Static Image Telepathology in Routine Surgical Pathology Diagnosis: A Report on the First Experience in the Arab World from Kuwait

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Key Words
E-mail · Telepathology · Telediagnosis · Telemedicine · Digital images · Internet

Abstract
Objective: Telepathology (TP) diagnosis is currently practiced in several countries. The present study presents the first documented experiment of static-image TP in Kuwait and the Arab world. Materials and Methods: Paraffin or frozen tissue sections of 100 cases of routine surgical pathology consisting of 40 malignancies, 10 benign neoplasms and 50 nonneoplastic conditions were studied. Diagnostic microscopic images captured by a microscope-attached digital camera were selected by a pathologist in each case and sent with the clinical history to a second pathologist via E-mail across the Internet. The diagnosis was sent back to the referring pathologist via E-mail. The specificity, sensitivity and diagnostic accuracy of TP was calculated. Results: For malignant versus benign lesions, the diagnostic accuracy was 97% with 3 false-negative and no false-positive results (100% specificity). Correct diagnosis by exact category was 92%. The deferral rate awaiting special stains was 5%, immunohistochemistry 6%, and extra images 2%. In 2 cases (2%), there was a request for original tissue glass slides. Conclusion: A simple E-mail-based TP system provides a high diagnostic accuracy for routine surgical pathology diagnosis. It can be utilized either as a primary or a secondary diagnostic tool.

Introduction
The term ‘telepathology’ (TP) has been coined to describe the process of establishing a pathological diagnosis at a distance using transmitted images rather than light microscopy [1, 2]. The potential value of distant
Fig. 1. Monitor view of a frozen section of an invasive lobular carcinoma of the breast correctly diagnosed by TP. Immunohistochemistry for cytokeratin was however requested to confirm the diagnosis. HE. × 20.

medical diagnosis was realized as early as the 1970s [3, 4]. However, it took experts several years to acquaint themselves with the technical complexities of this newly developing field [5, 6]. The availability of Internet communication has provided experts with a simple and economic way to exchange information for medical diagnosis including that of pathology [6]. Nowadays several countries run various types of TP diagnostic services, and pathologists are becoming increasingly confident using this modality [6–9]. TP has been used either for primary or secondary diagnosis, or as a means of exchange of scientific data and teaching material. Several academic pathology departments have developed their own web pages on which TP services are offered to distant users. The current paper describes the first documented TP study in the Arab world.

Material

For this study, representative tissue sections of 100 cases were blindly chosen by one pathologist (I.M.F.) from the pathology archives of the Mubarak Al-Kabeer teaching hospital. These cases represented a spectrum of histological diagnoses, roughly reflecting the practice in the hospital. The 100 cases consisted of 15 frozen sections (fig. 1) and 85 paraffin sections stained routinely with hematoxylin and eosin (HE). The 85 paraffin sections belonged to either large surgical resections (65 cases) or small endoscopic or core needle biopsies (20 cases; fig. 2–5). The average number of glass slides per case was 2.1 (range 1–5). Special histochemical stains or immunohistochemical tests were only reviewed but were not included in the initial phase of the study until asked for as explained below. Table 1 summarizes the distribution of the 100 selected cases by organ/site and diagnosis.

Methods

Each case was given a serial identification number known only to the selecting pathologist (I.M.F.). Tissue sections were examined with an Olympus light microscope (BX50) equipped with a color video camera (JVC Model No. TK-8690E). The video camera was connected to an IBM compatible personal computer (PC; 166 MHz processor speed and 32 megabyte (Mb, RAM) via a commercially available video capture device (PixelView, PV-CL544XP+). The video card had a built-in 2-Mb memory capacity. The video card and its software allowed direct live viewing of each microscopic field on the PC monitor. Once a representative microscopic field was seen, it was captured and
Fig. 2. a High-magnification monitor view of a signet ring cell carcinoma in a gastric biopsy paraffin section. The diagnosis was suggested, but the final opinion was deferred awaiting cytokeratin immunostaining of the lesion. HE. × 400. b Positive cytokeratin staining of the lesional cells permitted a definitive final TP diagnosis of a signet ring cell carcinoma. Avidin-biotin immunostain for cytokeratin. × 200.

