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REVIEW

Improved access to histopathology using a digital system could increase the organ donor pool and improve allocation

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Summary

Improvements in digital slide scanners have reached a stage that digital whole slide images (WSIs) can be used for diagnostic purposes. A digital system for histopathology, analogous to the systems used in radiology, would allow the establishment of networks of subspecialist histopathologists to provide a regional, national or even international rota to support out of hours histopathology for emergency frozen sections, urgent paraffin sections and to generally improve efficiencies with the provision of histopathology services. Such a system would promote appropriate organ utilization by allowing rapid characterization of unexpected lesions in the donor to determine whether donation should occur and further characterization of the organ, such as the degree of fibrosis in the kidney or steatosis in the liver, to determine whether the organ should be used. If introduced across Europe, this would promote safe and effective exchange of organs and support a cost efficient use of pathologist expertise. This review article outlines current issues with the provision of an urgent out of hours histopathology service and focuses on how such a service has the potential to increase organ donors, improve allocation, sharing and the use of available donor organs.

Introduction

The demand for organs for transplantation far out numbers available donors resulting in patients dying on the waiting list [1]. By necessity, surgeons have extended the criteria for donors, such as by taking more organs from donors with a less favourable clinical history and using organs from donors after circulatory death (DCD) [1–7]. An increasing number of living donors has improved the situation for selected kidney and liver transplant recipients so that more patients have access to transplantation and waiting times, at least in some countries, are falling. Surgeons faced with the decision of whether to use donated organs have to balance risks of transplantation against risks of waiting on the list: while there exists some guidance and some prognostic models, much is based on ill-defined, subjective or unquantifiable data such as state of the organ [8]. In general, many units adopt a risk-averse policy in situations where information is lacking on aspects of the donor which are considered unfavourable such as solid lesions of uncertain nature. This risk-averse philosophy is greatest where the transplant has least lifesaving potential for example kidney transplantation compared with urgent liver transplantation.

Availability of histopathology

Timely availability of histological information about the state of the organ or of uncertain lesions allows a more critical evaluation of the donor and the organ and leads to more appropriate use scarce organs. Provision of such a

service during the normal working day may be a challenge if the donor is in a small hospital with no routine emergency histopathology service. Furthermore, the majority of donor retrieval operations occur out of normal working hours and so this necessitates the use of an on-call histopathology service. This is not available in all hospitals; a survey of renal pathologists conducted in the UK in 2005 found that many renal transplant centres do not have a pathology on-call service, in other centres renal pathologists are on a 1 in 2 rota, and in some nonrenal pathologists are contributing to the renal on-call service. This is similar in many other European countries. Whilst there may be no formal on-call, in some there are informal arrangements. A lack of on-call or informal on-call often requires extensive searching by the retrieval teams to find an available pathologist, sometimes with the specimen having to be transferred over long distances and potentially the donor becoming unstable in instances where cardiothoracic retrieval is being delayed until a knowledge of the pathology is known. A pathologist is not always available, in which case the organs are not used except under urgent life threatening conditions when the benefit outweighs the potential risk of transferring malignancy from the donor to the recipient.

An additional factor in providing out of hours histopathology is that histopathologists working in large departments are becoming increasingly subspecialized, routinely reporting limited numbers of organs or systems. They have consequently become relatively deskilled in other areas of histopathology. The Royal College of Pathologists have stated that pathologist should not be coerced into reporting out of hours what they do not report during their routine work [9]. For these reasons the maintenance of an out of hours pathology service within an individual hospital is becoming increasing difficult without pathologists being on-call continually for their subspecialty.

