Institution: King's College London

Unit of Assessment: UoA5

Title of case study: Excimer laser technology for the correction of refractive disorders

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

Laser eye surgery is one of the most performed and successful types of surgery in the world. King's College London (KCL) researchers have been intimately involved in the development and improvement of techniques for both surgery and after-care to provide optimal results for the tens of millions of patients who undergo this type of treatment. KCL work is used by the world-penetrating companies Zeiss and Avedro to show evidence of the development of their latest techniques such as ReLEx and corneal cross-linking and by guidelines both in the UK (NICE) and abroad (the American Academy of Ophthalmology) to provide information on the long-term benefits and side-effects of laser eye surgery.

2. Underpinning research (indicative maximum 500 words)

Many millions have undergone laser eye surgery where the cornea is precisely reshaped to correct eyesight defects. In the 1980s Prof John Marshall (1991-2009, Frost Professor of Ophthalmology) was one of the pioneers in developing the Excimer laser technology used in this procedure. Since moving to King's College London (KCL) in 1991 he worked with colleagues to examine long-term outcomes of, and refine, laser eye surgery.

The main difference in the most common forms of laser eye surgery lies in how the cornea is prepared prior to correction. In laser in situ keratomileusis (LASIK) a flap is cut then folded back. In photorefractive keratectomy (PRK) surface cells are removed mechanically or by laser. In laser sub-epithelial keratectomy (LASEK) the epithelium is loosened and a skin-only flap is slid upwards. Each technique has its pros and cons. With LASIK, around 200 million fibres are cut, which can weaken the structural integrity of the eye. In PRK, less than 5 million fibres are cut, however healing time is longer and may be more uncomfortable than LASIK. With LASEK, recovery time is longer than for LASIK but it may be safer if the cornea is thin.

KCL researchers show long term outcomes for PRK and LASIK

In the early 1990's KCL researchers and colleagues at St. Thomas' Hospital Refractive Surgery Unit carried out the first UK clinical trials of PRK for short-sight (myopia). A 12-year follow-up included 68 patients who received corrections between -2 and -7 diopters (D) (a measurement of the cornea's optical power). They found that the majority whose correction was between -2 and -4 D were likely to stay within 1 D of the intended correction; however, this was the case for only 25% and 22% respectively in the -6 and -7 D groups. One concern of PRK is the side effects, here corneal haze, experienced by most patients initially but subsiding in the majority, decreased over time for all but 4%. Night halos remained persistent for 12% but dry eyes were only encountered in 3% (Rajan et al. 2004).

PRK can also be used to treat long-sight (hyperopia) and some of the first patients to receive this treatment (n = 21) at St Thomas' were followed at 7.5 years. Improvements in uncorrected near and/or distance acuity was achieved in 87.5% of eyes. The refractive correction remained stable for all and 67% of eyes with corrections of +1.5 or +3 D were within +1 D of the predicted correction. Predictability was poorer with +4.5 and +6 D corrections. While a peripheral ring of haze appeared in most eyes following surgery, with greatest intensity at 6 months, no patient complained of night-vision problems (O'Brart et al. 2005). KCL researchers also showed greater success for those with a lesser diopter correction 5 years after LASIK for hyperopia (n = 47 eyes). However, in those aged 43-55 (the maximum age in this study) there was regression greater than would be expected and it was concluded that long-term stability of hyperopic LASIK refractive corrections was uncertain, especially in older patients who eyes tend toward hyperopia as they age (Jaycock et al. 2005).

Refinement of PRK and LASIK techniques

KCL researchers have been intimately involved in finding optimum regimes for laser eye surgery. One variable they investigated was the circular area in which correction is delivered: the optical zone. Initial protocols had this at 4.0 mm diameter but in a study involving 123 eyes treated with PRK for myopia, the refractive outcome at 1 and at 10-12 years was significantly better with a 6.0

mm optical zone (especially for -6 D corrections), compared to 4.0 mm or 5.0 mm. Haze and night vision problems were also less with 6.0 mm (Rajan et al. 2006a). Another KCL study aimed to find the best cutting protocol when producing the flap during LASIK. They showed that the vertical side cuts of LASIK contribute to the loss of structural integrity during flap creation. Angulating side cuts such that the stromal diameter of the flap exceeds its epithelial diameter can decrease this effect and there is little disruption when only the corneal bed is cut (Knox Cartwright et al. 2012).

