TITLE: Telepathology: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines

DATE: 12 July 2010

CONTEXT AND POLICY ISSUES:

Telepathology is the use of telecommunications technology to facilitate the transfer of image-rich pathology data between remote locations for the purposes of diagnosis, education, research, and external quality assessment.[1,2] The use of telepathology applies to any patient's pathology data that can be transferred using telecommunications technology. This technology is useful when there is no on-site pathologist such as in remote regions with limited access to pathology services, for intraoperative diagnoses, teletraining or for obtaining second opinions.[3,4] Alternatives to telepathology are conventional light microscopy and on-site pathologist consultation or direct face-to-face evaluation as per Appendix 1.

Telepathology systems are divided into three main types: static, dynamic, and virtual slide systems. Static or delayed-time telepathology involves capturing, digitizing, and transmitting still images of a gross or microscopic specimen to a consulting pathologist.[4] Static telepathology has the advantages of being reasonably priced and useable in the widest settings, but has the significant drawback of only being able to capture a select subset of microscopic fields.[1] Dynamic or real-time telepathology transmits and permits viewing of histological images (in real-time) from a remote microscope that the consultant pathologist is able to manipulate from a distance.[1,4] Dynamic systems are useful for teaching and research and perform best on local area networks (LANs); however, performance can suffer during periods of high network traffic or if using the Internet for transmission.[1,4] Virtual slide systems utilize an automated scanner that takes a visual image of the entire slide which can then be forwarded for diagnosis at a remote location.[1] Virtual slides reduce sampling errors and permit the production of identical copies, fast transmission, and archiving.[4] A disadvantage of both dynamic and virtual slide systems is that the costs may be prohibitive.

Equipment requirements for telepathology generally include a light microscope (or slide scanner), a high resolution digital camera and/or video camera, a document camera for gross examinations, a personal computer with image reading software, and a telecommunications medium at the site making the consultation request.[4] A high performance workstation is

generally required for the consulting pathologist and factors that should be considered in optimizing the telepathology workstation and digital reading environment are reviewed in the literature.[3,5] While these equipment requirements represent an ideal telepathology platform, other means of telecommunication such as use of mobile phones with multimedia messaging services (MMS) capability have been investigated for telepathology.[6]

The purpose of this report is to review the evidence for the clinical and cost-effectiveness of telepathology and any guidelines for its use compared with conventional methods of pathologist consultation. This information will be used to inform decision makers looking at alternate methods of confirming laboratory results or for obtaining a second opinion in smaller centres where there may be limited access to a pathologist.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of telepathology for sharing and interpreting laboratory specimens?

2. What is the cost-effectiveness of telepathology for sharing and interpreting laboratory specimens?

3. What are the evidence-based guidelines regarding the use of telepathology for sharing and interpreting laboratory specimens?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including Medline, Embase, The Cochrane Library (Issue 5, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and June 15, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, economic studies, and guidelines.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by RCTs, non-randomized studies, economic evaluations, and evidence-based guidelines.

SUMMARY OF FINDINGS:

The literature search identified two RCTs,[2,7] 13 non-randomized trials,[8-20] one economic evaluation,[21,22] and one guideline.[23] No health technology assessments or English language systematic reviews or meta-analyses were identified. One systematic review published in French with an English abstract[4] was identified.

Systematic reviews and meta-analyses

A report on telepathology published in 2008 by the *Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS)* was identified in the grey literature search that appeared to be a systematic review; however, it was only available in the French language. An English language summary of the report[4] implied that both static and dynamic telepathology were considered in the report. The report appeared to include an analysis of the diagnostic reliability of each method and discussed the different applications, technical requirements, archiving, training, remuneration, and infrastructure requirements associated with telepathology. Since the report was not available in English, this report was not reviewed.

