Institution: King's College London

Unit of Assessment: UoA3 - Dental

Title of case study: Early Detection of Oral Cancer and Potentially Malignant Disorders

1. Summary of the impact

King's College London (KCL) researchers have improved early detection of oral cancer, particularly in the pre-cancer stage, through the creation of a new diagnostic service for patients that is utilised both locally and nationally. Their work has also focused education, prevention and screening resources for oral cancer and pre-cancer on to high-risk communities, especially younger tobacco users and those who chew areca nuts. Information from KCL studies regarding causes, incidence and screening has also been disseminated widely through continuing education packages for healthcare professionals.

2. Underpinning research

King's College London (KCL) has a strong foundation in oral cancer research and is a World Health Organisation collaborating centre for oral precancer and oral potentially malignant disorders. This work is led by Prof Saman Warnakulasuriya (1990-present, Professor of Oral Medicine) and Prof Edward Odell (1988-present, Professor of Oral Pathology and Medicine).

Oral Cancer Epidemiology

Cancer in high-risk populations is a primary focus for KCL. Utilising 1986-91 data from the KCL-based Thames Cancer Registry, researchers found oral cancer incidence significantly higher among South Asian emigrants (95/232 = 40.9%) with age at diagnosis significantly younger (51.6 +/- 34.8) than the rest of the population (64.8 +/- 15.6) (1). One reason for the higher incidence may be through chewing paan, a mixture that can include areca nut and sometimes tobacco. In a 2001 East London Bangladeshi community study, 28% of 204 teenagers given a self-completing questionnaire chewed paan, with 2% adding tobacco. The median age of starting was 9 years and chewers were less inclined to think it could cause cancer (2).

Screening for Oral Cancer

As shown in a number of KCL studies, visual screening has low specificity for oral squamous cell carcinoma (OSCC), which develops in 6-20% of dysplastic lesions. KCL researchers proposed analysis of DNA aneuploidy (an abnormal number of chromosomes) as an alternative/additional screening method. As such, a long-term study (1993-2003) compared conventional dysplasia grading (n = 1401) with DNA ploidy analysis also carried in 273 of these patients. Malignant transformation occurred in 12% of the DNA ploidy analysis group and, of these, 63% of pre-existing index lesions were aneuploid. The positive predictive value for malignant transformation by DNA ploidy was 38.5% (65.2% sensitivity, 75% specificity) and by severe dysplasia grade 39.5% (30% sensitivity, 98% specificity). Combining these two screening techniques gave a higher predictive value than either technique alone, double that for previous tests (3).

Cancer Awareness and Late Presentation

Late presentation with oral cancer contributes to suffering and increases treatment complexity and costs. The KCL team postulated late presentation was due to limited public knowledge. Indeed, in a 1995 Health Education Authority commissioned study, of 1,894 people interviewed only 56% were even aware that there was such a disease as oral cancer, compared with 97% who had heard of lung cancer. There was a 76% awareness of the link between smoking and oral cancer but only 19% were aware of its association with alcohol misuse and 43% believed developing cancer was a matter of chance and therefore unavoidable. This survey pointed to a clear need to educate the public in oral cancer risk (4).

To investigate late presentation in younger people, another KCL study involving 53 patients under 45 with OSCC (recruited from 14 hospitals in southeast England from 1999-2001) found a median 5 week delay (range 1-104 weeks) from first noticing symptoms to seeking treatment. Lack of further education, perceptions of being under stress prior to diagnosis and lower amounts of tobacco smoked together explained 43% of the delay variance (5). In an examination of possible causes of OSCC in this age group, KCL researchers studied 116 patients and 227 matched

controls under 46. The majority reported exposure to the major risk factors of tobacco and alcohol, however, only smoking for over 20 years significantly elevated the odds ratio (OR=2.1), suggesting other factors are involved. Long term consumption of fresh fruits and vegetables appeared to be protective (6).

