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The validity of telepathological frozen section diagnosis with ISDN-mediated remote microscopy

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Abstract We investigated 109 randomly selected frozen section specimens from lung surgery patients in a retrospective blind mode using telepathology equipment. The telepathology system applied (HISTKOM) used one ISDN B-channel and telemicroscopy with a remotely operated robotic microscope. The performance of telepathological frozen section diagnosis was compared with that of conventional frozen section diagnosis. The false-positive rate achieved was identical for both methods. The sensitivity (P=0.03), but not the specificity, was significantly lower for the telepathological method. The time needed to establish a diagnosis with the remote microscope was too high; therefore, upgrading to multichannel technology is recommended. The quality of the images transmitted was judged to be sufficient by the pathologists involved in the study. In conclusion, with further technical improvements in telemicroscopy and additional experience in telepathology, remote diagnosis seems to be feasible.

Key words Telepathology · Frozen section diagnosis · Remote microscopy · Telemicroscopy

Introduction

"Telediagnosis" is a new and fascinating upcoming field in pathology. It allows the local separation of the site of treatment of a patient and the diagnostic pathology service [9, 12, 13, 21].

Telepathology comprises several types of pathological services at a distance:

- Beginning with a simple exchange of images between pathologists to get a second opinion on selected fields of view [12];
- And ending with inspection of a slide with a microscope at a remote station which is controlled operationally from a home station.

This second procedure allows a remote diagnosis beyond the possibility of providing a second opinion [31]. This paper is limited to the second scenario of remote diagnosis made possible by the availability of telemicroscopic tools adequate to inspect and screen a slide as if it was in the pathologist's own laboratory [23, 24]. Within the community of already active and tentative users continuing discussions are in progress concerning the minimum telecommunication channel capacity necessary to provide working conditions acceptable for the pathologists and also whether small-band connections (e.g. one telephone channel) can provide an adequate quality of diagnostic results [29]. This contribution reports the results of a study carried out with a single-ISDN-channel telemicroscopy station to evaluate the quality of such a configuration.

Experience with remotely operated microscopes in telepathology has been reported by Dunn et al. [4], Krupinski et al. [14] and Weinstein et al. [31, 32] in the USA; a research group around Nordrum and Eide [5–7, 17, 18] in Norway; Oberholzer et al. [21] in Switzerland; Fujita et al. [9] and Shimosato et al. [26] in Japan; Martin et al. [15] in France; Miaoulis et al. [16] in Greece; Gombas et al. [10] in Hungary; Szymas and Wolf [28] in Poland; Kayser and Schwarzmann [11] and Schwarzmann et al. [25] in Germany; and Cataldi et al. [3] in Italy. The most recent review of telemicroscopy-mediated telepathology can be found in a publication from Nordrum's group [19]. In the European Union an international project, EUROPATH [8], supports investigations of the opportunities of telepathology.

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The most ambitious and attractive application of telepathology is the frozen section diagnostic service for requesters without an available pathologist. This paper reports on an experiment in providing such a service based on requests for immediate and complete investigation of frozen sections in a retrospective study. The aim of the study was to evaluate the validity of frozen section diagnosis based on a remote microscope in thoracic surgery.

Materials and methods

Patients, materials and study design

The frozen sections of 109 consecutive unselected thoraco-surgical cases, which had been primarily diagnosed in routine pathology service during the period from January 1993 to March 1994, were analyzed telemicroscopically. The data from the 109 patients are listed in Table 1.

The frozen sections had been prepared according to standard frozen section procedures (using H&E staining). Based on paraffin-embedded tissue, 63 cases (58%) had been diagnosed as benign and 46 cases (42%) as malignant. Before re-examination, the frozen section specimens had been encoded and both the conventional frozen section and the conventional final diagnosis based on paraffin-embedded tissue had been separated from the written information that was made available to the pathologists in this study. The information was identical to that available at the time of primary conventional frozen section diagnosis and included clinical data and questions as well as the macroscopic description of the tissue sample. The 138 frozen sections were brought to the microscope station to ensure that the pathologists could not obtain information about the conventional diagnoses.