Randomized controlled trials

Two RCTs were identified that compared the diagnostic accuracy of conventional light microscopy and virtual microscopy. Li et al. (2007)[7] investigated the diagnostic accuracy of two pathologists blinded to the diagnoses who reviewed digital images of single glass slides from each of 400 surgical pathology cases (e.g., seminoma, invasive ductal carcinoma of the breast, colon carcinoma) using virtual microscopy with a telepathology workstation. Three weeks later, the glass slides from each case were randomized and re-reviewed by each of the two pathologists using conventional light microscopy. Diagnoses and time spent was recorded for each method. At least two senior pathologists had previously reviewed the slides in each case to form consensus diagnoses, which in turn, were confirmed by at least four senior pathologists. Diagnostic accuracies were 97.25% and 96.25% for conventional microscopy and 95.50% and 94.75% for virtual microscopy for the two pathologists, respectively. There was no significant diagnostic discrepancy between the two methods. Discordant diagnoses were 4.50% and 5.25% with virtual slides and 2.75% and 3.75% with glass slides, for the two pathologists, respectively. The average time each individual pathologist took for viewing a virtual slide were 3.41 and 5.24 minutes compared to 1.16 and 3.35 minutes for viewing a glass slide, which was statistically significantly different between the two methods ($P<0.05$). The increased time to view the virtual slides was considered to be acceptable as it was less than the time required when using dynamic telepathology or traditional consultation. The study was conducted in China and utilized a customized telepathology workstation developed by the authors so it is not known if the equipment would be available elsewhere and if the results are generalizable to North America. It was concluded that the newly designed system has acceptable diagnostic accuracy that is of practical value and may be suitable for application in China.

Furness (2007)[2] compared the diagnostic accuracy of Internet-based virtual microscopy with conventional light microscopy to assess renal biopsies by participating pathologists in the United Kingdom (UK) National Renal Pathology External Quality Assessment (EQA) Scheme. Two parallel circulations of virtual slides of current EQA cases were made available over the Internet to participating pathologists. Of 96 registered participants, 26 (27%) submitted telepathology diagnoses on 6 of 12 cases and 85 (89%) submitted conventional light microscopy diagnoses on all 12 cases. In total, 156 telepathology diagnoses and 1,018 light microscopy diagnoses were available. There were no statistically significant differences in diagnostic accuracy between the two methods when compared in various ways (e.g., all data, telepathology participants only, or paired diagnoses); however, virtual slides took pathologists longer to review. The study may have been limited by the method used to randomize pathologists (discussed further under the limitations section of this report). In addition, the pathologists who

chose to provide telepathology diagnoses could reflect a self-selected group of proficient users of telepathology, and therefore, may not be representative of all pathologists. It was concluded that the results were encouraging; however, that in failing to detect a difference in diagnostic accuracy, equivalence between the methods was not demonstrated because numerous other factors (e.g., financial, legal, professional and ethical issues) must be taken into consideration when comparing the technologies. In addition, the relevance of the results to other fields of histopathology has not been demonstrated.

Non-randomized studies

A total of 13 non-randomized studies were identified in which diagnoses by static telepathology (four studies), dynamic telepathology (seven studies) and virtual microscopy (two studies) were compared with reference diagnoses or conventional diagnostic methods (i.e., light microscopy, face-to-face evaluation and consultation). Details of each study are provided in Appendix 1. The majority of studies investigated the diagnostic accuracy or diagnostic concordance of telepathology with the reference diagnoses or conventional methods. The types of specimens varied across studies and spanned a wide range of dermatologic, gynecologic, neurological and oncology applications. A small number of studies considered the time implications of telepathology compared with conventional means. The majority of studies investigated a limited number of specimens and the number of pathologists providing interpretations was generally one or two. In many studies it was not stated if the pathologist was blinded to the reference diagnosis or patient information.

Static telepathology

Four studies were identified that compared diagnoses obtained via static telepathology with reference diagnoses.[8-11] The diagnostic accuracy of static telepathology for astrocytomas ranged from 81.6% to 91.8% (depending on review of images alone or with supporting tools) compared to 93.9% using conventional glass slides in one study.[9] Diagnostic concordance of telepathology for cervical cytology slides was 84% when compared to reference assigned diagnostic groups[8] and 74% compared with face-to-face diagnoses of malignant skin lesions. In one study[9] that considered static telepathology as a preoperative tool for nonmelanoma skin cancers, the diagnostic concordance between the pathologist and dermatosurgeon was κ=0.86 and agreement of surgical technique was κ=0.75. This study also investigated surgery wait times and on-the-day surgery cancellations, both of which were statistically significantly reduced with telepathology; P<0.005. In general, all studies concluded that static telepathology was a promising and effective tool that has value as a preoperative or triage tool or as a means of avoiding diagnostic errors with the potential to prevent unnecessary hospital visits, shorten wait times and improve healthcare access and delivery.

