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Research Article

# Consultation on urological specimens from referred cancer patients using real-time digital microscopy: Optimizing the workflow

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## Abstract

**Introduction:** Centralization of cancer treatment entails a reassessment of the diagnostic tissue specimens. Packaging and shipment of glass slides from the local to the central pathology unit means that the standard procedure is time-consuming and that it is difficult to comply with governmental requirements. The aim was to evaluate whether real-time digital microscopy for urological cancer specimens during the primary diagnostic process can replace subsequent physical slide referral and reassessment without compromising diagnostic safety. **Methods:** From May to October 2014, tissue specimens from 130 patients with urological cancer received at Næstved Hospital's Pathology Department, and expected to be referred for further treatment at cancer unit of a university hospital, were diagnosed using standard light microscopy. In the event of diagnostic uncertainty, the VisionTek digital microscope (Sakura Finetek) was employed. The Pathology Department at Næstved Hospital was equipped with a digital microscope and three consultant pathologists were stationed at Rigshospitalet with workstations optimized for digital microscopy. Representative slides for each case were selected for consultation and live digital consultation took place over the telephone using remote access software. Time of start and finish for each case was logged. For the physically referred cases, time from arrival to sign-out was logged in the national pathology information system, and time spent on microscopy and reporting was noted manually. Diagnosis, number of involved biopsies, grade, and stage were compared between digital microscopy and conventional microscopy. **Results:** Complete data were available for all 130 cases. Standard procedure with referral of urological cancer specimens took a mean of 8 min 56 s for microscopy, reporting and sign-out per case. For live digital consultations, a mean of 18 min 37 s was spent on each consultation with 4 min 43 s for each case, depending on the number of digital slides included. Only in two cases could a consensus regarding the diagnosis not be reached during live consultation; this did not, it should be noted, affect patient treatment. Complete agreement between conventional and digital histopathology diagnosis was reached in all the 53 patients referred to central pathology units. The participating pathologists were in general comfortable using live digital microscopy, but they emphasized that a fast internet connection was essential for a smooth consultation. **Discussion and Conclusion:** An almost perfect agreement between live digital and conventional

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microscopy was observed in this study. Live digital consultation allowed cases to be referred from local hospitals to central cancer units without the standard delay caused by shipment. Only a few preselected specimen slides for each patient were presented in live consultation, which reduced the time spent on diagnosis compared to using the conventional method. Implementation of real-time digital microscopy would result in quicker turnaround and patient referral time, and with careful selection of relevant specimen slides for consultation, diagnostic safety would not be compromised.

**Key words:** Digital pathology, digitalization, real-time consultation, telemedicine, telepathology, virtual microscopy

## INTRODUCTION

Centralization of cancer treatment in Denmark has resulted in an increase in subspecialist pathologists at large cancer center and a decrease at smaller local pathology units. This skewed distribution of subspecialty pathology areas entails the second opinion and reassessment of diagnostic tissue specimens at central pathology centers for patients referred for specialized cancer treatment. The standard procedure with regard to this reassessment is very time consuming due to CGI of the physical specimen glass slides from local to central pathology units [Figure 1]. The procedure involves shipping by standard courier and can take several days with the risk of specimen damage or loss. During the specimen reassessment process, the consultant pathologist may request additional tissue preparations, which would involve additional shipping expenses and take more time.[1]

In 2007, the Danish government introduced a procedure for standard cancer treatment to ensure cancer patients receive high-quality treatment without unnecessary delays. The entire process covers, from start to finish, reasonable suspicion of cancer through diagnosis to end of treatment. Each step in this process allows only a certain number of days depending on cancer type. The current logistics regarding the second opinion and reassessment of diagnostic tissue has made it difficult for Pathology Departments to comply with government requirements.

