Institution: Imperial College London

Unit of Assessment: UoA 15 (General Engineering)

Title of case study: Development of bipolar resection devices that improve outcomes in cancer surgery.

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

Dr Dickinson (Bioengineering) collaborated with Professor Habib (Surgery) to develop novel methods for removing or starving tumours. Resection (removing part of an organ) is theoretically an ideal method for treating liver cancer as the liver can regenerate, but it causes extensive blood loss. The Bioengineering team developed a bipolar electrode system that employs RF current to coagulate a track in the liver; the track can then be cut without bleeding. Prototypes were successfully tested in pre-clinical and clinical trials. 20,000 single-use devices (value: US$40M) have been sold under licence by AngioDynamics, with an estimated saving of >800 lives. Complications, intensive care, blood transfusions, and hospital stay have also been dramatically reduced. Dickinson developed further bipolar devices for maintaining the patency of ducts during pancreatic and biliary cancers, for ablating liver tumours and for blocking tumour blood supply. Sold by Imperial spin-out Emcision, these are also in current clinical use.

2. Underpinning research (indicative maximum 500 words)

Dr Dickinson was appointed to the Department of Bioengineering at Imperial College London in 2002. He developed close interactions with Professor Habib, a surgeon at the Hammersmith Hospital campus, intensifying an ongoing collaboration initiated by the then Head of Bioengineering, Professor Toumazou, and involving research fellow Dr Vandevoorde (2003-2004).

Resection (removing part of an organ) is theoretically an ideal method for treating some forms of liver cancer, as the liver can regenerate. However, the organ is highly vascular so resection by scalpel causes extensive blood loss, with associated morbidity, mortality and requirement for transfusions. Hot wires had been used to cauterise the cut vessels, but only sealed those <5mm in diameter; larger vessels required stitching, which is a long and therefore deleterious process. A new method was required that would seal larger vessels over a wider area.

Building on their earlier work concerning tumor ablation, Dr Dickinson and engineers from Imperial spin-out EMcision developed a method that employed radio frequency (RF) current to coagulate a track in the liver that could then be cut without bleeding. RF devices are widely used in surgery for ablation and coagulation. However, existing systems were monopolar – a knife, connected to an RF generator, constitutes one electrode and the return electrode consists of a pad under the patient. The sealing capacity is too limited for vascular tissues like liver and the poor contact of the return electrode often leads to severe burns.

To avoid these problems, the team developed bipolar devices. The work was conducted during 2003-2006. The key, patented [1] feature developed for the final design – the Habib 4X – was a square array of positive and negative electrodes, which coagulates a region 15 mm wide and seals large vessels. It works at 500 kHz, which is well above the frequencies affecting muscles and nerves and also provides good tissue conductivity by capacitative transfer across cells. Funding for the research came from a peer-reviewed project grant held by Dr Dickinson and Professor Habib [2], and from EMcision. Prototypes were successfully tested in pigs and Dr Dickinson then took the product through the CE mark and FDA approval processes; with his help, the device has been assessed in numerous clinical trials [e.g. 3].

Dr Dickinson and engineers from EMcision have subsequently developed and, with the assistance of clinicians, assessed [e.g. 4, 5] three further bipolar devices with geometries optimised for use in other situations:

1. *Hexablate* A hexagonal array of needles for ablating liver tumours. Developed in 2004-2006, it treats a larger (3 cm) cylinder of tissue over a shorter period of time than monopolar devices, and targets the tumour periphery where metastatic cells preferentially reside. Assessment of a further development – a miniaturised version for brain tumours – is underway.
2. *VesCoag* This device, developed in 2007-2008, is inserted into blood vessels, causing a blockage that starves tumours of blood. Current treatments rely on blocking vessels with glue, which is less long lasting.
3. *EndoHPB* An endoscopically-delivered device with two cylindrical electrodes, used for maintaining the patency of ducts during pancreatic and biliary cancers. Developed in 2008-2010, it keeps the patient strong enough for long enough to benefit from chemotherapy. Preliminary safety trials employing 30 patients have been completed.

