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Research article

Experiences with an International Digital Slide Based Telepathology System for Routine Sign-out between Sweden and Hungary

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Abstract: Digital microscopy combines the benefits of traditional optical microscopy and the advantages of computer sciences. Using digital whole slides in all areas of pathology is increasingly popular. Telepathology or long distance diagnosis is one such area. In our study we have evaluated digital slide based histopathology diagnosis in an international setting, between Sweden and Hungary. Routine cases from the Sundsvall County Hospital (Landstinget Vasternorrland) were collected. Glass slides were scanned using Pannoramic 250 Flash II. (3DHISTECH Ltd., Budapest, Hungary). During the first round of evaluation the glass slides were shipped to Hungary for primary diagnosis. Two pathologists from Hungary, reading glass slides and one pathologist from Sweden reading digital slides signed out 500 cases. Pathologists from Hungary reached the hospital information system with a secure connection. During the second round the pathologists in Hungary reevaluated 200 from the 500 cases using digital slides after three months washout period. Diagnostic accuracy was calculated and diagnostic errors was graded according to clinicopathological consequences. In 182/200 (91%) cases digital and optical diagnoses were in full agreement. Out of the remaining 18 cases, 1 (0.5%) critical error was identified. In this case the error had therapeutic and prognostic consequence and no uncertainty either because of case complexity or poor image quality was recorded by the pathologist. We think language and communication issues as well as differences in minimal data sets of pathological reports and in guidelines used in Sweden and in Hungary are factors potentially limiting the widespread use of digital slides in a teleconsultation service provided to Sweden from Hungary. We found the quality of digital slides in our study setting acceptable to reach correct primary diagnosis in routine, unselected, random cases of a small-to-medium sized pathology department in Sweden.

Keywords: virtual slide; telepathology; surgical pathology; quality control; diagnostic confidence

1. Introduction

Digital microscopy combines the benefits of traditional optical microscopy and the advantages of computer sciences. Using digital whole slides in all areas of pathology is increasingly popular. As digital pathology solutions became more and more sophisticated their spread in histology teaching and in the scientific field is unstoppable, however routine application of digital slides (DS) in surgical pathology is still controversial [1–3]. There is an increasing number of studies validating DS based histopathology diagnosis [4–9]. This study summarizes our approach to launch a digital telepathology service from Hungary to Sweden.

In Sweden there is a severe shortage of pathologists due to historical factors. In total there is approximately 200 pathology specialists on a population base of 10 million people (20/million). This is among the lowest rates in all european countries and only half the number as compared with Nordic neighbour countries, like Norway and Denmark with similar organization of health care systems. Many attempts are being pursued to ease the shortage. Increased resident education and international recruitement are the mainstay of slowly improving conditions. However in the short run Sweden also needs to try other solutions to improve the situation and one possible way could be to outsorce selected biopsy material for external international diagnosis.

Sweden is at the forefront in digital pathology applications and today approximately 50% of the 31 swedish laboratories scan all slides with different systems. The number of laboratories participating in various developmental projects increases every year and within a few years probably all Swedish laboratories will apply whole slide imaging (WSI) techniques. Many different projects with support from the state are coordinated by regional cancer centers and common experience is being extracted and generalized for all users [10]. This also includes integrating digital pathology with the more common laboratory information systems and sharing regional information between smaller units and larger university hospitals. One of the driving forces is shortage of pathologists, but other important advantages of digital pathology are also driving development. Since Sweden is a large country with a small population more surgical units and pathology laboratories are needed than optimal. This also reduces the size of the individual pathology departments. In north of Sweden the smaller departments handle less than 10,000 samples a year and this also means that the number of pathologists can not be more than 2–4 limiting the possibility for subspecialized signing out. Hence, the promise of digital pathology is that subspecialization could evolve in the virtual space to give a good daily service to patients and clinicians and at the same time render the highest possible quality in diagnoses.

This study was initiated as the first step in establishing and outsourcing digital pathology service between Sweden and Hungary. The aim was to overcome initial problems and to see if quality of diagnosis and reporting could be high enough to maintain daily routine diagnosis within an ISO accredited system.

2. Materials and Methods

There were two separate phases of the study.