Dynamic telepathology

Seven studies were identified that compared diagnoses obtained via dynamic telepathology with reference diagnoses.[12-18] Three studies were retrospective comparisons.[13-15] and in three studies was it was stated that the pathologist was blinded to the diagnoses.[14-16] The diagnostic accuracy of dynamic telepathology was 95.3% for frozen sections of breast lesions[12] and 91.6% to 97% (depending on pathologist in the study) for surgical pathology specimens of various origins.[16] Diagnostic concordance ranged from 78% with conventional cytology of fine needle

aspirations of breast lesions[12] to 100% with conventional light microscopy for frozen section slides originating from Mohs surgery.[18] Two studies[13,14] compared intraoperative neuropathology diagnoses using dynamic telepathology with the final diagnoses. Overall concordance rates ranged from 78.2% to 81.8% (depending on telepathology system used) compared with 85.7% to 86.8% for conventional microscopy and consultation. The concordance rates for diagnoses of pancreatic lesions via telecytopathology compared with on-site diagnoses was κ=0.65 and with the final diagnoses was κ=0.61; both not statistically significant.[15] The time spent ranged from 1 to 5 minutes for pre-screening and 2 to 20 minutes for the telecytopathology diagnosis. A comparison of diagnoses derived from intraoperative frozen sections of various neoplasms demonstrated concordance rates of dynamic telepathology with light microscopy of κ=0.97 and with final diagnoses of κ=0.97.[17] This study also measured the average time spent for telepathology (4.5 min) which was considerably shorter than for routine interdepartmental consultation (18.6 min). In contrast, another study reported the mean time for telepathology diagnoses was 17.0 minutes and the time to review a slide 3 to 4 times longer than that of standard light microscopy.[16] Overall, study conclusions were generally positive with regard to the value and potential use of dynamic telepathology compared to conventional methods; however, caution was expressed regarding the importance of considering inter-site differences in surgical procedures and types of cases when making comparisons. Furthermore, the length of time required for diagnoses by dynamic telepathology may be prohibitive in a busy practice.

Virtual microscopy

Two studies were identified that utilized virtual microscopy to compare diagnoses of melanocytic lesions[19] or classification of breast cancer cases[20] with the original diagnoses or with expert evaluation, respectively. The first study[20] was a retrospective assessment of digital slides by four pathologists which reported agreement of telepathology and original diagnosis in 90.4% to 96.4% of cases (κ=0.80 to 0.93), depending on the pathologist. The median time required for a diagnosis was 22 seconds. It was concluded that correct reporting on digital histopatholgic images is possible with little time exposure. The second study[20] compared the evaluation and classification of Internet-based virtual slides of histologically complex breast lesions by 10 pathologists with each other and with the results by an experienced expert. The level of reproducibility compared with the expert was poor (median κ=0.60) as was the inter-observer reliability (median κ=0.53); however, it was concluded that results were comparable to quality control studies using slides when analyses are done on borderline cases.

Economic evaluations

One economic evaluation of telepathology conducted in 2005 by Miyahara and colleagues was identified.[21,22] Information was collected by postal questionnaire from 622 medical institutions in Japan that reported using telemedicine. The response rate to the survey was 35% and of the responding institutions, 29 used telepathology. As part of the survey, institutions were asked to estimate values of willingness to pay (WTP) (i.e., the maximum amount customers are willing to pay to access the service) and the willingness to undertake (WTU) (i.e., the minimum charge to undertake the service). A non-parametric method, the Kernel Estimation Method, was used to obtain WTP ($86.60) and WTU ($162.89) for telepathology due to the small numbers of responses. The estimated economic benefits for one year of telepathology were $2,760,423.70 for WTP and $363,572.50 for WTU. Various factors influencing WTP and WTU (e.g,. type of institution, staffing, technical requirements, satisfaction, quality, etc.) were also analyzed.