3. References to the research (* References that best indicate quality of underpinning research.

*1. Patent: Habib N, Dickinson R, Pacey A. Surgical Resection Device. Worldwide, WO/2005/030071, 2005 http://patentscope.wipo.int/search/en/WO2005030071

2. Grant: N Habib and R J Dickinson. “Radio frequency bipolar bloodless liver tumour resection device.” BUPA Medical Foundation. 01/01/2004 – 31/12/2006; £161,904

*3. Ayav A, Jiao L, Dickinson R, Nicholls J, Milicevic M, Pellicci R, Bachellier P, Habib N. Liver Resection With a New Multiprobe Bipolar Radiofrequency Device. Arch Surg 2008;143:396-401. DOI: 10.1001/archsurg.143.4.396.

4. Kallis Y, Phillips N, Steel A, Dickinson R, Nicholls J, Jiao L, Vlavianos P, Habib N, Westaby D. Mo1291 Radiofrequency Ablation for Biliary Metal Stent Occlusion: Evolution of a Novel Endoscopic Technique and Proof of Concept. Gastrointestinal Endoscopy 2012;75:377-378. DOI: 10.1016/j.gie.2012.03.997.

*5.Mizandari M, Pai M, Xi F, Valek V, Tomas A, Quaretti P, Golfieri R, Mosconi C, Guokun A, Kyriakides C, Dickinson R, Nicholls J, Habib N. Percutaneous Intraductal Radiofrequency Ablation is a Safe Treatment for Malignant Biliary Obstruction: Feasibility and Early Results. Cardiovasc Intervent Radiol. 2013;36:814-819. DOI: 10.1007/s00270-012-0529-3.

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

Imperial spinout EMcision Ltd licensed the Habib 4X to RITA Medical [A], which was then acquired by AngioDynamics, a global, NASDAQ-listed public company employing 1,400 people in the USA, Europe and Asia; it is the market leader in RF ablation. The terms of the 2005 agreement, which has remained in place throughout the 2008-2013 assessment period, included an upfront payment of $50,000, a payment of $200,000 upon 510(k) regulatory approval by the FDA, and royalty payments based upon specific revenue targets. RITA also issued EMcision 150,000 unregistered shares of RITA common stock at the signing of the agreement and paid EMcision $500,000 on the first anniversary of the agreement. As part of the licensing deal, the Habib 4X will be made available to developing countries in Africa at cost price.

Between April 1st 2007 and June 30th 2013, AngioDynamics sold 23,723 Habib 4X units with a total value of US$48M throughout Europe, the USA and Canada, widely in Latin America, in Asia and the Pacific (China, Russia India, Taiwan, Singapore, Australia, Japan, Saudi Arabia, Gulf States and Israel), and in some African countries [B]. *Pro rata*, approximately 20,000 units (US$40M value) will have been sold during the REF period. Since it is a single use device, this means that the **reach** of this part of the impact is 20,000 patients, equivalent to roughly half of all liver resections in the USA. (Resections are used in 20% of liver cancer operations.)

The clinical **significance** is apparent from the following table (derived from references C-F):

	Conventional liver resection n=80 [C], [D]	Habib 4X Initial study n=62 [E]	Habib 4X Later study n=311 [F]
Total mortality	7.5%	0%	3.4%
Complications	43%	18%	21%
ICU/HDU admission	85%	0%	4%
Blood transfusion	49%	2%	5%
Post op stay	19 days	8 days	12 days
Pringle or TVE*	76%	0%	0%
Bile leak	9%	0%	2%

*Pringle or TVE are procedures to isolate the liver from its blood supply

For example, the reduction in mortality from 7.5% to 3.4% equates to 820 lives saved. (The difference between the figures for total mortality in columns 2 and 3 is thought to represent the involvement of less senior surgeons as the technique became more routine.) At least 4,416 fewer patients suffered complications. The reduction in the cost of blood transfusions derives not only from the smaller number of patients requiring one but also the reduced volume of blood needed for those who do. Similarly, the reduction in cost of the postoperative stay derives not only from the shorter stay (12 vs 19 days on average) but also from the fact that it is 81% less likely to involve the Intensive Care Unit or Higher Dependency Unit – that is, 16,200 fewer patients required such care. The device has thus had a large clinical impact. When the first 100 patients were followed up over a period of between 2 and 20 months, tumours had not returned in any of them [G]. Furthermore, the device has enabled surgeons to remove smaller parts of the liver than would otherwise have been practicable [F]. Additional evidence of clinical benefit for liver and renal procedures is provided in reference [H].

