

Submission

Date: June 2014

Anal Cancer - Diagnosis, Monitoring and Management in Sydney and South East Sydney Local Health Districts

Epidemiology: Anal cancer is uncommon in the general population, but is increasing quite rapidly. Between 1982 and 2005, incidence of anal cancer in Australia increased from 0.65 to 1.00 per 100,000 person yearsⁱ. Approximately 85% of anal cancer is caused by the human papilloma virus (HPV). HPV16 is by far the most common cause, accounting for 90% of all HPV-related anal cancer. Anal cancer has a very uneven population distribution. Groups with elevated and high risk include:

- HIV-negative gay men, relative risk 5 or more (10+ per 100,000py)
- HIV-positive heterosexual men and women, relative risk 10 or more (incidence 20 per 100,000py)
- HIV-positive gay men, relative risk up to 50 (incidence 100 per 100,000py in some studies). This makes it one of the most common of any cancers in this population. In a study of the Australian HIV cancer registers, it was found that anal cancer had become the most common non-AIDS defining cancer, and the third most common cancer overall among people with HIV in Australiaⁱⁱ.
- Other groups at higher risk include transplant patients and women with previous anogenital dysplasia/abnormalities (approx. 10 per 100,000py).
- Smoking appears to be an independent, additional risk factor in all populations

Burden of anal cancer in Gay and Bisexual men in inner Sydney: Depending on the definition used, Gay Men comprise 2-8% of the adult male populationⁱⁱⁱ. In Australian postcodes where more than 10% of the male population identifies as Gay, rates of anal cancer in the total male population have been described at about 8 per 100,000py^{iv}. This is higher than rates of cervical cancer among women in the general population. Rates are even higher in the areas surrounding St Vincent's hospital in inner Sydney, where between 25% and 50% of men identify as homosexual^v. Postcodes with high populations of Gay Men include: 2010 (Darlinghurst, Surry Hills); 2011 (Potts Point, Elizabeth Bay, Rushcutters Bay, and Woolloomooloo); 2016 (Redfern); 2021 (Centennial Park, Moore Park, and Paddington); 2042 (Enmore, Newtown); 2008 (Chippendale, Darlington); and 2204 (Marrickville).

Burden of anal cancer in Gay men with HIV and Heterosexual men and women with HIV in Sydney: The incidence of anal cancer in Gay Men was estimated at around 35 per 100,000 per year before the HIV/AIDS epidemic. This is clearly greater than current rates of cervical cancer in women and similar to that of cervical cancer in the era prior to the implementation of organised cervical cancer screening programs. For HIV-positive Gay Men, the risk is even further elevated. In a recent meta-analysis of all studies describing anal cancer incidence in Gay Men living with HIV, it was reported that anal cancer incidence increased to 78 - 100 per 100,000 per year in reports published after 1996^{vi}. These data demonstrate that the incidence of anal cancer is increasing in HIV-positive men, despite the improved general health associated with effective HIV therapies.

The incidence of anal cancer in men and women who identify as heterosexual and have HIV is about 20 per 100,000. This population has a relative risk of anal cancer of 10 or more than the general population. Heterosexual people living with HIV (PLHIV) report experiencing stigmatisation and isolation. This emanates from discrimination from external sources such as health services, but also through self-stigmatisation. This populations' knowledge of HIV and other associated health risks is low.

Inner Sydney and Eastern Suburbs have 43% of NSW population with HIV: Associate Professor David Wilson of the Kirby Institute conducted modelling to estimate the total number of people living with diagnosed HIV by statistic region in 2010. Sydney remains the capital city with the largest number of PLHIV in Australia with 10,170 in 2012. Of these, 3,080 (30%) live in the Inner Sydney region and a further 1,288 (12.7%) live in the Eastern Suburbs^{vii}. Wilson and Jansson estimate the number of gay HIV positive men living in the Sydney region to be as follows:

- Aged 35 and older: 5758 men
- Aged 45 and older: 4115 men
- Aged 55 and older: 2056 men.