Research into aftercare

Researchers at KCL have also investigated how aftercare can affect outcome. 'Haze,' a mostly transient side-effect of PRK, is due to synthesis of extracellular material during wound healing. As collagenases are enzymes involved in the formation of this material it was thought that collagenase inhibitors (CIs) could prevent this process. However, in a laboratory study, CI's were not shown to demonstrate significant benefits (Corbett et al. 2001). Another study looked at the optimal use of mitomycin C (MMC) to reduce haze. MMC works by limiting the activity of the cells involved in the formation of the extracellular material and is applied immediately after the surgical procedure. Using an *in vitro* human cornea model, they found MMC promoted better healing conditions following PRK when applied for 60 seconds (Rajan et al. 2006b).

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

All studies have been published in international, peer-reviewed journals

- Corbett MC, O'Brart DP, Patmore AL, Marshall J. Effect of collagenase inhibitors on corneal haze after PRK. Exp Eye Res 2001;72(3):253-9. Doi: 10.1006/exer.2000.0959 (22 Scopus citations)
- Jaycock PD, O'Brart DP, Rajan MS, Marshall J. 5-year follow-up of LASIK for hyperopia. Ophthalmology 2005;112(2):191-9. Doi: 10.1016/j.ophtha.2004.09.017 (47 Scopus citations)
- Knox Cartwright NE, Tyrer JR, Jaycock PD, Marshall J. Effects of variation in depth and side cut angulations in LASIK and thin-flap LASIK using a femtosecond laser: a biomechanical study. J Refract Surg 2012;28(6):419-25. Doi: 10.3928/1081597X-20120518-07 (3 Scopus citations)
- O'Brart DP, Patsoura E, Jaycock P, Rajan M, Marshall J. Excimer laser photorefractive keratectomy for hyperopia: 7.5-year follow-up. J Cataract Refract Surg 2005;31(6):1104-13. Doi: 10.1016/j.jcrs.2004.10.051 (18 Scopus citations)
- Rajan MS, Jaycock P, O'Brart D, Nystrom HH, Marshall J. A long-term study of photorefractive keratectomy; 12-year follow-up. Ophthalmology 2004;111(10):1813-24. Doi: 10.1016/j.ophtha.2004.05.019 (87 Scopus citations)
- Rajan MS, O'Brart D, Jaycock P, Marshall J. Effects of ablation diameter on long-term refractive stability and corneal transparency after photorefractive keratectomy. Ophthalmology 2006a;113(10):1798-806. Doi: 10.1016/j.ophtha.2006.06.030 (20 Scopus citations)
- Rajan MS, O'Brart DP, Patmore A, Marshall J. Cellular effects of mitomycin-C on human corneas after photorefractive keratectomy. J Cataract Refract Surg 2006b;32(10):1741-7. Doi: 10.1016/j.jcrs.2006.05.014 (33 Scopus citations)

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

Laser eye surgery is the most common and most successful form of surgery in the world. For example, with photorefractive keratectomy (PRK) carried out using modern advanced Excimer lasers, over 98% of eyes with corrections between +4.5 and -8 will be within +/-1 diopter of zero, allowing patients to see clearly in the distance without the use of spectacles or contact lenses. King's College London (KCL) researcher Prof John Marshall was one of the pioneers of laser eye surgery and while the ground work was carried out in the 1980s-90s, current best practices have also been substantiated and informed by KCL work refining both the technique and aftercare.