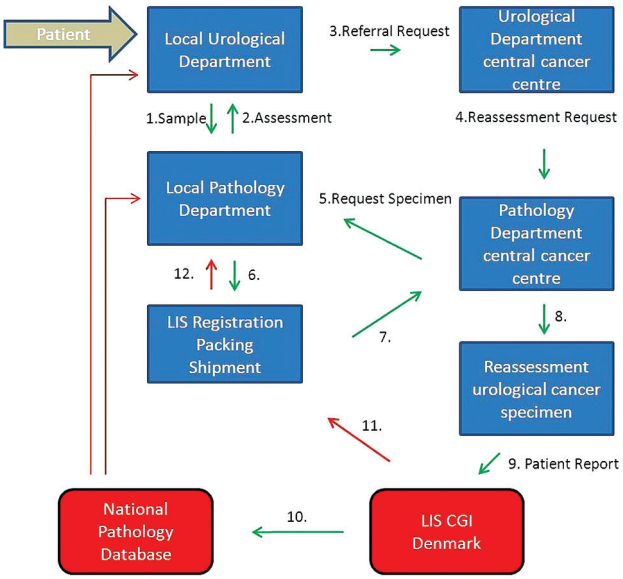


**Figure 1: Specimen workflow of the reassessment process: ordering and handling of the diagnostic specimen, including all glass slides and in some cases also the tissue blocks, where the patient is referred to a university hospital for further specific cancer treatment**

The search for new ways to improve this time-consuming procedure has led to the whole slide image (WSI) solution and use of digital microscopy (or telepathology) in diagnostic pathology. The digital solution offers a unique opportunity for pathologists to collaborate over large geographical distances. However, it also presents new IT challenges respecting large-scale routine consultations. WSI files require a server solution with sufficient storage allocation for consolidating images inpatient cases and connection to a scanning platform via either a direct connection or a high-speed network, which again raises questions regarding time for access of stored image files. In addition, viewing image files requires access for the consultant pathologist via network resource sharing or a vendor-supplied web-based viewing system, and this requires a connection that can dodge IT security and firewalls, especially between different institutions. This raises issues regarding patient information safety.[1] Introducing real-time digital microscopy overcomes several of these challenges.

Real-time digital microscopy involves streaming of image information in real-time to a connected client viewer, where the pathologist provides the consultation; this solution thus enables pathologists to gain immediate access to a consultant pathologist with specific knowledge of a particular subspecialty. Real-time digital consultation can be set up relatively simply without the need for image file transfer or expensive server solutions for storage.[1] In this study, a VisionTek digital microscope was used for real-time digital consultations. The digital microscope is a hybrid between a small desktop slide scanner and a conventional microscope that can be used to view up to four slides side-by-side simultaneously. The system operates via software through a PC interface

and an internet connection that makes it possible for pathologists to collaborate on the same physical specimens by simultaneously viewing the same live images. Computer software for remote access and control provides the consultant pathologist with the opportunity to remotely navigate the specimen slides and pinpoint areas of interest while discussing any challenges regarding the diagnosis with the other pathology user. During the live consultation dialog, the consultant pathologist is able to request additional tissue preparations if the material is deemed insufficient, and the new workup can be presented to the consultant pathologist on a later occasion, thus saving valuable time.

This study mainly focused on the use of digital microscopy as a replacement for the procedures in conventional consultations and the reassessment of cancer specimens of patients potentially to be referred to a specialized cancer treatment unit at a university hospital. The aim was to assess the use of real-time digital microscopy for urological cancer specimens during the primary diagnostic process and decide whether it can replace subsequent physical slide referral and reassessment in connection with a patient referral, in accordance with government requirements regarding cancer treatment and without compromising diagnostic safety.

## METHODS

From May to October 2014, 130 urological cancer specimens received at Næstved Hospital's Pathology Department, and expected to be referred to a central Pathology Department, were diagnosed using both standard procedures and digital microscopy. The urological specimens included prostate, urinary bladder, and kidney cancers. A VisionTek desktop digital microscope (Sakura Finetek, Tokyo, Japan), with a capacity of four slides and the ability to stream live images to remote viewers, was used [Figure 2].