In our study, the distance between the microscope and display station was about 15 km. The re-examination started in June 1995, about 15 months after the last case in this study had been diagnosed for routine pathology, and ended in November 1995. It was performed by three pathologists (the authors P.F., V.V., U.W.) experienced in frozen section diagnosis; it should be noted that no collective diagnosis was made because we intended to simulate a routine frozen section service as realistically as possible in a retrospective study. At the beginning of the re-examination, the pathologist reviewed the written clinical information and questions and also the macroscopic findings of each case. Macroscopic examination of the tissue sample was not possible as the study was retrospective. At the end of the re-examination the pathologist documented the telepathological diagnosis reached, the time elapsed during the diagnostic procedure, technical disturbances and a subjective score estimating his individual acceptance of the telepathological procedure, which ranged from 0 (no acceptance at all) to 10 (acceptance equal to that of the conventional procedure). A score of 10 signifies, therefore, that the pathologist felt there was no difference in user-friendliness between the two methods.

Data assessment

After all frozen sections had been re-examined, a thoracic surgeon and two pathologists compared the telepathological and conventional frozen section diagnoses with the final diagnoses based on paraffin-embedded tissue, which were regarded as reference diagnoses or gold standard, respectively. The two pathologists came from a difference hospital than the pathologists who had performed the reexamination in this study and had not been involved in the re-examination of the frozen sections.

The telepathological and conventional frozen section diagnoses were categorized into the following groups according to how close they were to the final diagnoses:

1. Absolutely correct diagnosis
2. Essentially correct diagnosis
3. Incorrect diagnosis without implications for ongoing surgery
4. Incorrect diagnosis with implications for ongoing surgery
   a. False-negative diagnosis
   b. False-positive diagnosis
5. Deferred diagnosis

Table 1 Clinical data of the patients in the study

No. of cases	109
Gender	74 males/35 females
Age (mean±SD)	53.99±11.64
Benign lesions	63
Malignant lesions	46
Resection margin of the bronchus	11
Open lung biopsies	69
Pleura	7
Mediastinal masses	10
Pulmonal or mediastinal lymph nodes	12

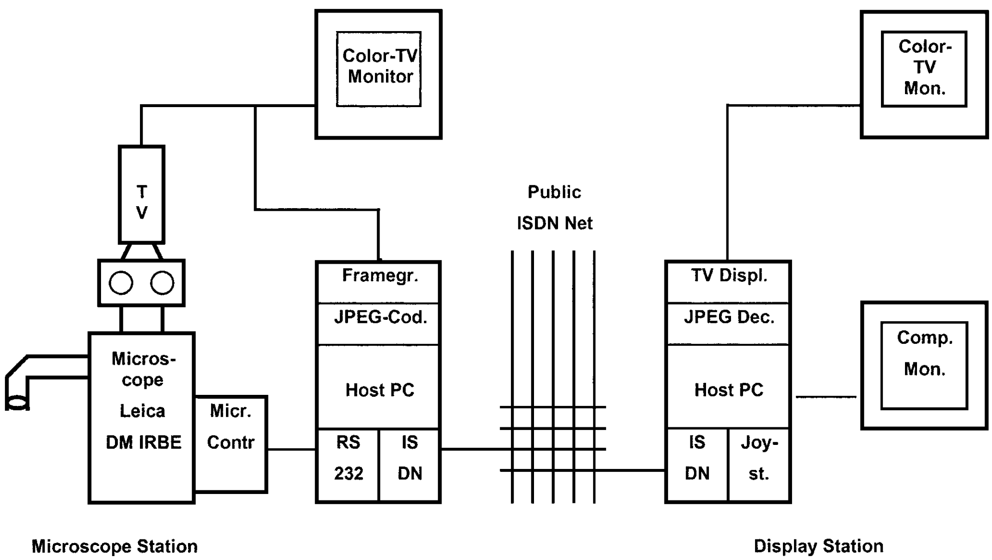

Fig. 1 Block diagram of the telemicroscopy equipment applied in the study. The display station provides a permanent macroscopic image of the tissue on the computer monitor together with the control interface for the remote microscope or an overview image of the slide under the macro channel of the microscope and the field of view of the microscope on the color TV monitor

Table 2 Comparison of the conventional and telepathological frozen section diagnoses with the reference diagnoses (paraffin section as gold standard)