In the first phase between the period from January 2014 to October 2014 two Hungarian pathologists (TM, LF) provided pathology service for the Sundsvall County Hospital. Five hundred cases of biopsy specimens (glass slides) had been shipped to Budapest (Hungary) from Sundsvall

(Sweden) for primary diagnosis. No surgical resection specimens, smears or cytology samples were selected, otherwise the cases represented the daily routine of Sundsvall pathology. There was no preselection of different sample types, location or difficulty. Before shipping them, the glass slides had been scanned and DS had been uploaded to a dedicated slide server (Case Center, 3DHISTECH Ltd., Budapest, Hungary) behind Sundswall hospital firewall. The Hungarian pathologists both have the permission to work as pathologists in Sweden, they have been working as consultants for at least 5 years and are using DS in a daily routine for graduate histopathology training and for research purposes [11–13]. They had remote access to the local laboratory information system (LIS) in Sundsvall (Sympathy) to have the necessary clinical information for the cases. Further studies, like recuts, immunohistochemical reactions and special stains had been requested electronically and these glass slides (after scanning) had also been shipped to Budapest. Microscopic description and diagnosis was given to each case in English. A Swedish supervising pathologist (GE) had access to DS and Sympathy. He checked the case slides and descriptions and if it was necessary, he made formal corrections in the descriptions to be in line with Swedish standards of reporting.

In the second phase, reevaluation of cases by the Hungarian pathologists had been performed reading digital slides. Clinical history was available from Sympathy, digital slides from the already mentioned slide server. We have designed this reevaluation study in accordance with the current guideline from the College of American Pathologists (CAP) for validating WSI for diagnostic purposes [14].

2.1. Cases and slides

According to the CAP Guideline, the validation process should include a sample set of at least 60 cases for one application (e.g., H&E-stained sections of fixed tissue, frozen sections, cytology, hematology) and should include another 20 cases for each additional application (e.g., immunohistochemistry, special stains) and the involved cases should reflect the spectrum and complexity of specimen types and diagnoses likely to be encountered during routine practice. We wanted to evaluate H&E-stained sections of fixed tissue, immunohistochemistry and special stains and altogether 200 cases of biopsy specimens were sequentially selected from the 500 hundred previously diagnosed cases. (Table 1). All slides (H&E, immuno, special) of the original cases were scanned and available for digital evaluation. Alltogethre, more than 500 slides were scanned (366 H&E slides, 73 immunohistochemical slides and 74 special stain slides—PAS, AB-PAS, VanGieson, Giemsa).

2.2. Slide scanning

Slides of the selected cases were scanned using Pannoramic 250 Flash II. (3DHISTECH Ltd., Budapest, Hungary) equipped with CIS VCC-FC60FR19CL 4 megapixel camera, 20× objective and 1.6× camera adapter, resulting in 0.24 μm/pixel resolution. A technician in Sweden manually checked each slide of the given cases before shipping to Hungary to confirm that all of the material presented on the glass slides had been scanned and included in the digital image.

Table 1. Origin of samples.

	Cases - primary diagnostic phase - n(%)	Cases - digital evaluation phase - n(%)
Gynecological	135 (27)	42 (21)
Lower gastrointestinal	71 (14.2)	37 (18.5)
Skin	192 (38.4)	66 (33)
Upper gastrointestinal	56 (11.2)	33 (16.5)
Urological	39 (7.8)	22 (11)
Other	7 (1.4)	0 (0)
Sum	500 (100)	200 (100)

The distribution/localistaion of cases were not significantly different in the primary and the digital evaluation phase. (t-probe = 0,9681)

2.3. Evaluation procedures

For the second evaluation round the two pathologists in Hungary reevaluated the same cases they previously signed out based on glass slides now using exclusively DS after at least three months washout period. (CAP Guideline recommends a washout period of at least 2 weeks.) A Clinical Research Form, previously described [9], was filled out for each case (Table 2).

Table 2. Clinical Research Form.

Scan quality (each slide)	**Explanation**
1-Unacceptable	critical deficiences (out of focus, missing scan)
2-Poor	major deficiences (large areas out of focus, missing parts)
3-Adequate	region of interests are proper, minor deficiences
4-Good	region of interests are focused, good color fidelity, minor deficiences
5-Excellent	whole material is focused, good color fidelity
The reason of dissatisfaction with scan quality	**Polar questions**
Important areas of the slide are out of focus	(y/n)
Incomplete scan	(y/n)
The color fidelity is poor	(y/n)
Diagnostic confidence (per case)	**Explanation**
1-Uncertain	consultation should be requested, no definite idea of diagnosis
2-Likely	consultation should be requested for confirmation
3-Confident	no consultation required
The reason of uncertainty is due to:	**Polar questions**
Case complexity	(y/n)
Poor image quality	(y/n)

Table 3. Four types of incoherency and the list of incoherent cases.