During standard pathology workup, the local Pathology Department (in this case Næstved Hospital situated in the Southern part of Zealand approximately 100 km from Copenhagen) receives patient samples from the local urological department for assessment and diagnosis. For Næstved Hospital, patient cases that require assessment by a specialist because of a request by the patient, or the stage or progress of cancer, are referred to the central urological department of Rigshospitalet or Odense University Hospital. The urological cancer center at either of these university hospitals will commission a reassessment of the specimen originally evaluated by their own Pathology Department. The local Pathology Department registers all slides relevant to each case in the national laboratory information system (LIS) (CGI Denmark, Aarhus, Denmark), packs the slides and sends them by national postal services to the central


**Figure 2: Arrangement of the VisionTek Digital Microscope workstation (a) and the digital workstation of the consultant pathologist (b). Remote access to Næstved Hospital is achieved on the rightmost computer, in this case showing a split screen with a prostate core biopsy at the top and the corresponding immunohistochemical stain at the bottom. The middle screen shows the LIS with an open speech recognition window at the front. The leftmost screen is used for correspondence and access to the electronic patient case record**

pathology unit. The Central Pathology Department will unpack and register the referred slides in the LIS before the slides, and the corresponding paperwork is presented to a pathologist for microscopy and reporting. A full report with text and SNOMED diagnoses is compiled and recorded in the LIS, where via access to the national pathology database, the patobank that covers every pathology report made by Danish pathologists since 1999, it can be read by the local pathologist. Subsequently, the slides are registered, packed and sent back to the local Pathology Department, where once again they are unpacked, registered and archived locally.

In our setup, one consultant pathologist and two residents were stationed locally at Næstved Hospital where there was a VisionTek digital microscope. Three consultant pathologists were stationed at Rigshospitalet with workstations optimized for digital microscopy (HP computers; Intel Core i5-3470 CPU at 3.20 GHz, 12 GB RAM, 64-bit operative system, HP ZR2440w 24" screens, NVIDIA GeForce GT 630 graphic card (GeForce) and Windows 7 Enterprise (Microsoft)), using normal pointing devices (mouse) and keyboards. Whenever the local pathologist at Næstved Hospital encountered a case expected to be referred to the university hospital for further treatment, or a case presenting diagnostic uncertainties, the pathologist contacted one of the specialist pathologists at Rigshospitalet. The local pathologist had previously selected a maximum of four slides to be presented to the consultant pathologist and loaded them into the VisionTek digital microscope.

The local pathologist would contact the consultant pathologist by telephone, sms/text message or E-mail to

find a suitable time for consultation, and at the agreed time, he or she would call the uropathologist over an ordinary telephone line. Accepting the call, the consultant pathologist would receive a specific code for online connection with the VisionTek workstation, using the remote access software. This allowed the uropathologist to take over the VisionTek workstation, performing telepathology from his or her own computer. The system operated through a PC software interface and remote control software (TeamViewer GmbH, Göppingen, Germany) that gave remote access to the consultant pathologist and thereby the ability to navigate through the slides. A dialog between the local pathologist and the consultant pathologist regarding tumor type, grade and stage of urological cancer took place simultaneously over the telephone, and a consensus diagnosis was reached.

All 130 urological cancer specimens were examined by pathologists stationed at Rigshospitalet regardless of which hospital the patient cases would potentially be referred to afterwards according to standard procedure. Time of start and finish for each consultation case was logged in the VisionTek viewer software. Time from arrival to sign-out of the physically referred cases was logged in the LIS, and time spent on microscopy and reporting was noted manually for each consultation case. Diagnosis, including a number of involved biopsies to reach the diagnosis by digital microscopy, disease grade and stage, if applicable, and overall time spent on each diagnosis were compared between digital microscopy and conventional microscopy.