Guidelines and recommendations

In 2005, the Royal College of Pathologists in the UK published a guidance document on telepathology.[23] Guidance recommendations pertain to the urgent need for accreditation standards for telepathology, training and assessment of pathologists in the acquisition, manipulation and use of digital images, assurance of diagnostic proficiency using both conventional microscopy and telepathology, and adequate audit and quality control programs. It is also noted that if telepathology is to be used to provide a diagnostic service that does not involve a responsible pathologist, numerous legal and communication issues arise. Overall, recommendations were that the best pathology services are delivered in a context of clinical governance, laboratory accreditation, and well-functioning laboratory and clinical teams with good communications. Local reporting by trained pathologists who work closely with the relevant clinical teams must be regarded as the preferred approach in most situations and distant reporting of large and complex specimens is particularly unlikely to be appropriate.

Limitations

No health technology assessments or English language systematic reviews or meta-analyses were identified from the literature search.

Two RCTs were identified, both of which dealt with virtual slide microscopy, therefore no RCT evidence was identified from the search for either static or dynamic telepathology. The first RCT[16] is limited by including interpretations from two pathologists. The majority of non-randomized studies are also limited by including interpretations from a limited number of pathologists (i.e., one or two). Across all studies, it is not known what level of telepathology expertise the included pathologists possessed. Therefore, it is possible that these studies reflect a small, selected group of pathologists who are skilled in the use of telepathology and therefore the generalizability of results to all pathologists is unclear. The second RCT[2] is limited by being unblinded and having potentially questionable randomization. As the study was based on an existing EQA scheme, the allocation of participating pathologists to groups of cases was not formally randomized for the study, but rather was done by alternating the allocation of pathologists to each group as they joined the scheme.

The identified studies encompass a wide variety of pathological specimen types from diverse therapeutic areas, thereby making comparisons or generalizations difficult. This is especially true for the time required to review digital images and/or make a diagnosis. The time involved may be a reflection of the complexity of making a differential diagnosis, which is unrelated to the type of technology used. The studies also utilized different types of hardware, software and transmission methods to exchange data and information amongst study participants. It is possible these factors influenced results and adds to the difficulty in making comparisons between studies. All of the identified trials (both RCT and non-randomized) investigated the diagnostic accuracy and/or diagnostic concordance of telepathology with conventional methods or known diagnoses. Many studies reported the degree of concordance using kappa (κ) statistics; however, there does not appear to be consensus as to what an acceptable level of concordance (κ value) is required to prevent the serious implications of misdiagnosis. None of the trials measured an impact of telepathology on clinical outcomes, therefore, based on these data, it is not possible to assess the true clinical impact of telepathology. Lastly, some of the non-randomized studies are limited by being retrospective comparisons, and only a small

number of the non-randomized trials indicated that the reviewing pathologist was blinded to the reference diagnoses or patient information.

The one economic evaluation[21,22] identified was not a cost-effectiveness analysis, but rather an analysis of the WTP and WTU for various aspects of telemedicine based on a postal survey in Japan. The evaluation is limited by only 29 out of 622 (5%) of Japanese institutions providing telemedicine at the time of the survey providing input into the telepathology results.

There was no information on the methodology used to develop the one identified guideline.[23] It does not appear that a systematic review of the literature was conducted as part of the guideline development process or that the recommendations were formulated by expert consensus (i.e., although the guidance was provided to the membership for consultation, no comments were received). The summary recommendations were also not graded by the strength of the supporting evidence.