Clarification of possible malignant lesions

During the procurement of organs, the retrieval surgeon assesses the donor for contraindications to transplantation such as malignancy in the donor which may be transmitted to the recipient. For this, they explore the thoracic and abdominal cavities for any abnormality; detection of a possible malignant lesion is not uncommon as the majority of organ retrievals occur in adult patients many of whom are 50–75 years of age. Many of these lesions are readily identifiable by experienced surgeons, such as simple liver or renal cysts. Other lesions such as haemangiomata in liver or kidneys or focal nodular hyperplasia of the liver or biliary hamartomas can present considerable diagnostic difficulty. Histopathology has an important role in identifying the nature of these lesions and excluding the finding of a malignant neoplasm that would preclude safe transplantation and, conversely, allowing safe transplantation where appropriate. Similarly, lesions outside of the liver may also be detected and accurate histopathology of lymph node and other lesions plays an important role in reassuring the team about the safety of proceeding to transplantation. A retrospective high level audit, by NHSBT in the UK found that histopathology would have potentially increased available donors by 28 in a 6 month period, potentially over 300 more donor organs/year. If such conclusions can be extrapolated across Europe, then there is a potential for significant gains.

Assessment of liver steatosis

The more fat within the donor graft, the more likely the graft will not initially function optimally (delayed graft function) or never function (primary graft failure) [5]. The degree of perceived steatosis at which to discard the liver varies between centres [5,10], ranging from moderate to severe, but severely steatotic livers can be successfully transplanted, suggesting that matching of the degree of steatosis to the ability of the recipient to cope with an element of early graft dysfunction are important. The current gold standard for the assessment of donor steatosis is microscopic assessment of a frozen section, preferably with a robust but simple approach to quantification such as a Chalkley graticule. However, difficulties in obtaining prompt out of hours pathology, necessitate use of potentially less reliable methods. Surgeons traditionally assess the amount of fat macroscopically, both by assessing the colour of the liver (the paler the graft the more fat) and by assessing the liver edges which are less sharp in fatty livers. However, while such assessments are rapid and can perform well in experienced hands, they can vary significantly from the histopathological evaluation in individual cases [10]. Liver texture is the most reliable correlate with large droplet macrovesicular steatosis, but small droplet steatosis is underestimated [11]. Small droplet steatosis in post-reperfusion biopsies can impact on outcome [12], whilst the effect when seen in pretransplant donor biopsies is less clear. The accuracy of surgeons' opinions can be enhanced by use of noninvasive imaging and some physical approaches [11,13].

Knowledge of the degree of steatosis in donor biopsies can provide a more accurate way to decide which livers are not safe to transplant, and improve utilization by matching moderate and severely steatotic livers with patients' ability to cope with a period of initial graft dysfunction.

Assessment of kidneys and use of paired kidneys

Extended criteria (marginal) kidneys from elderly donors are being used, often with excellent results. The assessment of whether to use an elderly donor is based on the surgeon's

clinical assessment of potential risk factors such as a history of diabetes or hypertension, set against consideration of the donor age. Biochemical analysis around the time of organ donation can be unreliable predictors of renal function due to acute physiological changes in the potential donor around the time of brainstem or circulatory death [14]. Histological assessment and scoring can help the surgeon not only decide whether to use the organs but also whether to use as a single or double kidney transplant [15]. Studies in America on kidneys discarded by surgeons on clinical grounds were assessed by biopsy and used at another centre, either as a single or dual kidney transplant and showed that a significant number of these discarded kidneys could have been used [16]; a study in the UK found that kidneys discarded by one centre on clinical grounds were considered useable or potentially usable pending histology [17]. In many centres in Europe, it has become routine to biopsy all kidneys over the age of 60, to determine whether the kidneys can be used as 2 single, 1 single and 1 discarded or 1 pair of kidneys. Donor kidneys are matched to the recipient based on these criteria with excellent results [3,15,18,19]. It was found that kidney allocation using an algorithm based on histological score increased the donor pool by 24% with comparable functional outcomes between optimal donor single kidneys, extended criteria single kidneys and extended criteria double kidney transplants. Extended criteria kidneys transplanted without a biopsy had a worse outcome [15].

How can a reliable out of hours histopathology service be created?

