Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: F: By defining the minimum liver remnant required, volumetric analysis is now the pre-operative standard of care in liver cancer surgery worldwide

1. Summary of the impact (indicative maximum 100 words)

Impact: UoE-developed techniques to determine liver volume and define, pre-operation, the minimum liver remnant required have transformed the viability and success of liver surgery and stimulated commercial development of imaging software/hardware.

Significance: Precise functional liver volume measurement prior to surgery is now the standard of care and, for example, renders 85% of patients previously deemed irresectable to be resectable with a perioperative mortality of 2–4%.

Beneficiaries: Patients with liver cancer; the NHS and healthcare delivery organisations; imaging software/hardware companies.

Attribution: Pivotal studies were led by Wigmore and Garden at UoE.

Reach: Worldwide; technique recommended in guidelines in Europe, N America, Asia, Australasia; deployed in the management of 3600 patients per annum in the UK alone; the use of open-source software increases accessibility in developing world.

2. Underpinning research (indicative maximum 500 words) (currently 499)

Between 1999 and 2000, a team led by Professor Stephen Wigmore (Professor of Transplantation Surgery, UoE, 1997–2005 and 2007–present) and Professor O James Garden (Regius Professor of Clinical Surgery, UoE, 1988–present) developed at UoE a new technique in which a three-dimensional (3D) reconstruction of the liver was created from contrast-enhanced computed tomography scans using volume-rendering software [3.1]. Subsequent research has led to this approach being adopted worldwide. This was supported by a European Society for Organ Transplantation Senior Fellowship and a £57K award from the Royal College of Surgeons of Edinburgh and Tenovus.

In 2008, an estimated 520,000 new cases of primary liver cancer and 165,000 cases of liver metastases from colon cancer were reported worldwide. The only possibility of cure for these patients is surgical resection, ablation or liver transplantation. The treatment of choice in patients without cirrhosis is liver resection where possible. In UK terms, the 7–8% of affected patients with colon cancer who will either present with or develop metastatic disease amenable to resection equates to approximately 3600 per annum. Prior to the 1990s, liver resectional surgery was dangerous, with an estimated 25% mortality owing to post-operative liver failure. The establishment of dedicated and specialised units started to reduce this figure, but continued to rely on global clinical assessment to predict perioperative mortality, which lacked rigour and was inherently inaccurate. The key to understanding an individual's risk of post-operative liver failure is the ability to accurately measure liver volume. Using the virtual livers created by 3D volume reconstruction, a simulation of a planned liver resection could be performed and the software used to determine predicted residual and resected liver volumes. This approach was validated by comparing virtual resection volumes with actual liver volumes in patients who underwent liver resection. This was published in the highest-ranking surgery journal (Annals of Surgery) and not only established a novel technique, but defined a new language for describing liver volumes in the radiology and surgical communities [3.1].

Having established an accurate technique for measuring liver component volumes in surgery, this was applied pre-operatively to a cohort of patients undergoing liver resection. Patients underwent pre-operative volumetric analysis with 3D reconstruction of the liver and virtual hepatectomy to calculate future remnant liver volumes. This manuscript defined for the first time the percentage liver volume associated with resection for all common liver resectional procedures [3.2]. More importantly, by combining a postoperative scoring system for liver dysfunction with the measured future liver remnant volume, a relationship between liver volume and function after surgery was established. Crucially, the work demonstrated that a residual functional liver volume of at least 26% is required for non-cirrhotic livers to avoid serious postoperative liver dysfunction. The team also made an important link between liver volume and risk of postoperative sepsis [3.2].

Having developed a new technique for accurate preoperative measurement of liver volume, and confirmed the clinical utility of such measurements in defining the complications of liver surgery, the UoE team analysed two key aspects of liver function in human subjects undergoing liver resection. The first, on reticuloendothelial function, identified that a major liver resection produced a profound reduction in reticuloendothelial clearance capacity, which was only partially restored one week after resection [3.3]. This may be the link between liver surgery and postoperative immunocompromise, leading to sepsis and multiorgan failure.