Correspondence with the reference diagnosis	Telepathology	Conventional procedure
Absolutely correct	66 (60.5%)	71 (65.1%)
Essentially correct	22 (20.2%)	32 (29.4%)
Incorrect without implications for treatment	0	0
Incorrect with implications for treatment		
False-negative	9 (8.3%)	3 (2.8%)
False-positive	1 (0.9%)	1 (0.9%)
Deferred	11 (10.1%)	2 (1.8%)
No.	109	109

Table 3 Comparison of frozen section diagnoses established either by telemicroscopy or conventional frozen section technique

Frozen section diagnoses	Classification	Reference diagnoses	
		Benign	Malignant
No.		63	46
	benign	57	9
Telemicroscopy	malignant	1	31
	deferred	5	6
	benign	60	3
Conventional frozen section	malignant	1	43
	deferred	2	0

Telepathology equipment (HISTKOM)

Figure 1 outlines the device configuration of the study in a block diagram. According to the design aim (frozen section telepathology) the system is operated fully online in all functions. At the surgeon's site the equipment consists of a microscope (Leica DM IRBE with objectives 2.5×, 5×, 10×, 20× and 40×) with all functions remotely controllable. The microscope station is equipped with a high-quality color TV-camera (Sony DXL-930, 768×576 pixel); a macro imaging device (Leica Drawing gadget) to provide images of the removed tissue to guide sectioning; a monitor to display the actually transmitted scene (13-in. color TV studio monitor, Sony PVM 1370 QM); telecursors in the image to allow visually assisted communication between pathologist and surgeon and a host computer (PC). The monitor image is about half the area of the field of view in the microscope. The computer provides a framegrabber with an integrated JPEG coder (ANT FB 64) for the camera signal, the microscope control interface (RS 232) and the interface to the telecommunication network (AVM B1) and controls the complete station.

The counterpart of the microscope station is the display station at the pathologist's location. This device hosts facilities to display the transmitted image scenes of the TV camera (field of view of the microscope and macroimages of the tissue and total view of the slide, 13-in. color TV studio monitor, Sony PVM 1370 QM); a user interface to operate the remote microscope (computer monitor 15-in., Sony Multiscan 15sf2) and a host computer with JPEG decoder, D/A TV signal converter and software to control the whole station and to connect it to the telecommunication net (ISDN-net board AVM B1). The ISDN interface is connected to the software via a CAPI protocol.

In this study the two stations were connected with one active ISDN B-channel (64 kbit/s).

The channel configuration of an ISDN connection consists of the basic channel S_0, which is subdivided in two B-channels (telephone connection) with 64 kbit/s capacity each and one D-channel for signalling with a capacity of 16 kbit/s normally not used by applications.

The configuration described has an image transmission capacity (full screen) of about 0.1 frames/s depending on the richness of image details. Depending on the user activity the system control automatically selects different levels of data compression in the JPEG standard, ranging from not visible (no current request to move the slide) to only just visible compression (if the user requests continuing movement of the slide). Besides the transmission of complete images, in the scroll mode only the newly appearing parts of consecutive image frames are transmitted, which saves channel capacity and allows a moving impression of the slide (about 0.5 frames/s). The whole study was carried out with the same hardware and software configuration.

Table 4 Confusion matrix of conventional and remote frozen section diagnoses

	Conventional frozen section diagnosis	Telepathology
Correct[a]	103	88
Incorrect[a]	4	10
Correct[b]	103	88
Incorrect[b]	6	21

[a] Deferred diagnoses not included
[b] Deferred diagnoses included and classified as incorrect

Statistics

The parameters of diagnostic validity (sensitivity, specificity, positive predictive value, negative predictive value and accuracy) were calculated for both diagnostic methods and compared using the Chi-square test. In addition, kappa statistics were performed for both frozen section diagnostic methods (conventional and telemicroscopical approach).

Results

Diagnostic validity

For the 109 frozen section diagnoses 138 frozen sections were provided. The results of the comparison between the frozen section and the reference diagnoses are presented in the Tables 2–4. In Table 4, the results are ar-

Table 5 Parameters of diagnostic validity of the telemicroscopical and conventional frozen section diagnoses

	Deferred diagnoses excluded			Deferred diagnoses included		
	Telemicroscopy	Conventional method	*P*	Telemicroscopy	Conventional method	*P*
Sensitivity	0.78	0.93	0.03	0.67	0.93	0.002
Specificity	0.98	0.98	n.s.	0.90	0.95	n.s.
Negative predictive value	0.86	0.95	0.08	0.86	0.95	0.08
Positive predictive value	0.97	0.98	n.s.	0.97	0.98	n.s.
Accuracy	0.90	0.96	0.07	0.81	0.94	0.002