It is evident that improving access to histopathology can increase the donor pool, avoid inappropriate transplantation of very high risk organs and improve the utilization of donor organs into suitably matched recipients. The increasing subspecialization of histopathologists makes it impractical and cost prohibitive to have an on-call specialist histopathology service at all potential donor hospitals. An alternative approach is to have the histopathology service based at the retrieval centres where the on-call for individual subspecialists would be onerous and probably also not sustainable. However, even in those states where there is a national organ retrieval service, such an approach is viable only where the number of retrieval centres is small.

The similarities between histopathology and radiology provide a solution using a digital system [20,21]. A histopathologist assesses images of tissues and cells looking for patterns based on colour, shape and texture variations to arrive at a diagnosis. This is a similar to a radiologist who assesses lower magnification images of the body and looks for variations in the grey scale to arrive at an interpretation or opinion on any abnormalities present.

Radiology has been revolutionized in recent years by the introduction of Picture Archiving and Communication System (PACS), a digital image, organizational and reporting system, allowing sharing of images between treating hospitals, efficiencies in working practice, supporting better audit and allows ease for obtaining second opinion. Histopathology is about to undergo a similar revolution with the potential for similar improved efficiencies and also for improved diagnosis [22,23]. It was recognized by General Electric™ (GE), one of the PACS providers, that there were similarities between the working practices of radiologists and histopathologists and they set about designing a pathology version of PACS. Digital scanners had been around for several years, led by Aperio™, but had been used for research and teaching purposes predominantly. Digital systems had been used in the US and in isolated remote areas to assist pathologists give second opinions or remotely report small numbers of cases, although in the early scanners image quality was of significantly lesser quality compared to conventional microscopes [24]. More recent data suggest that with current generation scanners this is reversed with diagnostic accuracy improved. In Canada, a remote digital system of reporting frozen sections has been employed with excellent results [25] and similar excellent correlation between whole slide images (WSI) and glass slide diagnosis have been found [26]. Certification of second generation scanners for diagnostic use has begun with the GE system obtaining European CE (Conformité Européene) marking in March 2013, Health Canada Class II device license April 2013 [23], where Leica™ (for first generation Aperio™ scanner) was also certified in May 2013, Australian Register of Therapeutic Goods Certificate August 2013, for diagnostic use in Australia and New Zealand, and certification is well underway in the USA. Other second generation scanner vendors will be following, so the system requires the ability to be able to use images from any scanner, there are regulations being established towards compatibility - digital imaging and communications in medicine (DICOM) [27,28].

The introduction of high quality WSI scanners within the histopathology departments of organ retrieval centres or other designated centre(s) would allow the establishment of a national or international network of on-call pathologists within all organ systems, significantly reducing the costs of providing an on-call service. Biomedical laboratory scientists are now taking on extended roles and could perform the initial macroscopic assessment of the specimen brought to the retrieval centre pathology laboratory. Digital photographs or secure video internet connections between the biomedical laboratory scientist and the remote on-call pathologist of the intact and/or sliced specimen could be established to allow this system to work in difficult cases. The histopathologist based at any remote location with

broadband internet access would report the frozen section, or rapid paraffin section for optimal kidney scoring [19]. Broadband bandwidth influences speed of downloading/'focusing' the WSIs, however, compression and streaming algorithms have been developed by Omnyx™ to overcome these issues. There are two methods of accessing WSIs via secure routes, one is using a secure client based system equivalent to PACS, the other is using a webviewer via a virtual private network (VPN) with a link to the webviewer sent to a secure email address. The pathologist would then liaise with the relevant surgeon or donor coordinator to discuss the findings. The reassurance that a surgeon would have in gaining access to high quality images would further reinforce mutual confidence and support appropriate risk taking.

As this means that these WSIs can be reported from anywhere in the world this raises a number of licensing and quality standard 'issues [22]. For an individual country, the reporting pathologist would be required to be registered with the appropriate national body and, where relevant, on the specialty register for histopathology. They should also be participating in EQAs (external quality assurance) [29,30], regular mini assessments, to show they are of an appropriate standard. To allow for international reporting, a different international validation/registration system will be required to ensure quality standards are maintained and provide reassurance for the surgeons.