Risk of anal cancer and high-grade squamous intra-epithelial lesions (HSIL) increase with age: It is clear that anal cancer rates increase with age in both men and women. Between 2000 -2005, the incidence of anal squamous cell carcinoma (the cancer related to HPV) in people aged less than 50 was 0.27 per 100,000, whereas in people aged 65 and above this increased to 3.40 per 100,000. The risk of (HSIL) is reported to increase with age among HIV-positive homosexual men, with men aged 40-49 years having 3 times the risk of HSIL, and men older than 50 having almost 5 times the risk of HSIL compared with men less than 40 years^{viii}.

Age of the population with HIV is increasing: The proportion of PLHIV over 55 years of age has substantially increased. In 1985 the proportion of the population aged over 55 years was 2.7%. By 2000 it was 11.2%. In 2010, it was 25.7% and by 2020 it is expected to be 44.4%^{ix}.

Smoking: Tobacco smoking has been reported to be associated with risk of anal cancer in univariate analyses in all studies which examined this association. Two studies with careful control for confounders did report an association at a multivariate level, suggesting that, as in cervical cancer, smoking may be an independent risk factor^x.

Figures from the National Drug Strategy Household Survey (NDSHS) show smoking rates for the general population at 18.9%, while the smoking rate for those identifying as homosexual/bisexual is 39.5% (AIHW 2011, p. 28)^{xi}. In 2010, rates fell respectively to 17.5% for the general population and 34.2% for homosexual/bisexual populations (Ibid.).

Descriptive and small studies of transgender health also suggest high rates of smoking. 44.1% of trans men and 35.4% of trans women surveyed in the Private Lives study smoked on more than five occasions in the preceding month (Pitts et al. 2006, p. 35)^{xii}.

The HIV Futures study surveys people with HIV across Australia every two years. Between 2002 and 2013, reported smoking rates dropped from 54.6% (Grierson et al. 2002, p. xii) to 30.2% (Ibid. 2013, p. vi). This remains an alarmingly high rate compared to 18.9% of the general population. While rates of smoking have dropped among Gay Men and PLHIV, the Sydney Women and Sexual Health (SWASH) survey shows that high rates of smoking among lesbians and other same sex attracted women have not altered between 2006 and 2012 (Mooney-Somers et al. 2013, p. 26)^{xiii}. Given that many lesbians and bisexual women are exposed to HPV, are similarly geographically concentrated to Gay Men, and that older lesbians report lower rates of cervical cancer screening, there is potentially a higher rate of anal cancer among women residing in these LHDs.

The SPANC Study: The SPANC study^{xiv} follows men at 5 visits over 3 years and is one of the largest prospective studies of HPV in Gay Men. It is the only large-scale study to follow high-grade squamous intra-epithelial lesions HSIL, rather than treating them. The rationale for this is that although HSIL is believed to be the precursor to anal cancer, progression rates are uncertain and there are no current proven effective treatments. Based on a comparison of data on prevalence of HSIL and incidence of anal cancer, an estimated progression rate of about 1 in 377 HIV-positive men per year was published and less than one in 4,000 per year in HIV-negative men.

It is too early to give any precise estimates of progression and regression rates. Nevertheless, baseline data from SPANC is currently available on 350 participants. Preliminary results presented at the Australasian HIV Conference in 2013 are as follows:

1. The prevalence of high-grade squamous intra-epithelial lesions (HSIL) is very high, at 46%
2. Clearance of HSIL is common, at about 36 per 100 person-years
3. Clearance of HSIL is less common in the following groups:
 - a) Older men (>55 years);
 - b) Men with high risk HPV infection (HPV16) and increasing numbers of high risk-HPV infections detected; and
 - c) Larger lesions (biopsy proven disease in at least two octants) are also much less likely to regress.