The second study investigated the impact of major liver resection on a key liver metabolic pathway: urea synthesis. In collaboration with the University of Maastricht, the team demonstrated an almost instantaneous increase in metabolic activity following major liver resection to compensate for loss of liver cell mass [3.4]. A linear relationship between increased metabolic activity and resection volume (up to approximately 26%) validated the earlier clinical study demonstrating this as a critical volume in non-diseased liver, beyond which the liver cannot metabolically compensate.

Importantly, the UoE team has ensured accessibility to surgeons in resource-poor countries, by publishing the techniques using open source software [3.5, 3.6].

3. References to the research (indicative maximum of six references)

3.1 Wigmore S, Redhead D, Yan X,…Garden OJ. Virtual hepatic resection using three-dimensional reconstruction of helical computed tomography angioportograms. Ann Surg. 2001;233:221–6. DOI: 10.1097/00000658-200102000-00011.

3.2 Schindl M, Redhead D, Fearon K, Garden OJ, Wigmore S; Edinburgh Liver Surgery and Transplantation Experimental Research Group (eLISTER). The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut. 2005;54:289–96. DOI: 10.1136/gut.2004.046524.

3.3 Schindl M, Millar A, Redhead D,…Garden OJ, Wigmore S. The adaptive response of the reticuloendothelial system to major liver resection in humans. Ann Surg. 2006;243:507–14. DOI: 10.1097/01.sla.0000205826.

3.4 van de Poll M, Wigmore S, Redhead D,…Garden OJ, et al. Effect of major liver resection on hepatic ureagenesis in humans. Am J Physiol Gastrointest Liver Physiol. 2007;293:G956–62. DOI: 10.1152/ajpgi.00366.2006.

3.5 Dello S, van Dam R, Slangen J,…Wigmore S, Dejong C. Liver volumetry plug and play: do it yourself with ImageJ. World J Surg. 2007;31:2215–21. DOI: 10.1007/s00268-007-9197-x.

3.6 Dello S, Stoot J, van Stiphout R,…Wigmore S, et al. Prospective volumetric assessment of the liver on a personal computer by nonradiologists prior to partial hepatectomy. World J Surg. 2011; 35:386–92. DOI: 10.1007/s00268-010-0877-6.

4. Details of the impact (indicative maximum 750 words)

The original description of this work [3.1] has had a major impact on the field, even defining a new language and terminology used to describe liver volumes in the context of resectional surgery. Pre-operative liver volume analysis has become the standard of care incorporated in guidelines internationally, and has reduced mortality related to liver surgery.

Impact on public policy
The utility of liver volume analysis, and the finding that the critical volume of liver required for safe liver function is around 26%, has been corroborated by others and incorporated into guidelines worldwide for the safety of liver surgery and its practice, for example in the UK (2012), USA (2013), Japan (2008) and Australia [5.1–5.4].

Impact on clinical practice
The techniques of 3D modelling and virtual hepatic resection developed in this work have been universally adopted in major centres performing complex liver surgery and are now the standard of care worldwide. Evidence of this is the use of liver volume analysis as a baseline in initiatives to improve surgical and oncological outcomes. For example, registries of novel surgical techniques that seek to extend what is achievable by liver resection require liver volume analysis [5.5] and randomised controlled trials of neoadjuvant chemotherapy in unresectable secondary liver cancer that use "resectability" as an outcome measure require liver volume analysis where an extended resection may be required [5.6]. Furthermore, the UoE team's approach to measuring liver volume has been adopted for a wider context than just liver resection and it is now a particularly important component of the assessment of living liver donors as part of the transplant assessment process [5.7].

The association between liver volume and functional metabolic adaptation has been recognised and it has been shown that functional recovery of the liver precedes volume recovery [5.7]. This important observation permits surgery to take place considerably earlier after portal vein embolisation than hitherto considered. The importance of liver volume analysis and critical liver volume has also been recognised in association with the small-for-size syndrome that can occur after liver resection or partial liver transplantation [5.7].