Oral Cancer Prevention

As a number of oral cancer cases are first detected by dentists and risk factors include tobacco, KCL researchers investigated the feasibility of dental practices provide smoking cessation advice. Training and educational materials were supplied to 22 practices and at 9 months follow-up of 74 patients who smoked 10 or more cigarettes a day, 11% were successful in giving-up tobacco, a figure similar to those reported in general medical practice settings (7). KCL researchers also investigated the effectiveness of smoking cessation at a dysplasia clinic. Out of 130 tobacco users referred to the clinic, five gave up following advice from their primary care physician/dentist (a quit rate of 3.8%); 17/100 quit following brief advice in the clinic (17% quit rate) and 10/30 quit after attending a smoker's clinic (33% quit rate). This was one of the first studies to show that pro-active work at a dysplasia clinic could increase the quit rate for tobacco users (8).

3. References to the research

1. Warnakulasuriya KAAS, Johnson NW, Linklater KM, Bell J. Cancer of mouth, pharynx and nasopharynx in Asians and Chinese immigrants resident in the Thames region. Oral Oncol 1999a;35:471-75. Doi http://dx.doi.org/10.1016/S1368-8375(99)00019-6 (28 Scopus citations)
2. Prabhu NT, Warnakulasuriya K, Gelbier S, Robinson PG. Betel quid chewing among Bangladeshi adolescents living in east London. Int J Paediatr Dent 2001;11(1):18-24. Doi: 10.1046/j.1365-263x.2001.00235.x (20 Scopus citations)
3. Sperandio M, Brown AL, Lock C, Morgan PR, Coupland VH, Madden PB, Warnakulasuriya S, Moller H, Odell EW. Predictive value of dysplasia grading and DNA ploidy for malignant transformation of oral potentially malignant disorders. Cancer Prev Res (Phila) 2013 6(8):822-31. Doi: 10.1158/1940-6207.CAPR-13-0001 (No Scopus citations, recent publication)
4. Warnakulasuriya KA, Harris CK, Scarrott DM, Watt R, Gelbier S, Peters TJ, Johnson NW. An alarming lack of public awareness towards oral cancer. Br Dent J 1999b;187(6):319-22. Doi: 10.1038/sj.bdj.4800269 (80 Scopus citations)
5. Llewellyn CD, Johnson NW, Warnakulasuriya S. Factors associated with delay in presentation among younger patients with oral cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004a:97(6):707-13. Doi: 10.1016/j.tripleo.2004.01.007 (27 Scopus citations)
6. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya S. An analysis of risk factors for oral cancer in young people: a case-control study. Oral Oncol 2004b;40(3):304-13. Doi: 10.1016/j.oraloncology.2003.08.015 (113 Scopus citations)
7. Smith SE, Warnakulasuriya KA, Feyerabend C, Belcher M, Cooper DJ, Johnson NW. A smoking cessation programme conducted through dental practices in the UK. Br Dent J 1998;185(6):299-303. doi:10.1038/sj.bdj.4809796 (45 Scopus citations)
8. Poate TW, Warnakulasuriya S. Effective management of smoking in an oral dysplasia clinic in London. Oral Dis 2006;12(1):22-6. Doi: 10.1111/j.1601-0825.2005.01146.x (15 Scopus citations)

Grants

- 1999-2002. PI: Warnakulasuriya K. Study of squamous cell carcinoma of the oral cavity in patients 45 years and younger. NHS Executive South Thames Research & Development, £68,306
- 2002-3. PI: Warnakulasuriya K. Identification of gaps in training dentists in treatment of tobacco dependence. European Commission, £56,948
- 2002-2005. PI: Odell EW. Ploidy analysis in oral dysplasia. Charitable Foundation of Guy's and St Thomas' Hospitals, £222,000
- 2005-6. PI: Warnakulasuriya K. Screening for Oral Cancer and Precancer in General Dental Practice. Department of Health, £49,062
- 2012-14. PI: Warnakulasuriya K. The use of lifelong and e-learning as an educational tool to improve oral cancer screening and early detection by medical and dental professionals in Europe. European Commission, £16,000

4. Details of the impact

The impact of King's College London (KCL) research on oral cancer and oral potentially malignant disorders (OPMDs) has been in targeting at-risk communities and practices, introducing novel diagnostic tests and in providing diagnosis and treatment information and education to healthcare professionals and the general public.