stored as computer files under its case serial number. The video card software allowed storing color images as microsoft bitmap format usually abbreviated as BMP. The image color depth was set to 24 bits (true color) which is the highest color depth obtained on our PC monitor. Image depths of lower color content (8 and 16 bits) could not be captured by our video card. The image resolution ranged between 320 × 440 and 640 × 840 pixels. The initially captured BMP image size ranged between 400 and 1,000 kb (average 630 kb). Using a commercially available image processing software (Adobe photoshop 4), each image was converted into a JPG format, compressed into a smaller size and stored in a unique file under its corresponding serial number. The new JPG images ranged in size between 40 and 80 kb (average 74 kb). Image conversion to JPG format and compression were necessary to permit easy transfer via the Internet. Each image was evaluated before and after conversion and compression and was judged to be of equal quality. Depending on the diagnosis, the number of images taken per case ranged between 4 and 14 (average 6). The average total size of all images per single case was 880 kb (range 760–1,200). A clinical history extracted from the original pathology request form in addition to information on specimen or tissue site was included as a text file.
Fig. 3. High-magnification monitor view of an intralymphatic adenocarcinoma metastasis in a gastric biopsy. The diagnosis was suggested but deferred awaiting the actual glass slide of the lesion. HE. ×400.

Fig. 4. Monitor view of a cytomegalovirus-infected renal transplant correctly interpreted by TP. No further confirmatory test was requested. HE. ×400.

and stored under its respective case serial number. Using an E-mail software provided with an Internet browser (Netscape 4.03), each case was sent as an attachment file identified by its respective serial number to a second pathologist (T.A.J.) who was unaware of the final diagnosis. The receiving pathologist had to open his E-mail, download the images and read the accompanying clinical data. His task was to interpret the images as actual microscopic fields and to formulate a diagnosis similar to real-life practice. The recipient pathologist had more than 25 years of experience in surgical pathology diagnosis but had had no previous experience with TP or image interpretation on a computer monitor prior to this study. If a diagnosis was possible to make on the received HE images, it was E-mailed back as text file, marked with the case serial number, to the referring pathologist or alternatively additional tests could be asked for. When a final diagnosis was formulated on the 100 cases, the sensitivity, specificity and diagnostic accuracy were calculated with the proper formulae [10, 11]. The E-mailed images were transferred to the second pathologist via a local Internet server of our faculty computer department to simulate real TP situations. For image downloading the distant pathologist required only his PC, a monitor and a connection to the Internet. For image
Fig. 5. A monitor view of a testicular seminoma in a 29-year-old male. Several images representative of the entire lesion were sufficient to render a diagnosis by TP. HE. ×400.

Results

Table 2 provides a summary of the overall diagnostic accuracy of TP in the 100 studied cases. With regard to malignant versus benign diagnoses the false-positive rate was 0.0% and the false-negative rate was 3.0% with 100% specificity and 97.0% diagnostic accuracy. The diagnostic accuracy was highest in the paraffin sections taken from the large resection specimens (98.4%) and was lowest for the frozen sections and paraffin sections of small biopsies (93.3 and 95.5%). The overall diagnostic accuracy for precise categorical diagnosis was generally lower in all biopsy types ranging between 86.6 and 95.0%.

Three false-negative diagnoses of malignant cases were made (3.0%). One case was a frozen section taken from a small ductal carcinoma in situ lesion of a female breast. No invasive component was seen in the section used for TP, but the in situ part was missed by the recipient pathologist. During the actual frozen section diagnosis other areas of the tumor were seen permitting a definitive diag-

<table>
<thead>
<tr>
<th>Source of specimen</th>
<th>Total</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>21</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Kidney</td>
<td>9</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Breast</td>
<td>18</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>16</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Bone</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Lymph node</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>9</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Prostate</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 1. Summary of 100 pathology cases used in the static image TP study
nosis of malignancy. The second false-negative case was an extensively necrotic gastric lymphoma which was diagnosed as a benign gastric ulcer. When shown the original glass slide, the pathologist had no hesitation in arriving at the correct diagnosis. On the other hand, when the TP images were re-examined by the same pathologist, he accepted that at least a suggestion of a malignant process could have been made. The third case was a lymph node from a 21-year-old male who was diagnosed as having lymphocyte-predominant Hodgkin’s lymphoma. The TP diagnosis based on the referred images was that of a reactive lymph node. Review of the referred TP images disclosed that only one Reed-Sternberg cell could be seen against a background of benign-looking lymphocytes. On reviewing the images the pathologist could not confidently arrive at a diagnosis of Hodgkin’s lymphoma. An incorrect diagnosis by category or disease entity was rendered in 8 cases (8%; table 2). Among these, 2 were made for frozen sections including the false-negative result of a female ductal carcinoma in situ called benign fibrocystic disease and a thyroid col-
Table 2. Summary of sensitivity, specificity and diagnostic accuracy of E-mail-based TP diagnoses in 100 surgical pathology specimens compared to primary diagnosis

