($\times 400$). **b** Metastasis of adenocarcinoma: cylindric cells with excentric nuclei ($\times 400$). **c** Melanoma: cells with pigment granules ($\times 400$).

Table 2. Quality of the evaluable cytological and histological images of all cases and of the cases with a final diagnosis

Category	Cytology images	Histology images
Adequate	31 (50.0%)	25 (41.5%)
Sufficient	18 (29.7%)	30 (49.2%)
Insufficient	12 (20.3%)	6 (9.2%) ^a
Total	61 (100%)	61 (100%)

^a Includes 1 case with lacking images.

was observed in 3 cases, deemed as HCC by other tests [26–28].

Final Diagnosis

On the basis of these IHC results, a final diagnosis of malignant tumor could be made in 50 patients [33 HCC and 17 N-HCC (9 adenocarcinomas and 8 neuroendocrine small cell carcinomas)]. In another 12 cases, a definite diagnosis was made without immunochemical tests on the basis of characteristic features: 7 adenocarcinomas, 3 small cell carcinomas, 1 melanoma and 1 lymphoma (examples in fig. 1, 2).

Accuracy of Preliminary Diagnoses Compared to Final Diagnoses

The initial pathologist made preliminary diagnoses in 62 cases, the cytopathologist in 61 because of unavailability of images in 1 case, and the histopathologist in 57 because of unavailability of images in 2 cases and insuffi-

cient image quality in 3 cases. Regarding the differentiation between HCC and N-HCC, the initial pathologist achieved an overall accuracy of 80.6%, the cytopathologist of 82.0%, and the histopathologist of 87.7%. The correspondent sensitivity values were 93.9, 84.8 and 90.3%, and the specificity values were 65.5, 78.6 and 64.6%, respectively.

Influence of the Number and Quality of Images

The mean numbers of cytological and histological images per case were 4.34 and 3.95, respectively. The number of images had no influence on the accuracy of the preliminary diagnoses. The overall quality of cytological and histological images did not differ considerably, although the number of cytological images regarded as insufficient was twice that of histological images, mostly due to nuclear overstaining (table 2).

Correlation between Cytological Patterns and Final Diagnosis

A detailed morphological analysis performed in the 61 cases with confirmed HCC or N-HCC diagnoses showed that none of the thirteen criteria described in HCC can be regarded as specific. Bile pigment suggested in single cases could not be confirmed after image revision. Nuclear or cytoplasmic vacuoles occurred in only 1 of our cases and were probably artifacts.

As shown in figure 3, four or more of the seven most important cytological HCC indicators could be demonstrated on the cytological images in 18 (54.5%) of the 33 HCC, but only in 4 (14.3%) of the 28 N-HCC ($p = 0.016$). Trabecular cell agglomeration, endothelial cells wrapping the epithelial cell clusters and a porous chromatin pattern

Fig. 3. Occurrence of the seven most important HCC criteria in HCC ($n_1 = 33$) and N-HCC ($n_2 = 28$). N/C = Nuclear/cytoplasmic.

were noted 5–8 times more frequently in HCC than in N-HCC. Only one indicator was demonstrable in 4 poorly differentiated HCC. Surprisingly, even all seven parameters were found in a case of neuroendocrine large cell carcinoma (positive for TTF1 and synaptophysin).

Association between Cytological Pattern and Preliminary Cytological and Histological Diagnoses

The cytopathologist missed the correct diagnosis in 4 of the 33 HCC cases where three or less HCC criteria were present, e.g. 1 case with six demonstrable HCC indicators. Conversely, he diagnosed HCC in 6 of the 29 N-HCC cases presenting only four or less HCC indicators (fig. 4a, b). Four of the 5 cytologically misdiagnosed HCC showed only scattered naked nuclei, relatively fine nuclear chromatin pattern and no macronucleoli. Consequently, his diagnosis was ‘carcinoma’ or ‘malignant tumor’ and in 1 case ‘lymphoma’. One of the incorrectly diagnosed HCC showed elongated nuclei and was therefore misdiagnosed as adenocarcinoma.