The Science Ethics Committee of the Capital Region of Denmark regarded the study as a quality assurance investigation, not requiring official permission according to Danish legislation and the Helsinki Declaration (report no. H-15002358).

A paired *t*-test was used to compare mean times for conventional versus digital microscopy and a Chi-square test to compare diagnostic consensus. Linear regression analysis was used to test development in consultation time and number of consulted cases. A *P*-value of 0.05 was considered statistically significant. The statistical analyses were performed using SPSS 23.0 software (IBM, Armonk, NY, USA).

## RESULTS

A total of 130 urological cancer specimens were included in the live digital consultation study, and complete data were available for all cases. The specimens included 97 prostate cancers, 31 urinary bladder cancers and two kidney cancers from 119 men and 11 women, and the age of the patients ranged from 37 to 85 years. The gender skewness was caused by there being a majority of prostate cancer specimens. Diagnosis for each case was noted, including the number of involved biopsies when relevant, growth depth of cancer cells (i.e., stage) and for prostate cancer the Gleason score. For each live consultation, 1–4 H and E specimen slides were selected for evaluation, and in 36 cases 1–7 additional immunohistochemically stained slides were presented. In two cases, additional IHC slides were required after the first digital consultation. The thickness of the sections made it difficult to distinguishing between lymphocytes and tumor cells and additional HIS slides were required.

Of the one-hundred and thirty patients, 53 were referred to one of two central cancer units following the previously described standard procedures. Thirty-four cases were referred to Rigshospitalet (Copenhagen University Hospital) and 19 were referred to Odense University Hospital. In all 53 referred cases, complete agreement between the digital diagnosis and the reassessment performed using conventional microscopy was reached, regardless of the fact that not all slides had been presented during the digital real-time consultation.

The standard procedure for referral of urological cancer specimens by submission of slides using postal services took a mean of 8 min 56 s for microscopy, reporting and sign-out. Unpacking, registration, repacking, etc., were not included in this time measurement. For live digital consultations, a mean of 18 min 37 s was spent on each telephone call, corresponding to a mean of 4 min 43 s for each patient case (mean 3.95 cases per call), depending on the number of digital slides included. Time spent on each patient case in real-time digital consultations was significantly lower than time spent using conventional microscopy (mean time conventional 8 min 56 s [standard deviation (SD), 3 min 50 s], mean time digital 4 min 43 s [SD 2 min 55 s]; $P < 0.001$).

A slight improvement in the time spent on each specimen slide during the live consultations was observed during the study [Figure 3a], although the decrease in time spent on a weekly basis did not reach statistical significance ($P = 0.274$). Simultaneously, the number of presented cases tended to increase during the study ($P = 0.183$) [Figure 3b].

For 128 of the 130 urological cancer specimens, it was possible to reach a consensus regarding the diagnosis during the live digital consultation. Only in two cases could a consensus between the local pathologist and the consultant pathologist not be reached ($P < 0.001$, Chi-square test). The disagreement in the two nonconsensus cases had no impact on patient treatment. In patient one there was disagreement regarding urinary bladder biopsies as to whether the diagnosis was squamous carcinoma or urothelial carcinoma with squamous differentiation. In patient two there was disagreement regarding a prostate adenocarcinoma as to whether the Gleason score was 3 + 3 or Gleason score