The timeline for the literature search for this report encompassed only the last five years and retrieval was limited to English language studies only. As a result, there may be studies or systematic reviews published prior to this time or in other languages that were not included.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Based on the evidence reviewed in this report, telepathology appears to be a promising and valuable technology, with particular relevance to remote or financially constrained regions with limited access to pathology services. The highest level of evidence identified to support the use of telepathology was from two RCTs that evaluated the diagnostic concordance of virtual slide microscopy (presently the most advanced form of telepathology) with conventional light microscopy. No RCTs of static or dynamic telepathology were identified. All non-randomized trials identified also evaluated either the diagnostic accuracy or concordance of static, dynamic or virtual microscopy telepathology with reference diagnoses or diagnoses achieved by conventional methods. Overall, the diagnostic accuracy of telepathology appears to be comparable to that of conventional microscopy, especially when used in conjunction with other supporting tools or a decision making framework. No trials were identified in which the direct impact of telepathology on clinical outcomes was investigated, so the clinical effectiveness of telepathology for sharing or interpreting laboratory specimens is uncertain.

One economic evaluation of telepathology was identified; however, it was not a cost-effectiveness evaluation, but rather an analysis of WTP and WTU for telemedicine (including telepathology) conducted in Japan. As a result, the cost-effectiveness of telepathology is also uncertain, especially in a Canadian context, due to the paucity of available information. Although one guideline from the UK was identified, it was unclear if it was evidence-based and for the most part, it put forth recommendations pertaining to standardization and quality assurance for telepathology rather than guidance on sharing and interpreting laboratory specimens.

There are numerous considerations and potential implications for decision and policy making that pertain to telepathology. Many of the drawbacks of static and dynamic telepathology have been addressed with virtual slide microscopy; however, the cost of implementing a virtual system is higher than for other forms of telepathology. While the diagnostic accuracy and concordance of telepathology with conventional microscopy has been shown to be comparable

for a variety of specimens and therapeutic applications, the technology may not be sensitive enough for complex cases. Limitations of telepathology in this regard include the lack of interaction with the patient, limited access to patient history and records, and the inability to palpate lesions or to perform additional tests on laboratory specimens. There may also be barriers to the uptake of telepathology as evidenced by a national survey of UK pathologists published in 2005.[24] The survey identified that only 12% of histopathologists had any sort of telepathology equipment, 24% had ever used telepathology in a diagnostic situation, 59% had received no training in digital imaging and 58% felt that the medical/legal implications of duty of care were a barrier to use of telepathology. Many of these barriers may be overcome as familiarity with the technology and telecommunications advance. In contrast, a 2009 publication discusses the current trend in medical schools in the United States to provide entirely digital pathology courses, which the authors hypothesize, may create a generation of pathology trainees who prefer digital pathology imaging over traditional hands-on light microscopy.[3]

Additional considerations associated with telepathology include issues that result from the geographic separation of histopathologists, clinicians and patients, which could lead to miscommunication, misdiagnoses and legal liability. There are also cost issues to consider, including the cost of equipment and implementation and the potential for costs associated with increased time for the pathologist to review and interpret digital slides as compared with conventional microscopy.[2] Over time, costs may reduce once users become more familiar with the technology and transmission and processing speeds advance.

The decision to implement a telepathology system requires consideration of numerous factors beyond diagnostic accuracy and concordance with conventional methods, including financial, legal, professional and ethical issues.[2] Factors important for the success of telepathology are the adequate training and demonstrated competence of all personnel involved (e.g., pathologists, technicians, surgeons), audit and quality assurance, confidentiality, remuneration, professional liability and resolution of medical/legal issues.[4] In order to better inform decision and policy makers, well-designed, prospective studies that investigate the direct effects of telepathology on clinical and economic outcomes are needed in order to generate high quality data upon which the clinical and cost-effectiveness of telepathology can be evaluated and upon which practice guidelines can be based.