Laser surgery guidance uses KCL research

Research carried out at KCL has contributed widely to both national and international guidelines on laser eye surgery. Current National Institute for Health and Care Excellence (NICE) guidance on 'Photorefractive (laser) surgery for the correction of refractive errors' (developed in 2006 but checked for updates in 2012 and affirmed current) (1a) is predominantly based on a systematic review that included Rajan et al. 2004 when looking at the evidence for long-term PRK effectiveness. This paper was not only used when assessing overall effectiveness, but was also

among a select group of references picked to help identify long-term benefits and complications of PRK for myopia (1b). As NICE guidance provides best practice it is widely used in professional and patient-centred literature, for instance in a Patient.co.uk piece aimed at healthcare professionals discussing outcomes of PRK (1c) and on the NHS choices website information on laser eye surgery (1d). While at KCL, Prof Marshall was also on the board of several key organisations, including being a member of the Royal College of Ophthalmologists' Working Group for Laser Refractive Surgery, which produced a number of guidelines aimed at both patients and professionals (1e).

KCL research is also extensively used in the 2008 clinical handbook 'Management of Complications in Refractive Surgery.' This was the "first book devoted to refractive complications" and contains "practical hints and case reports on outcomes providing ophthalmic surgeons with the most adequate solutions for the most frequent problems." As an example, Rajan 2006a is used when discussing complications of PRK (2a) and O'Brart 2005 and Rajan 2006a and 2006b are used when discussing complications of LASEK (2b).

Further afield, the American Academy of Ophthalmology (AAO) recently published 'Preferred Practice Pattern' guidelines on 'Refractive Errors & Refractive Surgery' that cite a number of KCL papers. For instance, Jaycock 2005 when discussing how LASIK "is associated with more regression in hyperoptic procedures than in myopic procedures" and Rajan 2006a when discussing long-term PRK studies (3a). The Jaycock paper is also used in AAO's continuing medical education exercise on managing complications of LASIK and PRK to discuss how regression can occur following these procedures (3b). Similarly, the American Academy of Optometry uses Jaycock 2005a, along with O'Brart 2005, in their 2009 'Position Paper on Refractive Surgery' when discussing how there are "excellent outcomes reported for PRK" (3c).

From policy to practice

A number of the team who worked with Prof Marshall on refining laser eye surgery at KCL practice both within the NHS and in their own private surgeries. For instance, Bristol Laser Vision, part of University Hospitals Bristol NHS Foundation Trust, is run by Consultant Ophthalmologist, Mr Philip Jaycock. He uses a large amount of the work he was involved in to provide an evidence-based website for patients and healthcare professionals, especially Rajan 2004 and O'Brart 2005, which he cites when discussing the long-term effectiveness of laser eye surgery (4a). Similarly, Mr David O'Brart, who carried out pivotal work with Prof Marshall, is a Consultant Ophthalmic Surgeon in private practice and at Guy's and St Thomas' NHS Foundation Trust (a King's Health partner). His website also provides a thorough overview of laser eye surgery, using the majority of the above-discussed references (4b).

Another big success of laser eye surgery is allowing people to enter professions where there are stringent requirements regarding eye sight such as in the military. A recent article in the Review of Ophthalmology includes input from a Navy ophthalmologist who recommends laser surgery saying that "for the best chance at a good result, surgeons should use the latest technology." He goes on to say, citing Knox Cartwright 2012 that "if someone elects to perform LASIK, create the flap with a femtosecond laser, preferably with one that allows a reverse-bevel side cut, which has been shown to be stronger than an externally angulated side cut" (4c).

KCL research used by Industry leaders

One of the big factors in laser eye surgery is the machines used to carry out the procedures. These are predominantly made by Zeiss, AMO (now owned by Abbott) and Alcon. KCL research has been used by all of these companies to help develop their latest technology. For instance, one of the newest techniques launched by Zeiss in the last year is ReLEx (Refractive Lenticule Extraction), where corneal correction is performed without creating a flap. Their product literature discusses how applying the findings of Knox Cartwright 2012 regarding cutting techniques proves that with ReLEx "since no anterior corneal sidecut is created, there will be slightly less increase in corneal strain compared to thin flap LASIK and a significant difference in corneal strain compared to LASIK with a thicker flap" (5a).