The use of open-source software has been important to increase the accessibility of the techniques to surgeons worldwide. The software developed at UoE used in study [3.6], OsiriX, is the most widely used healthcare image viewer with 50,000 active users and >1000 downloads/150 000 hits per day. These methods have subsequently been used in reporting outcomes in clinical trials [5.8].

Impact on health and welfare
The principal beneficiaries of this work are patients undergoing liver surgery, through gains in the number of patients made resectable and improvements in safety, with implications for the treatment of 3600 patients annually in the UK alone. The safety of liver surgery, in which liver volume analysis has become an integral part, has improved significantly in the past two decades. Death from haemorrhage or liver failure is now a rare event with mortality rates of 2–4% in most major centres. The ability to determine the volume of the liver remnant accurately is an essential adjunct to treatments that render 85% of patients previously deemed irresectable to become resectable [5.9].

Impact on commerce
Using extensions of the techniques developed at UoE, commercial software and hardware companies have developed technologies for 3D reconstruction of vascular and biliary structures and the volumes of the territories they supply or drain [5.10]. Specific systems for 3D liver reconstruction currently being developed are Ova (Hitachi Medical Corporation, Japan), Synapse Vincent (Fujifilm, Japan), HepaVision (MeVisLab, Germany), Ziostation (Qi Imaging, Japan), VirtualPlace (AZE, Japan) and VR-Render (IRCAD, France). Other large multinational companies such as Siemens, GE Healthcare and Philips Healthcare are developing general 3D visualisation systems that can be applied to the liver. In 2013, Global Industry Analysts, Inc. projected that the global market for 3D medical imaging would reach US$2.2B by 2018.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 Khan S, Davidson B, Goldin R, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut. 2012;61:1657–69. DOI: 10.1136/gutjnl-2011-301748. *[British Society of Gastroenterology guidelines update.]*

5.2 Adams R, Aloia T, Loyer E, et al. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB. 2013;15:91–103. DOI: 10.1111/j.1477-2574.2012.00557.x. *[Statement from the Americas Hepato-Pancreato-Biliary Association; Society of Surgical Oncology; Society for Surgery of the Alimentary Tract.]*

5.3 Kondo S, Takada T, Miyazaki M, et al. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. J Hepatobiliary Pancreat Surg. 2008;15:41–54. DOI: 10.1007/s00534-007-1279-5.

5.4 Rahbari N, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011;149:713–24. DOI: 10.1111/j.1477-2574.2011.00319.x.

5.5 ClinicalTrials.gov. (2013). Registry of Major Liver Resections Including ALPPS and Other Liver Resections in Two Stages (ALLPSREG). http://clinicaltrials.gov/ct2/show/NCT01924741.

5.6 Folprecht G, Gruenberger T, Bechstein W, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010;11:38–47. DOI: 10.1016/S1470-2045(09)70330-4.

5.7 Clavien P, Oberkofler C, Raptis D, Lehmann K, Rickenbacher A, El-Badry AM. What is critical for liver surgery and partial liver transplantation: Size or quality? Hepatology. 2010;52(2):715–29. DOI: 10.1002/hep.23713.

5.8 Millet G, Truant S, Leteurtre E, et al. Volumetric analysis of remnant liver regeneration after major hepatectomy in bevacizumab-treated patients: a case-matched study in 82 patients. Ann Surg. 2012;256:755–61; Discussion 761–2. DOI: 10.1097/SLA.0b013e31827381ca.

5.9 Abulkhir A, Limongelli P, Healey A, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg. 2008;247:49–57. DOI: 10.1097/SLA.0b013e31815f6e5b.

5.10 Mise Y, Tani K, Aoki T, et al. Virtual liver resection: computer-assisted operation planning using a three-dimensional liver representation. J Hepatobiliary Pancreat Sci. 2013;20:157–64. DOI: 10.1007/s00534-012-0576-y.