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Appendix 1: Details of Non-Randomized Trials

Publication	Population/Type of Specimen	Intervention and Comparator	Outcomes	Key Findings	Conclusions
A) Static Telepathology					
Eichhorn et al., 2005[8]	Liquid-based cervical cytology slides	Comparison of pathologist (n=2) interpretation of 10 device-scanned images from 32 reference slides of known diagnoses with direct interpretation of the 32 reference slides.	Diagnostic concordance	Pooled interpretation from pathologists resulted in 84% concordance rate of reference and assigned diagnostic groups. False positive rate was 8.3% and false negative rate was 37.5%.	Procedure shows promise for allowing remote interpretation of device-selected images.
Ferrandiz et al., 2007[9]	Nonmelanoma skin cancer	Preoperative evaluation of digital images of lesions by a dermato-pathologist (n=1) via SFTD from 134 patients compared with evaluation by dermatosurgeon (n=1) and histopathologic diagnoses and with a sample of 92 patients managed through the conventional system.	Diagnostic concordance, surgery waiting times, on-the-day surgery cancellation	Diagnostic concordance was κ=0.86 (95% CI: 0.83; 0.89). Agreement of surgical technique was κ=0.75 (95% CI: 0.71; 0.79). Mean waiting interval for surgery was 26.10 (SFTD) vs. 60.57 days (conventional); P<0.001. On-the-day surgery cancellation was 2.99% (SFTD) vs. 8.85% (conventional); P<0.005.	SFTD was effective and accurate as a preoperative tool avoiding unnecessary visits to hospital and shortening the waiting intervals to surgical txt.
Glotsos et al., 2009[10]	Tissue samples of astrocytomas	Histopathologist (n=1) review of 106 tissue samples and inter-observer checked cases of conventional glass slide diagnoses compared with review of 5 static digitalized images from each patient and then review of same 5 images for tumour grading using WHO histological characteristics. An evaluation of a custom decision support system was also conducted.	Diagnostic accuracy	Diagnostic accuracy by conventional glass slide 93.9%, by 5 static images alone 81.6%, by 5 static images and WHO characteristics 88.8%, and with addition of custom decision support system 91.8%	Findings suggest that a TP system may be valuable for accurate grade diagnosis of astrocytomas providing a means for avoiding diagnostic errors without blocks or slides leaving the department.

Tan et al., 2010[11]	Skin lesions of concern (e.g., basal cell carcinoma, melanoma)	Face-to-face diagnoses of 200 patients (491 lesions) by 2 of 3 dermatologists compared with diagnoses of same patients by 2 of the dermatologists using digital and dermoscopic images 4 wks later.	Diagnostic concordance	Exact concordance was 74% (285/385 lesions) and 74% (219/296) for the 2 dermatologists who performed both exams; 12.3% of lesions had a clinically significant disparate diagnoses.	Use of TP as triage tool offers the potential to shorten waiting lists and thus improve healthcare access and delivery.
B) Dynamic Telepathology					
Hitchcock and Hitchcock, 2005[12]	Excisional biopsies and fine needle aspirations of breast lesions	Pathology assessment of 329 biopsy samples and 251 cytology specimens by TP compared with final diagnoses.	Diagnostic accuracy	For frozen sections, TP diagnoses had sensitivity of 81.6%, specificity of 100% and diagnostic accuracy of 95.3%. For fine needle aspirates, TP diagnoses agreed with conventional cytology in 78% of cases and for 109 specimens with tissue pathology available, diagnosis of malignancy had a sensitivity of 91.2% and specificity of 100%.	Routine use of TP compares well with conventional microscopy in the assessment of both frozen sections and fine needle aspirates of breast lesions.
Horbinski and Wiley, 2009[13]	Intraoperative neuropathology specimens	Retrospective comparison of 262 intraoperative consultations performed using a new dynamic robotic TP system with 159 consultations using a prior TP system and with 547 conventional consultations. All were also compared with final diagnoses.	Diagnostic concordance	Overall concordance rates with final diagnoses were 85.7-86.8% for conventional consults, 81.8% for the prior TP system and 78.2% for the new TP system. For most common diagnostic classes, overall concordance rates were similar.	Results support use of TP for intraoperative diagnoses. Inter-site differences in surgical procedures and types of cases must be considered when comparing diagnostic outcomes between TP systems or with conventional microscopy.