Type of diagnostic error	Description	% (n)	Site	POD	SDD
Type I.	non relevant incoherence - uncertainty recorded	2% (4)	upper GI	gastric metaplasia	normal histology
			endometrium	endometrial atrophy	normal histology
			skin	normal histology	non-specific perivascular dermatitis
Type II.	non relevant incoherence - uncertainty not recorded	5% (10)	upper GI	normal histology	fundic gland polyp
			upper GI	normal histology	mild chronic duodenitis
			lower GI	mild chronic non-specific/reactive colitis	normal histology
			skin	solar degeneration	actinic keratosis - mild dysplasia
			skin	actinic keratosis - severe dysplasia	in situ squamous cell carcinoma
			urinary bladder	recurrent transtitional cell cancer, high grade	recurrent transtitional cell cancer, low grade
			skin	actinic keratosis - mild dysplasia	actinic keratosis - severe dysplasia
			skin	actinic keratosis - mild dysplasia	actinic keratosis - severe dysplasia
			skin	normal histology	hyperkeratosis
Type III.	relevant incoherence - uncertainty recorded	1.5% (3)	endometrium	endometrial atrophy	benign endometrial polyp
			skin	verruca vulgaris	seborrheic keratosis
			endometrium	normal histology - proliferative phase	disordered proliferative endometrium
			endometrium	disordered proliferative endometrium	normal histology - proliferative phase
			endometrium	disordered proliferative endometrium	normal histology - proliferative phase
Type IV.	**relevant incoherence - uncertainty not recorded**	0.5% (1)	cervix	cervical low grade squamous dysplasia (LSIL)	cervical high grade squamous dysplasia (HSIL)

A diagnostic error was defined relevant when it had therapeutic or prognostic consequence. Diagnostic uncertainty was defined either because of case complexity or poor image quality recorded by the pathologist. (POD: primary optical diagnosis, SDD: secondary digital diagnosis)

After all data were available primary diagnoses (optical) (POD) and secondary diagnoses (digital) (SDD) of each case given by the same pathologist were compared and cases with different diagnoses were further analysed. (CAP Guideline suggests that the validation study should establish diagnostic concordance between digital and glass slides for the same observer -intraobserver variability) Errors were graded according to clinical significance [9] (Table 3).

3. Results and Discussion

TM digitally evaluated 102 cases and 310 digital slides, LF 98 cases and 201 digital slides. In 182/200 (91%) cases digital (SDD) and optical (POD) diagnoses were in full agreement. The mean diagnostic confidence was 2.66/3, mean slide quality was 4.45/5. These ratios for the incoherent cases were 2.1/3 and 4.12/5 respectively. The highest mean diagnostic confidence was found with cases from the lower gastrointestinal tract (2.84/3), the highest mean average slide quality was found with slides of gynecological samples (4.6/5). All cases taken into account, IHC slides received the highest scores in terms of quality (4.66/5) and giemsa stained slides the lowest (4.0/5). Mean diagnostic confidence and slide quality scores for Type-I and Type-III errors were 1.5/3, 3.92/5 and 1/3, 3.33/5 respectively. One case fell into the Type-IV category, with a POD of cervical low grade squamous dysplasia and koilocytic atypia (LSIL, CIN-I) where the SDD was high grade squamous atypia (HSIL, CIN-III). Results are detailed in Table 4.

Table 4. Diagnostic confidence (x) and mean slide quality (y) according to the type of diagnostic error, site and type of stain.

	sum	coherent cases	incoherent cases	T. I. error	T. II. error	T. III. error	T. IV. error
diagnostic confidence (x/3)	2.66	2.72	2.1	1.5	2.64	1	2
slide quality (y/5)	4.45	4.47	4.12	3.92	4.44	3.33	4
no of cases (n)	200	182	18	4	10	3	1
	sum	**skin**	**upper GI**	**lower GI**	**gynecological**	**urological**	
diagnostic confidence (x/3)	2.66	2.61	2.79	2.84	2.36	2.79	
slide quality (y/5)	4.45	4.31	4.32	4.55	4.6	4.48	
no of cases (n)	200	66	33	37	42	22	
	sum	**HE**	**IHC**	**special**	**giemsa**		
slide quality (y/5)	4.45	4.46	4.66	4.29	4		
no of slides (n)	511	366	72	63	10		

Rating the quality of DS had very similar results to one of our previous study from 2012 (Figure 1) [9]. This was an unexpected finding considering that the slides for that study were digitized in 2010 with an earlier scanner version and lower pixel resolution (Scan 1.11, Hitachi 3-chip camera, 20× Plan-Apochromat objective, 0.5× camera adapter magnification, 0.465 μm/pixel resolution—3DHISTECH Ltd. Budapest, Hungary). We hypothesize that as the scanner systems are

improving in speed and image quality, our eyes are getting more and more critical, too. To address this question we reevaluated 50 random digital HE slides from the previous set. The result was a mean quality of 3.9/5 whereas during the first evaluation the HE slides received a score of 4.41/5. The incoherency rate found in that first study was 11.8% while we had 9% incoherency during recent international validation. In our opinion these similar results and the discussed matter of slide quality further confirms our concept, that the reason for the non-disappearing difference between the optical and digital diagnostic approach using leading edge scanner technology and display, lies behind intrinsic human factors, intra- or inter-observer variability (depending on the study approach) and not a technical issue anymore.