Areca Nut Usage/Targeting at-risk Communities and Practices
KCL's work on oral cancer risk associated with areca nut use has been widely used in documents aimed at both healthcare professionals and patients. For instance, 2012 NICE guidance on 'Smokeless Tobacco Cessation: South Asian Communities' utilised Prabhu 2001 and a review by Prof Warnakulasuriya containing both this paper and Warnakulasuriya 1999 when highlighting the use of areca nuts as stimulants in the UK by South Asian communities (1a). The Committee on Carcinogenicity of Chemicals in Food, an independent advisory committee that provides advice to Government departments and agencies on potential carcinogenicity of chemicals released a statement in 2008 on 'Betel Quid, Pan Masala and Areca Nut Chewing' that utilised Warnakulasuriya 1999a when coming to the conclusion that "there was sufficient epidemiological evidence to conclude that areca nut, when used in the form of betel quid or pan masala, is carcinogenic to humans" (1b). This paper was also cited to highlight oral cancer in South Asian migrants in a 2012 report on 'Tobacco and Oral Health' by ASH (Action on Smoking and Health), a campaigning public health charity established by the Royal College of Physicians that works to eliminate the harm caused by tobacco (1c).

Screening for Oral Cancer and OPMDs: From local service to worldwide resource
Underpinning research from KCL showed that the most accurate cancer predictor is DNA ploidy analysis. Based on this, there is now a routine ploidy analysis service at Guy's and St Thomas' Hospital (a King's Health Partner). It is the only such service in the UK and since its inception in 2005 has tested over 2,500 patients. A guidance leaflet that utilises the findings of Sperandio 2013 explains to clinicians how the test result can be used (2a). Patients with a high risk lesion are now more accurately identified and directed to treatment. Those with low risk lesions can be discharged to primary care, saving and focusing NHS resources and avoiding many years of recall appointments. Diagnostic ploidy analysis is marketed commercially through GSTS Pathology LLC (2b) and the service is being used by external units such as Queen's Hospital, Romford, Essex (2c). KCL has hosted visits from representatives of dental services from around the world, including from the University of Malaya, Malaysia; Kaohslung Medical University, Taiwan and the University of Toronto, Canada, with knowledge gained from KCL's experience being used to create other diagnostic ploidy services (2c).

KCL's research has been integrated into NHS UK-wide policy. The 2010 NHS UK National Screening Committee evaluation on oral cancer screening, which helped dictate UK-wide screening policy and was co-authored by Prof Warnakulasuriya. This utilises a number of KCL papers regarding risk factors for oral cancer (citing Llewellyn 2004b) and dentist-led smoking cessation (citing Smith 1998) and includes several reviews containing KCL studies when discussing epidemiology of oral cancer (2d).

Education for Diagnosis, Management and Prevention of Oral Cancer in Europe
Research by KCL regarding diagnosis, management and prevention of oral cancer and OPMDs has impacted Europe-wide guidelines and education. In 2011, the European Association of Oral Medicine (EAOM) produced a consensus European protocol for diagnosis and management of oral leukoplakia and erythroplakia aimed at oral healthcare practitioners. Co-authors include those from the KCL team and the report utilises Poate 2006 when discussing tobacco habits of patients (3a). This paper is also cited as a useful reference material with regard to ending tobacco use by the Swiss organisation The Oral Health Network on Tobacco Use Prevention and Cessation (3b).