Though the cytological parameters were used as the basis, the histopathologist misdiagnosed N-HCC in 3 of the 31 HCC cases. He also misdiagnosed HCC in 4 of the 26 N-HCC cases; all 7 misdiagnosed cases showed four or less HCC indicators in the cytological images (fig. 4c, d).

The submitting pathologist made the diagnosis of N-HCC in 2 of the 33 HCC cases, in which six HCC criteria were found on the cytological images. He made the diagnosis of HCC in 12 of 28 N-HCC cases. In most of these cases, four or less HCC indicators were present on the cytological images (fig. 4e, f).

Discussion

The aim of this study was to determine to what extent telemedical consultation can be used to improve the diagnosis of HCC and which factors influence the results. The accuracy obtained by other telemedical studies on various lesions varied between 48 and 99% [1, 2, 4, 5, 7, 8, 10, 29]. The accuracy of cytological and histological differentiation between HCC and N-HCC achieved in our study on the original slides and on digital images by the three pathologists was similar, ranging between 78.7 and 87.7%. A definite diagnosis based on morphological criteria alone, like pigmented cells in melanoma, or form and clustering of cells in some other tumors, could only be made in few cases. In the majority of cases, immunochemical tests were indispensable for a definite diagnosis.

The results of our study evoke the important question of what factors prevent an even higher level of accuracy. Known factors influencing diagnostic accuracy are the selection of the fields of view by the submitting pathologist, image quality and professional competence of the consultants [2, 4, 30]. In our study, however, these factors certainly did not play a prominent role because the participants are experienced pathologists having worked together for many years.

Khurana et al. [16], who compared subtyping of liver tumors on the original smears and on cell block sections, found that histology was slightly more successful (82%) than cytology (72%). In our study, diagnostic accuracy was also slightly higher on histological (87.7%) than on cytological images (82%).

It seems reasonable to assume that in our study the preliminary telemedical diagnoses were principally equivalent to the diagnoses made on the original smears and tissue sections. But it must be kept in mind that the diagnoses made by the three pathologists are mostly ‘hedged diagnoses’ [5, 31], i.e. they made their diagnoses with caution, e.g. ‘in favor of HCC’ or ‘immunochemical confirmation necessary’.

To check the reliability of diagnoses, they were correlated with the presence of the seven cytological criteria regarded most discriminating between HCC and N-HCC

Fig. 4. Accuracy of the diagnoses (Dg) with the immunochemically confirmed HCC diagnosis and N-HCC with a definite diagnosis in relation to the seven most important cytological HCC criteria. **a, b** Cytopathologist. **c, d** Histopathologist. **e, f** Submitting pathologist.

[15, 20, 22–24, 32–36]. Principally, the detailed morphological analysis confirmed the relevance of these HCC criteria: the more of these indicators were expressed, the more often the diagnosis of HCC was made, whereas the correct diagnosis of N-HCC was made more often in tumors in which only few of these parameters were demonstrated on cytological images. The relatively close relationship between diagnoses of the two consultants and the parameters evaluated on cytological images weakens the possible objection that their diagnoses could be biased, for instance, by the anticipation of a large number of HCC cases in an Asian country.

There were two kinds of understandable misdiagnoses. The first was a wrong diagnosis of N-HCC in immunochemically confirmed poorly differentiated HCC completely lacking HCC criteria or expressing only few of them, such as scattered stripped nuclei. It is well known that in these cases the spectrum of differential diagnoses comprises a lot of tumors like cholangiocellular carcinomas, lymphoma, and metastases from neuroendocrine

small cell carcinomas, islet cell carcinomas of the pancreas, amelanotic melanomas and even from granular cell tumors [21, 37]. The second misdiagnosis occurred in a case of neuroendocrine large cell carcinoma presenting all HCC indicators, which is in accord with other authors conducting similar studies [38]. Thus, the results of our study concur with observations summarized by the Cytology Committee College of American Pathologists: any single one of these HCC indicators is not specific for HCC and may also occur in N-HCC and vice versa [16, 39–41].

Conclusion

Telemedical consulting offers improvement in diagnostic efficiency [1, 42], but a fully accurate differential diagnosis between HCC and N-HCC is only possible by combining FNA with immunochemical tests, as suggested by others [15, 16, 39].

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