Based on these findings, further high resolution anoscopy (HRA) follow up of men at high risk is warranted. The study investigators have concluded the following schedule is required:

1. Men at low risk of anal cancer (16% of SPANC participants) – If HIV-negative, no further follow up is required. If HIV-positive, patient should see their GP for annual digital anal rectal examination (DARE)
2. Men at moderate risk of anal cancer (42% of SPANC participants) – annual DARE from GP and HRA follow-up within 3 years
3. Men at elevated risk of anal cancer (35% of SPANC) Annual DARE from GP and HRA within 2 years
4. Men at high risk (7.2% of SPANC) – DARE and HRA within 1 year

502 high resolution anoscopies (HRA) will be required as Standard of Care and follow-up arising from SPANC study participants exiting the study (See Table 2. appendix). In 2017 alone, 121 HRAs will be required.

Early diagnosis of anal cancer is critical to reducing morbidity and death: Early diagnosis is critical to reducing anal cancer morbidity and death. The five year relative survival decreases from 80% when disease is localised, to 36% when spread. If diagnosed very early, when the tumour size is less than one centimetre, even higher survival rates of around 95% are described. Most patients do not present early. In Australia, only 23% are diagnosed at Stage 1. This has been attributed by some researchers to a low rate of awareness among clinicians and community members. Shame and stigma are also likely to be a contributing factor in diminishing access to services and open discussion about risk factors.

Treatment is associated with significant deterioration of anorectal function and quality of life. Positive Life NSW is aware of a number of HIV-positive Gay Men who have been diagnosed with late stage anal cancer. A combination of radiation, 5-fluorouracil, and mytomyacin-C was prescribed and all patients experienced significant morbidity. Radical surgery was required in some cases and some individuals died.

Estimating the clinical cost of late stage anal cancer

Estimating the cost incurred by late diagnosis of anal cancer needs to include the costs of chemotherapy and intensity modulated radiotherapy (as compared to standard radiotherapy). It may be possible to diagnose and treat Superficial Squamous Cell carcinoma of the Anus (SISCCA) with simple excision, thus avoiding the problem of chemotherapy and their associated costs. Pelvic exenteration is a relatively uncommon procedure, and usually reserved for salvage situations. Dr Roger Garsia (RPA Hospital) has provided the results of an externally performed costing study. The average cost of pelvic exenteration and the pre-op and follow up care (when cancer has spread and cure by surgery is still possible) to be \$133,000. Dr Garsia goes on to state that some of the late spread anal cancer is too advanced for this procedure and is managed with a much less involved procedure. However, the cost is still significant.

HRA is the most effective means of confirming diagnosis of anal cancer in high risk individuals:

Anal high risk HPV is very common in HIV-negative Gay Men (37%, HPV16 in 16%) and HIV-positive Gay Men (74%, HPV16 in 35%). HSIL is very prevalent in HIV-negative Gay Men (22%) and HIV-positive Gay Men (30%+). There is no proven effective treatment for HSIL. HRA needs to be repeated on many occasions and is associated with biopsy and very significant morbidity and uncertain benefit. There is a very high rate of recurrence of HSIL. DARE has been suggested to be a useful screening procedure for early identification of anal abnormality and potential anal cancer. This is based on the detection of a lump at clinical examination, and follow-up diagnosis by HRA. HRA is not proposed at this time as a mass screening procedure.

Broadening the focus beyond SPANC follow-ups and quantifying need for HRA: Estimating the number of HIV-positive and HIV-negative gay men who are at risk of anal cancer and not in SPANC is difficult. No-one is proposing to screen all men who may be at high risk. Instead the proposal is to have HRA referral services for men who have symptoms and who are thought to be at high risk of progression. It is difficult to know how many of these men there might be. Prof Andrew Grulich estimates that if 5% of HIV positive gay men aged 35+ have anal symptoms such as bleeding in any one year, then that might lead on to 288^{xv} referrals for HRA in a year. Additionally, there is likely to be a considerable number of HIV negative gay men with anal symptoms who would also need referral. While the incidence rate of anal cancer among HIV negative men is lower than that of HIV positive men, HIV negative men are a larger population, such that numbers of each requiring screening will be approximately equal.