Provision of such a system would need to be coordinated and maintained by national organ procurement organizations. Developing codes of practice, agreeing standards, coordinating processes and maintaining rotas of suitably qualified pathologists takes planning, time, money and organization. The advantages of economy of scale and more efficient use of pathologist time, with subspecialist rotas e.g renal or liver covering several states, must be balanced against the complexity of variations in time zones and language, custom and practice. Some organizations, such as Eurotransplant and Scandiatransplant, have developed extensive expertise in working across national boundaries. The costs of developing, implementing, maintaining and quality assuring the system will require both time and money, although there are potential financial savings which could impact the complex changing economic benefits of transplantation [8,31]. There is a need for a prospective audit to determine the need, risk, cost and benefits of such a system.

Improved standardization of grading by digital algorithms

Whilst histopathology is the gold standard in assessment of donor organs pretransplant, it is not perfect due to inter- and intra-observer variation [10,11]. The use of a digital histopathology allows the development of standardization using inbuilt image analysis within digital systems after the development of algorithms, e.g to assess the degree of steatosis or fibrosis in a liver biopsy, or quantitative rather than semi-quantitative assessment of percentage cortical scarring or arterial intimal thickening, and indeed the assessment of a renal donor could be expanded to include the glomerular size which has been found to be an indicator of outcome [32–35]. Digital algorithms for quantifying hepatic fibrosis on WSIs are being developed. These systems would overcome inter- and intra-observer variability, but at least in the short-term, would be reliant on a histopathologist checking the accuracy.

Other uses for digital pathology within the health care system

In the same way as for donor organ lesions described above, digital pathology systems allow networks of specialist pathologists across several centres or states to provide sustainable out-of-hours cover rotas within their speciality, where one specialist is available 24/7 per speciality to provide expert opinion across the participating hospitals. The principle can be extended to promote simple and rapid access to a second opinion from a regional specialist using case referral or conference capabilities of the software, or to provide rapid access to view relevant previous biopsy material from another hospital. These innovations should reduce the incidence of significant diagnostic discrepancies that audits show to affect up to 50% of cases referred to tertiary referral centres [36–40] thereby streamlining both accurate early diagnosis and treatment. Related diagnostic and service management uses include facilitation of double reporting between specialists where a given hospital may have only one such expert (e.g. soft tissue sarcomas), provision of holiday cover across such specialities between hospitals, or redistribution of case workload excess across hospitals within a network, e.g. from workload initiatives or where there is local staff shortage. The move to digital pathology offers the capability to unify macroscopic images with routine histology, fluorescence imaging [skin, renal, fluorescence *insitu* hybridization (FISH)] and electron microscopy (renal, neuropathology) into a single accessible digital record that when linked with past biopsies accessible online, provides for a much more streamlined and efficient workflow.

There are also additional benefits for pathology teaching at undergraduate and postgraduate levels by the easy development of digital teaching sets without potential loss of original material. EQAs will be improved, particularly for specimens where it is not possible to cut enough spare sections to distribute amongst pathologists. Digital images also lend themselves to the development of computer

algorithms to either speed up the pathologist, e.g counting mitoses or looking for acid fast bacteria within tissue sections, or improve accuracy, e.g algorithms to assess the degree of fibrosis or fat within a liver biopsy. These algorithms are already available to quantify human epidermal growth factor receptor 2(Her2) status of breast tumours.

Conclusions

There are rapidly evolving digital options for a different way of providing histopathology cover for out of hours urgent cases which can support emergency surgical situations including transplantation. This has the potential to increase donor numbers as well as improve the allocation and use of organs. There is a significant potential for such a system to be introduced across national boundaries but it is uncertain yet whether the benefits of economies of scale would be balanced by the complexity that such international collaboration and organization would need.

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