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Malignant versus benign diagnosis</th>
<th>Total number</th>
<th>Overall TP diagnosis by category including benign and malignant incorrect¹ correct diagnosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FP</td>
<td>FN</td>
<td>SEN, %</td>
</tr>
<tr>
<td>Frozen section</td>
<td>0</td>
<td>1</td>
<td>90.0</td>
</tr>
<tr>
<td>Paraffin section</td>
<td>0</td>
<td>2</td>
<td>93.3</td>
</tr>
<tr>
<td>Large resection</td>
<td>0</td>
<td>1</td>
<td>95.0</td>
</tr>
<tr>
<td>Small biopsy</td>
<td>0</td>
<td>1</td>
<td>90.0</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>3²</td>
<td>92.5</td>
</tr>
</tbody>
</table>

There were 40 malignancies and 60 benign conditions in 100 cases. Figures in parentheses indicate malignancies. FP = False-positive; FN = false-negative; SEN = sensitivity; SPF = specificity; DA = diagnostic accuracy.

¹ This is defined as a definitive and incorrect TP diagnosis compared to the primary diagnosis and excludes cases in which a correct diagnosis was included as a differential diagnosis.

² These were: 1 case of breast carcinoma (frozen section), 1 case of a necrotic gastric carcinoma (biopsy) and a third case of lymphocyte-predominant Hodgkin’s lymphoma (node resection).

There were 40 malignancies and 60 benign conditions in 100 cases. Figures in parentheses indicate malignancies. FP = False-positive; FN = false-negative; SEN = sensitivity; SPF = specificity; DA = diagnostic accuracy.

The receiving TP consultant (T.A.J.) was able to establish either a single definitive or categorical diagnosis (84 cases, 84%) or differential diagnosis (16 cases, 16%) on all 100 cases referred to him. There was no specific complaint regarding the quality of images either with regard to size or color character; however, additional images were asked for in 2 cases (2%). A summary of the diagnostic specificity and accuracy is provided in table 2.

Glass slides were required in 2 cases (2%) including 1 gastric biopsy with a tiny focus of intralymphatic metastatic carcinoma (fig. 3) and 1 case of a degenerating benign nerve sheath tumor (ancient schwannoma). A correct differential diagnosis was however suggested in both cases based on the images prior to examining the glass slides.

Additional images (2 cases), special histochemical stains (5 cases), immunohistochemistry specimens (6 cases) or actual glass slides (2 cases) that were regarded as essential for diagnosis were sent to the pathologist upon his request. There was no request for additional clinical data on the patients. In general, downloading one E-mail case file did not exceed 1 min. The time taken to render and return a diagnosis was 24 h in most cases. An additional day was needed for cases requiring extra tests. In 12 cases (12%) special immunohistochemical and histochemical stains were
Table 3. Frequency of requested additional tests by a distant pathologist prior to establishing a final diagnosis on referred images from 100 cases of routine surgical pathology specimens

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>n</th>
<th>No additional requests</th>
<th>Special stains</th>
<th>Immuno-stains</th>
<th>Extra images</th>
<th>Glass slides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>40</td>
<td>35 (87.5%)</td>
<td>2 (5%)</td>
<td>3 (7.5%)</td>
<td>1 (2.5%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Benign</td>
<td>60</td>
<td>55 (91.6%)</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
<td>1 (1.6%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Frozen section</td>
<td>15</td>
<td>15 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Paraffin section</td>
<td>85</td>
<td>75 (88.2%)</td>
<td>5 (5.8%)</td>
<td>6 (7%)</td>
<td>2 (2.3%)</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Large resection</td>
<td>65</td>
<td>61 (93.8%)</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Small biopsy</td>
<td>20</td>
<td>14 (70.0%)</td>
<td>3 (15%)</td>
<td>4 (20%)</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

Discussion

Several studies including the present one, have now clearly established that high-quality tissue digital images viewed on a PC monitor are as good as actual light-microscopic examination of the same tissue to arrive at a correct histopathological diagnosis [12–14]. The transfer of such images to remote sites for the purpose of establishing such a diagnosis has been assigned the term TP.