The **reach** of the research is increased because other types of cancer can also benefit. The device is used not only in liver resection but also in resection of kidney, lung, pancreas, spleen and uterine fibroids. In a recent study [I], for example, 90 patients underwent open nephron sparing surgery, during which the surgeon resected sections of the kidney with tumors but other portions of the treated kidney were preserved; half were treated with the Habib 4X and half had blood flow controlled with foam bolsters, suture ligation and Bovie electrocautery. **Significance** was substantial: 68% less blood was lost when using the Habib 4X device, and there were 91% fewer adverse events and a 16% shorter operating time.

The other devices developed by Dickinson and colleagues have also had significant impact. EMcision itself markets EndoHPB, Hexablade and VesCoag, rather than licensing them to AngioDynamics. We consider VesCoag as an example. As well as reducing blood supply to tumours, it can also be used to arrest hemorrhage following trauma or biopsy, stop bleeding in benign disease, and occlude vessels for indications such as arterio-venous fistulae and varicocele.

It was proven in clinical studies to be effective in treating liver cancer when used in combination with chemo-embolisation; it reduces the risk of embolic material complications seen in current techniques and allows for precise occlusion of a vessel. VesCoag had a very high level of patient acceptability in clinical studies. [J]

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

[A] http://investors.angiodynamics.com/releasedetail.cfm?ReleaseID=419967
Announcement of 26.5.2005 that RITA (now AngioDynamics) acquired the exclusive worldwide license rights to the Habib Sealer Resection Device. Archived on 24/10/2013 at https://www.imperial.ac.uk/ref/webarchive/j1f

[B] Staff Accountant, AngioDynamics. *To describe the sales (number and value) of the Habib 4x units sold by AngioDynamics between April 1st 2007 and June 30th 2013.*

[C] Professor of Hepatobiliary Surgery, Department of Surgery & Cancer, Imperial College London. T*o confirm data in column 1 of the table, which was presented in a talk "Bloodless resection techniques in HPB surgery" at 13th World Congress International Association of Surgeons & Gastroenterologists, Estoril, Portugal on 5th December 2003.*

[D] Cunningham JD, Fong Y, Shriver C et.al. One hundred consecutive hepatic resections: Blood loss, transfusion and operative technique, Arch Surg, 129, 1050-1056 (1994). DOI: 10.1001/archsurg.1994.01420340064011. *This paper provides data for column 1 of the table.*

[E] Ayav A., Jiao L., Dickinson R., Nicholls J., Milicevic M., Pellicci R, Bachellier P., Habib N, "Liver Resection With a New Multiprobe Bipolar Radiofrequency Device" Arch Surg. 2008;143:396-401. DOI: 10.1001/archsurg.143.4.396. *This paper provides data for column 2 of the table.*

[F] Pai M, Jiao LR, Khorsandi S, Canelo R, Spalding DRC, Habib NA. Liver resection with bipolar radiofrequency device: Habib 4X. HPB, 2008;10:256-260. DOI: 10.1080/13651820802167136. *This paper provides data for column 3 of the table and for the finding that smaller amounts of liver can be removed with the Habib 4X.*

[G] Imperial College Press Release, 8th September 2005: "New surgical device for bloodless operations gets first US outing": http://www.imperial.ac.uk/college.asp?P=6802 *This document states that when the first 100 patients treated with the Habib 4X were followed up over a period of between 2 and 20 months, tumours had not returned in any of them. Archived on 24/10/2014 at https://www.imperial.ac.uk/ref/webarchive/k1f*

[H] Wagman LD, Lee B, Castillo E, El-Bayar H, Lai L. Liver resection using a four-prong radiofrequency transection device. Am Surg. 2009;75: 991-994. WOS:000270795300028,
Provides further evidence of clinical benefit for liver and renal procedures

[I] White WM, Klein FA, Waters WB. Nephron sparing surgery using a bipolar radio frequency resection device. J Urol. 2008;180:2343-2347. DOI: 10.1016/j.juro.2008.08.046.
Describes the outcomes of a trial of using the Habib 4X for kidney resection

[J] EMcision VesCoag brochure https://app.box.com/s/4f5bcfaf8dd5dbfbd024. *Summarises clinical uses and patient acceptability of the VesCoag device.* Archived here on 24/10/2013