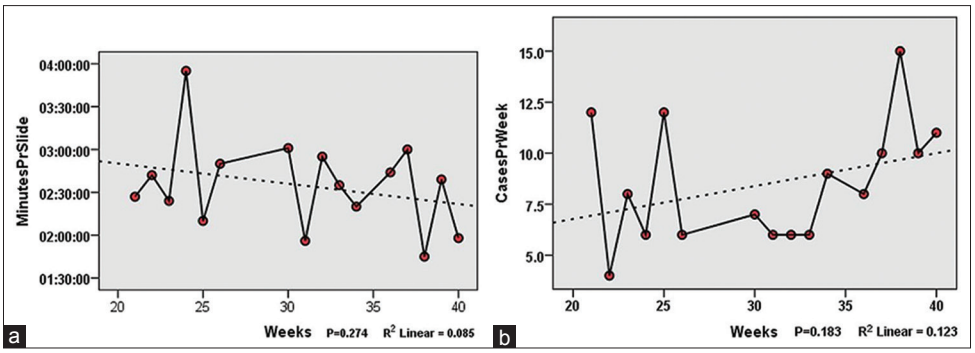


**Figure 3: Time expenditure and number of cases presented during the study. (a) Mean estimated time spent on individual slides on a weekly basis throughout the study. The red dots represent the actual time expenditure per week (minutes per slide), whilst the dotted line represents the regression ($P$ = 0.274, $r^2$ = 0.085). (b) Number of consultation cases on a weekly basis throughout the study. The red dots represent the mean number of cases during the individual week, while the dotted line gives the regression ($P$ = 0.183, $r^2$ = 0.123)**

3 + 4. The urologists subsequently entered this patient into an active surveillance program.

The speed of the internet connection influenced the remote control session, and in a couple of sessions short periods of up to a couple of seconds' delay were experienced during the live consultations, and focus fluctuations were consequently experienced in some slide images. No scheduled consultations were postponed due to slow internet connection. The time delay was reported subjectively by the participants and was dealt with by waiting for a sharp image. The participating pathologists were in general comfortable using live digital microscopy but emphasized that a fast internet connection was essential for a smooth consultation.

## DISCUSSION AND CONCLUSION

The technology for using WSI in pathology has been under development for the last decade, but it still awaits general acceptance as a diagnostic tool.[2] There are three main reasons for this: The need to invest in new equipment, patient safety issues, and diagnostic accuracy.

For digital pathology to be implemented in a Pathology Department, investments in WSI scanners, server solutions for retrieving and archiving image files, and high-performance computers and screen display have to be made. Financial projections have estimated, however, that a shift from conventional to digital microscopy would give savings of US$ 18 million over a 5-year period for a large academic institution with 219,000 annual accessions[3] and would break even at a 7% increase in effectiveness (Prof. Darren Treanor, personal communication).

The reluctance of IT managers to implement digital pathology is primarily because of patient safety issues and IT requirements related to security and file access. Patient safety issues mainly concern diagnostic accuracy, and some pathologists still do not trust the quality of digital images compared to the optical images of conventional microscopy. In response to this objection, several studies have compared WSI with conventional diagnosis, providing results that support the safety and efficiency of using digital images as a diagnostic tool.[4-6] Recently, the College of American Pathology has issued a set of guidelines for digital pathology in an attempt to redress these issues.[2]

Consultation and referral specimens may rank with the more difficult cases, and it would, therefore, be reasonable to question the diagnostic safety of using WSI as a diagnostic consultation interpretation tool. Validation studies that assess the diagnostic accuracy of WSI in consultation cases show no relevant differences between conventional and digital microscopy.[7,8] These results further confirm the safety and usability of WSI in diagnostic pathology. Another consultation study involved urological needle biopsies, focusing on the use of WSI in routine microscopy of consultation cases. The authors concluded that intra-observer agreement for Gleason grade and score was good to excellent, and that digital interpretation was comparable to that of conventional microscopy.[9] In light of the results of that study we were confident that our results would be comparable.

In our study, we observed a perfect agreement between live digital and conventional microscopy with no disagreements in 53 referred cases and only minor disagreements in two cases where a consensus could not be reached during the digital microscopy session. This confirms the results showing no relevant differences between conventional and digital microscopy in consultations of other groups.[7-9]

In two cases a consensus could not be reached during the live consultations. The first involved diagnosis of a bladder carcinoma where there was disagreement between squamous carcinoma and urothelial carcinoma with squamous differentiation. The second involved a prostate adenocarcinoma where there was disagreement in the final Gleason score (3 + 3 vs. 3 + 4). The treating urologists did not consider that the disagreements had any impact on treatment.