Various TP system networks have been installed and tested across Europe, North America and Japan. The basic difference between such systems lies in two main aspects. The first is whether the distant pathologist has any active role in the qualitative or quantitative control of image transfer or whether he is merely a passive recipient of such images. In the former, robotic microscopes integrated in the TP system allow the distant pathologist to control the slide examination as if he/she had the actual tissue sections down his/her microscope [15]. In contrast, a passive system, similar to ours, allot full control over image transfer to the primary sending pathologist. The second point of difference is the method of image capture and transmission. This could be either in real-time video image type sequences or still/static digital images like those used in this study. Hybrid systems incorporating the above contrasting technical and physical features have resulted in five classes of TP systems. These systems were reviewed by Weinstein et al. [6]. The adoption of still image TP via the Internet has several advantages. When compared to a dynamic robotic system, it is easier to run and maintain, is technically simpler and less demanding on the part of the pathologist and could be purchased at a much lower price [6]. Additionally, with the use of Internet communication, the system could be run practically from any site with direct Internet connection or linking via a modem across a telephone line. The images could be readily archived and retrieved and

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Francis/Junaid/Dajani

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could be viewed on the monitor in a panoramic display of thumbnails (fig. 7). The main disadvantage of this system remains the lack of control of the recipient pathologist on the quality and quantity of images sent for opinion. This could, however, be overcome in two ways. With small biopsies, the entire lesion could be captured on images and referred. With larger specimens, a minimum standard set of images could be decided upon for each case depending on the lesion in question.

There is a general consensus amongst TP experts that a relatively high diagnostic yield could be achieved using referred static images from preselected microscopic fields. Our results are clearly in support of such claims. Our overall diagnostic accuracy regarding benign versus malignant specimens was 97 and 92% for precise diagnosis by exact histological entity or category. Most published studies have reported results similar to ours. Weinberg et al. [12] and Shimosato et al. [16] both reported a diagnostic accuracy ranging between 88.1 and 93.2%. A higher accuracy has recently been reported by Mea et al. [17], who managed to achieve a definitive TP diagnosis in 96.7%. It was interesting that in their study, junior as well as consultant pathologists were involved in image selection unlike our study where only a consultant pathologist was involved. In their opinion an inexperienced pathologist could be trusted to choose a sufficient number of informative images used for remote TP diagnosis. This remains to be supported by other studies though presently we believe like others that field selections is detrimental to the level of TP diagnostic accuracy.

Our material consisted of a mixture of lesions in the form of frozen or paraffin sections comprising both large resections and tiny endoscopic or needle biopsies (tables 1 and 2). Case selection purposefully reflected the spectrum of pathology practice in our hospital in this country. Our diagnostic accuracy was higher for paraffin sections (97.6–98.4%) than for frozen sections (93.3%). This could be partly attributed to the nature of the frozen section where limited material is available for examination and the significant freezing artifact commonly encountered in such material. It is interesting that no false-positive diagnosis of malignancy was rendered by the tele-
pathologist in frozen as well as paraffin sections. Such a telediagnosis of frozen sections has been successfully reported by several experts with a diagnostic accuracy ranging from 89 to 96.9% [8, 17–19].

The difference between diagnostic accuracies in small biopsies (95.5%) and large surgical resections (98.4%) was not significant. These two types of biopsies however pose two different technical problems to TP. Small biopsies can be evaluated in total since, practically, the entire tissue can be captured in digital images which can be referred for TP. For such material even an inexperienced pathologist or technician can be trusted to refer the case to distant consultants. On the other hand, larger resections require particular sampling of the lesion demanding sufficient professional experience on the part of the referring person.

The qualitative (color, resolution) and quantitative (size) parameters of TP images have not been properly identified. High-resolution images containing a high color content (16–24 bits) provide large images with excellent resemblance to light microscopy. These images are however large requiring lengthy transmission time as well as large PC storage capacity. We have clearly demonstrated that smaller-sized images with reduced resolution were regarded adequate in quality by the distant pathologist. This resulted in few requests for additional images (2%). Conversion of the BMP images to the JPG format serves two advantages. Firstly, the JPG images are significantly smaller and could be compressed into even smaller sizes. Secondly, the JPG format is the preferred one for Internet transfer and browsing. Further reduction in image file size can be achieved by using a lower color content as illustrated by Doolittle et al. [20]. In their study, pathologists who were shown colored pathology images could not differentiate between 16- to 24-bit (millions of colors, ‘true color’) and 8-bit (256 colors) images. When forced to choose, they favored color images with less color content (8 bits). In effect the combination of low image size in our study and a low color content previously described will result in considerably smaller images and thus case files. For an E-mail-based TP, smaller image files permit more thorough lesion sampling and quicker and more efficient transmission and downloading on busy Internet lines. Such images bear a close resemblance to real light microscopy examination.

In support of our view is the study by Galvez et al. [21] on the successful use of static-image TP in diagnosing cytological smears of breast aspirates. In their evaluation almost all cytological features captured by images compared closely with those of light microscopy.

**Conclusion**

The study demonstrated that a simple and inexpensive TP system utilizing internet communication can provide a high diagnostic accuracy for routine surgical pathology. Not only can it provide the much needed expert opinion for distant medical centers, but it can also promote communication between pathologists and facilitate the learning experience.

**Acknowledgment**

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References