KCL has a long history of professional education and support through the development of Cancer Research Campaign's fact sheets on oral cancer aimed at the general public. Their fact sheet on incidence utilises Warnakulasuriya 1999a when discussing areca nut or betal quid chewing (4a); their one on prevention includes Warnakulasuriya 1999b and Llewellyn 2004a when discussing

screening by dentists and late presentation (4b); their one on risk factors includes a number of KCL reviews regarding causes of oral cancer including areca nut use and Llewellyn 2004b when discussing risk and protective factors for patients under 45 (4c).

Information from a number KCL studies (both those discussed here and a range of others) regarding causes, incidence and screening has also been disseminated through continuing professional development (CPD) packages for dentists and professions allied to dentistry written by KCL researchers and funded by the Department of Health. The first CD-ROM was sent free to every UK NHS dentist in 2005 (5a) and a second edition on DVD, entitled Early Detection and Prevention of Oral Cancer, was available free to UK dentists on request from 2008 (5b). Through a grant application to the EU Lifelong Learning Programme this CPD resource has been translated into Italian and Greek. It has been available free in an adapted Web resource for patients and healthcare workers since 2011 (5c).

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

1. Oral Cancer and Areca Nut Use
   a) Smokeless tobacco cessation: South Asian communities. Sept 2012. NICE public health guidance 39: http://www.nice.org.uk/nicemedia/live/13907/60914/60914.pdf
   b) Betel Quid, Pan Masala and Areca Nut Chewing: http://www.iacoc.org.uk/statements/documents/ArecanutandBetelQuidstatementCOC08S2.pdf
   c) ASH Research Report: Tobacco and Oral Health. January 2012 http://www.ash.org.uk/files/documents/ASH_598.pdf

2. Screening for Oral Cancer and OPMDs
   a) Guidance leaflet on ploidy analysis: http://www.kcl.ac.uk/dentistry/about/acad/05-Ploidy-analysis-ver-July-2013.pdf
   b) GSTS diagnostic service: http://www.gsts.com/assets/files/Oral%20Pathology%20Pricing%20Structure%20and%20Prices%20Jan%202012.pdf
   c) Letters of support from a Consultant Maxillofacial Surgeon at a UK hospital, from a research group seeking to implement ploidy analysis in Taiwan; A Canadian collaborator clinician and researcher in and a Malaysian Clinician researcher seeking to implement the technique in Malaysia: http://www.kcl.ac.uk/dentistry/about/acad/ref-cds.aspx
   d) NHS UK National Screening Committee recommendations
      - http://www.screening.nhs.uk/oralcancer
      - www.screening.nhs.uk/policydb_download.php?doc=56

3. Diagnosis and Management of Oral Cancer
   a) European Association of Oral Medicine. Diz P, Gorsky M, Johnson NW, Kragelund C, Manfredi M, Odell EW, Thongprasom K, Warnakulasuriya S, Bagan JV, van der Waal I. Oral leukoplakia and erythroplakia; a protocol for diagnosis and management. EAOM 2011. http://www.kcl.ac.uk/dentistry/about/acad/oral-leukoplakia-and-erythroplakia.pdf
   b) The Oral Health Network on Tobacco Use Prevention and Cessation: http://www.tobacco-oralhealth.net/material/material.asp

4. Cancer Research Campaign factsheets: http://info.cancerresearchuk.org/cancerstats/types/oral/
   a) Incidence: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oral/incidence/
   b) Prevention: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oral/prevention/
   c) Risk factors: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/oral/riskfactors/

5. Early detection and prevention of oral cancer: an interactive resource for primary care teams
   a) Reviewed in http://www.nature.com/bdj/journal/v204/n1/full/bdj.2007.1192.html
   b) Text and references at http://www.kcl.ac.uk/dentistry/about/acad/ref-cds.aspx
   c) Early Detection and Prevention of Oral Cancer: http://www.oralcancerldv.org/en/