We found conclusively that preselection of one to four slides based on the diagnostic question (e.g., presence of cancer, tumor type, or difficulties in reaching a Gleason score) was representative of a complete patient case when assessed by conventional consultation where the pathologist reviews all slides. The selection needed in real-time digital consultation, on account of slide loading limitations of the VisionTek digital microscope and keeping time expenditure down, did not hamper the diagnostic accuracy.

Hence, real-time consultation using digital microscopy does not compromise diagnostic safety. The procedure allowed patient cases to be referred from local hospitals to central cancer units without the standard delay caused by shipment of the diagnostic specimens for a second opinion. The few preselected specimen slides presented in live consultation from each patient case reduced the time spent on diagnosis compared to conventional microscopy and reporting, obviously because of the reduction in the number of slides to be assessed per case. Results achieved with this setup will reduce turnaround time for patients with urological cancer and make it easier to comply with current governmental requirements. In addition, the setup will ensure easy access to a second opinion and remove the need for slow and expensive shipping of physical slide specimens by standard courier in cases where a pathologist needs assistance during the initial specimen evaluation and diagnosis.

Throughout the course of this study, notably less time was spent on individual slides in the real-time diagnostic setting as compared to conventional consultation using physical slide referral [Figure 3a]. An explanation for this might be that the local pathologist and the consultant pathologist slowly develop a better understanding of how each individual pathologist interprets difficult cases. In live digital consultation, knowledge will inevitably be shared between the pathologists and a better diagnostic understanding of the more difficult cases that qualify for a second opinion will be achieved. From that perspective, using digital real-time consultation will improve the general level of competence through mutual education and ultimately may reduce the need for future second opinions. We did, meanwhile, observe an increase in the number of consultation cases throughout the period of this study [Figure 3b]. The explanation might be that cases of lesser complexity, which normally would not qualify for a second opinion, are included anyway because of easy accessibility. This overconsumption obviously needs to be eliminated in order for the procedure to be cost-effective.

The live streaming of images in this setup solves the problems of sorting and transfer of image files encountered in digital diagnostics using WSI files, and there is no need for backup storage capacity or staff resources to scan the slides. This setup is ideal for smaller Pathology Departments lacking subspecialty pathologists. Recruiting subspecialist pathologists for more remote or smaller Pathology Departments is increasingly difficult because of the general shortage of pathologists. A live streaming consultation setup could ultimately mean the survival of smaller and more remote Pathology Departments by providing a fast and safe way to communicate with subspecialist pathologists located at central cancer centers. For the patient, this would guarantee easy access to subspecialists regardless of hospital selection or referral, ensuring an optimal pathology service for all patients.

One of the limitations of this study was that 34 of the 53 referred cases were sent to the same central cancer unit (Rigshospitalet), meaning that the consultant pathologists who participated in the live digital consultations might be presented with a case they had already seen. To address this limitation, the referred cases were randomly distributed between the three consultant pathologists by a secretary who had no knowledge of the study, and the individual pathologist had no influence on the cases presented. Still, it cannot be excluded that a consultant pathologist saw a case twice. In the guidelines published by the College of American Pathologists and the Laboratory Quality Center, a washout period of 2 weeks is recommended.[2] All cases in this study met this recommendation. Another limitation of this study was the selection of slides for review. If the referring pathologists failed to recognize significant histological findings, these slides would not be selected for review by the subspecialists.

Implementing real-time digital microscopy would result in notable reductions in turnaround time and patient referral time, and furthermore, we have demonstrated that a few carefully preselected specimen slides for consultation are representative of a case without compromising diagnostic safety.

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Nil.

### Conflicts of Interest
There are no conflicts of interest.

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