Table 6 Time taken and acceptance of telemicroscopical frozen section diagnosis using a one-ISDN B-channel solution

	Time taken (min)		Acceptance	
	Mean	SD	Score	SD
Pathologist A	38.0	16.1	6.8	2.9
Pathologist B	37.2	19.6	5.4	2.4
Pathologist C	66.2	17.1	6.3	1.8
Mean	47.1	17.6	6.2	2.4

ranged in the form of two confusion matrices by reduction to two classes of diagnoses – correct and incorrect. The resulting parameters of diagnostic validity are listed in Table 5.

The most critical value concerning diagnostic validity is the false-positive rate; in this study it is equal for both procedures, namely 1/109. Accordingly, telepathological and direct light microscopy show similar values of positive predictive value and specificity. The conventional and telepathological false-positive diagnosis occurred in the same sample, which was misdiagnosed as a pulmonary metastasis of known breast cancer instead of pneumonia, partly with carnification, partly interstitial, with severe alveolar dysplasia.

In this study the telepathological method shows higher rates of false-negative (9/109 versus 3/109) and of deferred (11/109 versus 2/109) diagnoses than direct light microscopy, resulting in slightly lower test efficiency (0.90 versus 0.96, P=0.07) and moderately lower sensitivity (0.78 versus 0.93, P=0.03) of the telepathological method if deferred diagnoses are excluded from the evaluation. If the deferred diagnoses are included as incorrect, a significantly lower test accuracy (0.81 versus 0.94, P=0.002) and sensitivity (0.67 versus 0.93, P=0.002) of telepathological frozen section diagnosis results. All three cases in which the conventional method yielded a false-negative diagnosis were also incorrectly classified by telepathology. These misdiagnoses were caused by subtotal necrosis or by lack of tumor tissue in the frozen section (sample error).

The times needed for correct telepathological diagnoses and for incorrect (deferred, false-positive and false-negative) ones do not differ significantly (means 45.4 min versus 54.2 min).

The estimation of the concordance between the frozen section and the reference diagnoses without consideration of the deferred cases results in kappa values of 0.78 for the telepathological and 0.92 for the conventional method. With the deferred diagnoses included the kappa values fall to 0.61 and 0.89.

Technical details of the study

In the course of the study all technical process parameters were documented, and these form the basis for continuing development of the system technology and software. Most minor disturbances could be resolved by resetting the system and resulted in a prolonged investigation time.

To estimate the amount of data to be transmitted between microscope and display station and to obtain information about the number of necessary parallel channels for routine pathology, the time necessary for each case was recorded. In this study the average time interval was 47.1 min (means ranging from 37.2 to 66.2 min, Table 6).

In addition, an acceptance score (ranging from 0–10, 10 meaning perfect acceptance) was recorded by each pathologist, resulting in an overall acceptance score of 6.2 for telemicroscopy – lower than for conventional frozen section diagnosis (acceptance score = 10 by definition). Minimal differences surfaced between the three pathologists involved in this study.

It is difficult to give an average number of transmitted images per case, because HISTKOM, as already stated in the technical section, operates not only by transmission of complete images but also by transmission of part-images in the scroll mode. The situation in this study was that the pathologists screened the whole slide more or less completely in the scroll mode and switched to higher magnifications locally where necessary. With due consideration for the additional time needed to change magnifications and to adjust the autofocus and illumination, about three full frame images per minute were transmitted. According to the time taken, as shown in Table 6, this results in inspection of about 140 images per case, with SD of about 50.

Discussion

The most criticized point in this study was the long times needed for frozen section diagnosis by telemicroscopy (mean 47.1 min). In the assessment of the time needed for the diagnosis of a case, it has to be kept in mind that the study was designed to provide primary diagnoses and not just second opinions. In all cases the slide had to be inspected more or less completely at different magnifications. It is clear that these intervals are too long for routine application. An obvious way of improving the limited data transmission capacity would be the application of eight B-channels (equivalent to four S_0-channels) in parallel resulting in a capacity of 512 kbit/s. If the telepathological system available were equipped with four S_0-channels in parallel, the figures in Table 6 could be divided by 8, which promises investigation intervals of about 5 min.