The work of KCL researchers on aftercare following laser eye surgery led to the development by the company Avedro of Lasik Xtra, a 3 minute procedure used in conjunction with a standard LASIK or PRK surgery to add biomechanical strength to the cornea through accelerated corneal cross-linking using ultraviolet light and riboflavin to strengthen bonds between collagen strands (5b,c). Prof Marshall helped develop this technique and Corbett 2001 appears in the patent for this technology (5d). Lasik Xtra is now become standard procedure worldwide at, for instance, the London Eye Hospital in the UK (5e) and in the Jerry Tan Eye Surgery centre in Singapore (5f).

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

1. UK Guidelines
    a. Photorefractive (laser) surgery for the correction of refractive errors. March 2006 (minor maintenance Jan 2012): http://www.nice.org.uk/nicemedia/live/11251/31560/31560.pdf
    b. A systematic review of the safety and efficacy of elective photorefractive surgery for the correction of refractive error: http://www.nice.org.uk/nicemedia/live/11251/31559/31559.pdf
    c. Patient.co.uk. Surgical correction of refractive errors: http://www.patient.co.uk/doctor/Surgical-Correction-of-Refractive-Errors.htm
    d. NHS Choices. Laser Eye Surgery: http://www.nhs.uk/livewell/eyehealth/pages/lasers.aspx
    e. Royal College of Ophthalmologists' Working Group for Laser Refractive Surgery: http://www.rcophth.ac.uk/page.asp?section=368&sectiontitle=
2. Management of Complications in Refractive Surgery. Eds: Alió y Sanz JL, Azar DT. Springer; 2008:
    a. Corneal Haze after Refractive Surgery: http://link.springer.com/chapter/10.1007/978-3-540-37584-5_11
    b. Complications of LASEK: http://link.springer.com/chapter/10.1007/978-3-540-37584-5_11
3. US Guidelines
    a. Academy of Ophthalmology 'Preferred Practice Pattern' guidelines on 'Refractive Errors & Refractive Surgery.' 2012: http://www.corneasociety.ca/wp-content/uploads/Refractive-Errors-Refractive-Surgery-Preferred-Practice-Patterns.pdf
    b. American Academy of Ophthalmology CME module on LASIK and PRK: Managing Complications. 2009: http://one.aao.org/lms/courses/managing_lasik_complications/index.htm
    c. American Academy of Ophtometry Position Paper on Refractive Surgery. 2009: http://www.aaopt.org/Media/Default/Docs/Position%20Papers/AAO%20CCLRT%20Refractive%20Surgery.pdf
4. Policy to practice
    a. Bristol Laser Vision: http://www.uhbristol.nhs.uk/patients-and-visitors/your-hospitals/bristol-eye-hospital/bristol-laser-vision/why-choose-bristol-laser-vision/safe-techniques,-thoroughly-researched/
    b. David O'Brart: http://www.davidobrart.co.uk/refractiveeye.html and http://www.davidobrart.co.uk/publications.html
    c. Bethke W. Refractive Surgery is Good to Go. 1/17/2013: http://www.revophth.com/content/d/refractive_surgery/c/38695/
5. Industry use of KCL research
    a. ReLEx by Zeiss (pgs 7, 11): http://www.zeiss.co.uk/88256DE3007B916B/0/BC5E25C57CEAA988C1257760002A0EE6/$file/czm_relex_smile_studienfolder_b_en_lay01.pdf
    b. Avedro LASIK Xtra: http://lasikxtra.com/how-it-works/
    c. Lasik Xtra information: http://www.avedro.com/WP/wp-content/uploads/2011/08/2013-Innovations-in-Ophthalmology.pdf
    d. Patent US8366689 B2. Method for making structural changes in corneal fibrils. Filed 30.09.2009, published 5.2.2013. Inventors: Marshall J, Hussein A, Muller D: https://www.google.com/patents/US8366689
    e. London Eye Hospital: http://www.londoneyehospitallasik.com/#!lasik-extra/c15dv
    f. Eyeworld article. January 2013. International outlook strengthening corneas in Singapore http://eyeworld.org/article.php?sid=6653