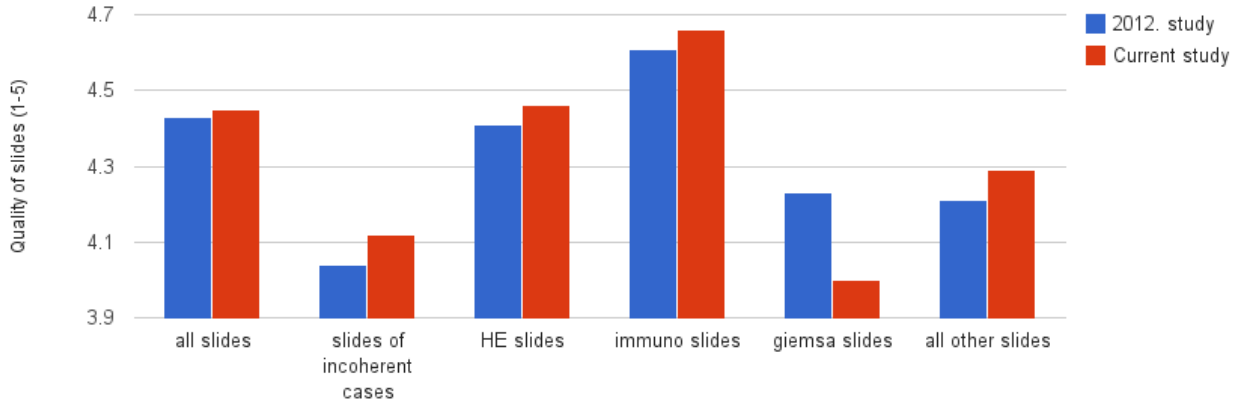

Figure 1. Comparison of the quality of digital slides of our 2012 and current study. The overall quality of digital slides, based on the examiners' subjective rating was very similar in this study (4.45/5), compared to our previous validation study (4.43/5) in 2012 [9].

Problematic areas of the telediagnostic process were related to language issues and differences between the Swedish and the Hungarian pathology systems and way of reporting. The Sundsvall LIS is in Swedish; one could learn to handle the user interface of the LIS, but the data (patient history, previous pathology reports, relevant clinical findings, etc.) is in Swedish, too. As long as the text was in a copiable format it was easy to use google translate, which is very good in terms of Swedish-English translation, but when the data is a captured image (The pathology request forms are stored as images in Sympathy.) copy/paste function is disabled. Also it happened several times that samples from the gynecologic ward came with a handwritten request and it was hard or sometimes impossible for a non-Swedish speaker to translate it. In these cases we had to contact the local staff - generally via email - resulting further delays in the turnaround time. Another serious question was which pathology reporting guideline to use. The differences between Swedish and Hungarian approach are mostly nomenclature issues, but in some cases minimal data set and content of the report or the terminology used for a given entity (e.g. reporting of gastric samples, reporting of HPV related cervical lesions, grading basaliomas, etc.) are different, too.

A problem is that the way Swedish reports are written may slightly differ from the way Hungarian reports are composed, but truly this can also vary between different departments within the same country. The Swedish Society for Pathology have recommendations on how reports should be composed and what minimal data sets should be used. These can be found on Society webpage KVAST in open format but written in Swedish [15]. The Swedish Society for Pathology now more and

more recommend that Swedish reports should follow international evidence based recommendations such as given by the College of American Pathologists or Royal College of Pathologists. But still there are some national and even regional differences often demanded by the clinicians in their national standard documents. Once clinicians got used to an old and perhaps not always scientifically sound classification system it is very difficult to get rid of it since their treatment algorithms often are based on those old classification and grading systems. Our goal is that in the near future both Swedish and Hungarian reports should be completely of international standard, evidence based, thus differences between individual countries will hopefully diminish and ultimately dissapear.