Closely connected to the time consumption is the score for convenience or acceptance of telepathology. In this study all three pathologists ranked the acceptability of the telepathological procedure at similar levels (means ranging from 5.4 to 6.8) with an overall mean value of 6.2 (on a scale from 0–10). In our view, this relatively high score is a positive result of this study.

The third point to be considered prior to the introduction of telemicroscopy for routine frozen section diagnosis is the frequency of technical disturbances, which must be minimized.

Frozen section diagnosis is an error-prone method in itself, and therefore new methods, such as frozen section diagnosis by telepathology, must be evaluated with reference to paraffin sections as gold standard. For comparison of data, the test accuracy ([true positive + true negative]/[true positive + false positive + true negative + false negative]) can be calculated. For frozen section diagnosis in breast surgery, Bianchi et al. [2] report a test accuracy of 95.8%.

Concerning the error rate and test accuracy of ISDN-mediated frozen section diagnosis, this study is, to the best of the authors' knowledge, the first to consider a frozen section service only in thoracic surgery. Oberholzer et al. [20] report a slightly higher sensitivity (85.7%) than was found in our study. Eide and Nordrum [6] and Nordrum and Eide [17] found similar values to ours, with, in particular, a test accuracy of 89.0% (11/100 misclassifications, 1 false-positive, 3 false-negative and 7 deferred diagnoses); Winokour et al. [33], a test accuracy of 96.9% (routine diagnoses without frozen section situation); Steffen et al. [27] found 89%; Fujita et al. [9], 94.9% and Adachi et al. [1], 93.2%. Our data are in the range of those reported above and reach a test efficiency of 90%, with deferred diagnoses excluded, and 81% if deferred diagnoses are included. These values represent either a trend or a statistical difference indicating a higher rate of correct diagnoses with conventional light microscopy (for discussion see below). These results, however, must be seen in the context of the following aspects of the study:

- An ISDN connection with one B-channel was used
- Frozen sections of only one organ system were investigated
- The rates of false-positive diagnoses are equal in both test systems
- A very conservative attitude preventing false-positive diagnoses was demanded from the pathologists establishing the diagnoses
- The technical progress in telemicroscopy should be kept in mind before negative conclusions on remote frozen section diagnosis are drawn on the basis of these data

The results presented in our study lead to the following conclusions:

The experimental telemicroscopy system tested in this study was awarded a moderate rank of convenience and subjective acceptance (6.2 compared to 10 for the conventional procedure) by all participating pathologists although they had never practiced telepathology before. Similar to other reports [9], technical problems never or hardly ever resulted in deferred frozen section diagnosis.

The error rates of telepathology with respect to the final diagnoses based on embedded tissue are also acceptable, especially since the false-positive rate was found to be identical to that of the conventional method. The test accuracy of frozen section diagnoses by ISDN-mediated telemicroscopy is lower than that of conventional frozen section diagnosis, but only because of a higher rate of false-negative and deferred diagnoses. In addition, the correctness of diagnoses was not influenced by the pathologist's diagnostic skill estimated by the time needed for the diagnosis.

The use of a remote microscope (dynamic robotic telepathology) provides good technical results, but a lot of time is needed for frozen section diagnosis (47 min in our study). Oberholzer et al. [21] describe a similar time requirement for a diagnostic session (between 25 and 40 min). However, this major disadvantage of frozen section diagnosis by telepathology with only one B-channel may be easily overcome by an ISDN solution with eight B-channels (currently in field testing).

Another critical issue is the future distribution of responsibility between surgeon and pathologist, especially when only the surgeon defines the location where the tissue is removed for frozen section [22]. This has legal implications for patient treatment.

In agreement with Weinberg et al. [30] and with views expressed in an editorial by Weinstein [31], and based on our own experiences [12] and present experiments, we conclude that static image telepathology is not optimal for frozen section diagnosis.

The technical insights gained in this retrospective study are being exploited in improvements of system technology and software. Currently, four successor prototype systems of the HISTKOM type are undergoing thorough field tests in about ten extended studies being carried out by different teams of pathologists and surgeons. The time needed has dropped to about 5 min and preliminary results indicate identical performance and accuracy characteristics as in the conventional procedure (data not shown here). This should lead to improved acceptance of telepathological frozen section diagnosis.

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