Horbinski et al., 2007[14]	Intraoperative neuropathology specimens Note: Two different TP systems were used during the time period of the study	Blinded pathologist (n=2) retrospective comparison of 402 TP and 1227 conventional cases involving intraoperative diagnoses with final diagnoses over a 5 yr period.	Diagnostic concordance	Overall rates of intraoperative and final concordance with conventional microscopy ranged from 85-87% annually and with TP averaged 81%. Deferral and discrepancy rates varied between methods but became similar over time.	Current technology is capable of facilitating TP intraoperative diagnoses in a timely manner with accuracy rates comparable to conventional methods.
Kim et al., 2006[15]	Endoscopic ultrasound guided fine needle aspiration of pancreatic lesions	Blinded cytopathologist (n=1) retrospective assessment of 40 slides using a real-time remotely operated tele-cytopathology system compared to previous on-site and final diagnoses.	Diagnostic concordance, time spent	Tele-cytopathology vs. on-site diagnosis (κ=0.65; 95% CI: 0.41; 0.88) and vs. final diagnosis (κ=0.61; 95% CI: 0.37; 0.85); both NS. Time spent for pre-screening was 1-5 min and for tele-cytopathology diagnosis 2-20 min.	Study demonstrated potential use of tele-cytopathology as a valid substitute for on-site evaluation of pancreatic carcinoma.
Li et al., 2008[16]	Surgical pathology specimens from 16 different organs	Blinded pathologist (n=4) review of 600 cases by TP and by light microscopy compared with 'correct' diagnoses (consensus of 2 experienced pathologists).	Diagnostic accuracy and concordance, time spent	Diagnostic accuracy by TP ranged from 91.6 to 97% depending on pathologist. A TP diagnosis was concordant with 'correct' diagnoses 94.2% and with light microscopy 99.26%; 85% of cases were diagnosed in 15-40 min (mean 17 min) with TP which was 3-4 times longer than light microscopy.	Robotic TP is sufficiently accurate for primary diagnosis in surgical pathology, but modifications in laboratory protocols, TP hardware and internet speed are needed to reduce time for diagnosis by TP before method is deemed suitable for use in a busy practice.

Liang et al., 2008[17]	Intraoperative frozen sections of benign and malignant neoplasms	Comparison of diagnoses on 50 cases made by 1) pathologist on duty, 2) subspecialist or senior using TP, 3) same pathologist using light microscopy and 4) final diagnoses.	Diagnostic concordance	Concordance between TP and light microscopy was κ=0.97 and with final diagnoses (κ=0.97). Average time span for TP (4.5±2.8 min) was short compared with routine intradepartmental consultation (18.6±4.1 min).	TP is a good tool for frozen section consultation and imposes little additional cost.
McKenna and Florell, 2007[18]	Fixed slides and frozen section slides from Mohs surgery	Comparison of diagnoses on formalin-fixed, paraffin-embedded slides and frozen section slides (20 each) using TP and conventional microscopy.	Diagnostic concordance	Agreement between TP and conventional microscopy was 95% for fixed slides and 100% for frozen section slides.	Dynamic TP can be accomplished accurately and inexpensively by use of readily available consumer products and software.
C) Virtual Microscopy					
Leinweber et al., 2006[19]	Histologic slides of melanocytic lesions	Dermatopathologist (n=4) retrospective assessment of 560 digital slides compared with original diagnoses.	Diagnostic concordance, time spent	TP diagnoses corresponded with original diagnoses in 90.4% to 96.4% of cases (κ=0.80 to 0.93) depending on pathologist. The median time for a diagnosis was 22 seconds.	Results demonstrate that correct reporting on digital histopathologic images is possible with only a little time exposure.
Zito et al., 2010[20]	Histologically complex needle core biopsies of non-palpable breast lesions	Pathologist (n=10) evaluation of 18 Internet-based virtual slides compared with each other and by evaluation by experienced expert (reference)	Concordance of classification of cases according to European guidelines for breast cancer screening and diagnosis	Comparison with expert showed poor level of reproducibility (median κ=0.60) and was poor inter-observer reproducibility (median κ=0.53).	Findings comparable to quality control studies using circulating slides when analysis is done on borderline cases.
SFTD=store and forward teledermatology; TP=telepathology; κ=kappa: a measure of inter-rater agreement					