Some problems with having Hungarian pathologists signing out Swedish samples were expected. The use of English language in Swedish reports is now legal in Sweden, but initially some clinicians raised concerns. We informed clinicians beforehand and every answer was sent out with a comment that this was part of a scientific project. In the long run usually most clinicians in Sweden will accept answers written in English if quality of diagnoses is high and turn-around time short. In many major Swedish academic centers today it is becoming common that internationally recruited specialists sign out in English for extended periods. Adopting a standardized synoptic reporting system might help to overcome the language barriers of communication as such reports are easy to formulate, interpret and also easier to monitor from the quality control point of view. Several studies also provided evidence of strong physician satisfaction with synoptic cancer pathology reporting [16,17]. Synoptic reporting also enables storing of medical data in a structured and standardized format which is essential in the era of "Big Data" and personalized medicine [18].

From a practical point of view the speed of internet has been a limitation that proved difficult to improve. The reason was not internet connection between Sweden and Hungary in itself, but the thresholds within the hospital IT infrastructure. Firewalls and security log on systems for remote work had clearly not been fully adapted to the needs of digital pathology yet and these problems may take quite a long time to overcome and big differences exist between different hospitals in how they can handle this situation. This problem is expected to be solved soon since digital pathology is now being introduced in majority of all Swedish pathology laboratories.

The histopathological laboratory process used during in the pilot phase of this study was optimized for standard microscopy slide based diagnostics and the hematoxylin eosin stains of slides are the standard ones used in routine work. During optimization of scanning and digital evaluation we found that the digital process had some problems with scanning, primarily due to tissue tending to pucker and create folds and these are devastating to the focusing in the digital scanning. To minimize the puckering and folding of slides the laboratory routine sectioning had to be changed. The slides were consistently cut thinner at 3μm thickness and then stretched out in a water bath before mounting on slides. In this way the problem was minimized and the general quality of sections, stains and mounting were improved. Immunohistochemical stains required a more thorough scanning since they result in lighter areas where focusing was more difficult. Tissues containing fat also had a tendency to need a more thorough scanning to provide good images. A basic ledger scanning is described as tighter focus points that can be set in the scanner software. Interesting spin-off from study was that the general quality of sectioning, staining and mounting had to be improved. In the standard slide based evaluation the human eye is adapting to various deficits in a much more flexible way than the digital pathology system. This was mainly seen as an advantageous influence of the laboratory process. In order to facilitate remote diagnostics by foreign pathologists also the documentation of specimen gross handling and sectioning conditions had to be improved in order to guarantee the correct interpretation

of the case and adequate reporting. Moreover a module for electronic ordering of ancillary stains had to be activated to shorten turn-around times. In summary the introduction of digital pathology stimulated the positive development of many processes regarding slide quality and tissue management in the laboratory, not specifically limited to scanning of slides per se.

4. Conclusion

The most important aspect of healthcare is to ensure patient safety. This general requirement is independent of the practitioner or any instrument he/she uses for medical practice. With the spreading of DS in routine pathology practice quality control of the pathology workflow has to be reconsidered and new checkpoints should be applied. The results from our study indicate that the quality of the international digital pathology link is very good and well comparable to traditional slide based microscopy. The discordances were few only representing grading differences. No case with serious mistakes such as malignant versus benign were encountered. Probably the rate of grading discordances is to a large part due to inherent interobserver variability not different from what could be expected when comparing two rounds of glass slide based diagnosis of 200 cases with a 3 months wash out period [19–21].

One serious issue is the question of liability that could arise in telepathology practice. Our opinion is very similar [9] how Kaplan et al. approached this question. “In telepathology, the reviewing pathologist must determine the adequacy of the specimen upon which a diagnosis must be rendered and liable for the diagnosis itself” [22]. Once the pathologist signs out a case he/she is responsible for the content of it and no longer could shift off responsibility in case of a wrong diagnosis. In traditional pathology, using optical microscopes, the analogous situation would be to blame the microscope company for a muddy image seen through their objective instead of clearing the lens or blame a histotech for a wrong diagnosis when there are section folds and floatings instead of asking for recuts.

Pathology reporting also needs to be harmonized within the EU. Each pathology board of every member state has its own set of guidelines. Some of those guidelines are updated continuously (like the guidelines of the Royal College of Pathologists) some others (like what we have in Sweden or in Hungary) are lagging behind. Today much emphasis is on developing synoptic reports and then all these problems will be much smaller.

In conclusion, we assume that medicolegal, logistic, and language issues remain at the forefront of concern and remain also a hindrance to spread DS in international routine telediagnostic services. These issues seem to be more urging to be addressed than the technical aspects of whole slide imaging.

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Conflict of interest

The authors has no conflict of interest to declare regarding this validation study.

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