Current capacity of St Vincent's HRA Clinic: Dr Richard Hillman advises that the current capacity at St. Vincent's HRA Clinic is unable to cope with the number of new referrals and known cases of high grade disease (HSIL). As of the 16 May 2014 there were 285 people on the Standard of Care list. The Clinic receives 1-2 new referrals per month and can see 6-7 patients per month. That is a maximum of 70 patients per year. Patients with more extensive HSIL are prioritised and seen annually. This means that the current waiting list is theoretically at least 4-5 years.

Conclusion: The SPANC study has shown that anal high risk HPV is very common in HIV-negative Gay Men, and even more common in HIV-positive Gay Men. 16% of HIV-negative Gay Men and 35% of HIV-positive Gay Men are infected with HPV16. Infection with HPV16 is associated with 90% of all HIV-related anal cancer. Substantial concentrations of HIV-positive and HIV-negative Gay Men reside in inner Sydney area. Heterosexual men and women with HIV also are at increased risk of anal cancer. Both they and Gay Men living outside these areas and who are not in SPANC will need appropriate referral pathways to screening services into the future. However, the highest burden of potential anal cancer in NSW, if not Australia, lies in the population areas surrounding St. Vincent's and Royal Prince Alfred Hospitals. This burden will only increase with the ageing of the population in these areas.

The number of people enrolled in SPANC who are at high risk and requiring follow-up HRA each year is modest (6-13 per year). However, the number of HIV positive and HIV negative gay men who are outside the SPANC Study and who are at risk of developing symptoms and require HRA, may be as many as 200-300 per year. Effectively meeting the future referral need for HRA will be important if we are to avoid high rates of avoidable advanced disease and subsequent higher demands on hospital services and greater morbidity and mortality amongst those at highest risk of anal cancer.

Further information: If you require further information in relation to this submission, please contact Lance Feeney, Policy Analyst, Positive Life NSW on (02) 9206 2174; or Alan Brotherton, ACON Director Policy, Strategy and Research on (02) 9206 2048.

Appendix:

Table 1

Anal cancer incidence in different populations		
Population	Relative risk	Annual incidence (per 100,000)
General population	1 (referent)	1-2
Women with previous anogenital HPV disease	5	10
Organ transplant recipients	5	10
HIV-negative Gay and Bisexual men	5+	10+
HIV-positive heterosexual men and women	10+	20
HIV-positive gay men	50	100

Table 2

Number of Standard of Care high resolution anoscopy (HRA) referrals arising from the SPANC study					
Year	Number of men completing SPANC	Number of men at highest risk (need for HRA within 12 months)	Number of men at elevated risk (need for HRA within 2 years)	Number of men at moderate risk (need for HRA within 3 years)	Number of HRA needed
2014	179	13	62	75	0
2015	114	8	40	48	13
2016	76	6	26	32	70
2017	142	10	50	60	121
2018	86	6	30	36	84
2019					88
2020					90
2021					36

ⁱ Jin F, AN, Conway EL, Regan DG, Law m, Brotherton JM *et al.* Trends in anal cancer in Australia, 1982-2005. *Vaccine* 2011, 29:2322-2327.

ⁱⁱ Van Leeuwen MT, Vajdic CM, Middleton MG, MC Donald AM, Law M, Kaldor JM, et al. Continuing declines in some but not all HIV-associated cancers in Australia after widespread use of antiretroviral therapy. *Aids* 2009,23:2183-2190.

ⁱⁱⁱ Grulich AE, de Visser RO, Smith AM, Rissel CE, Richters J. Sex in Australia: Homosexual experience and recent homosexual encounters. *Aust NZ J Public Health* 2003, 27:155-163.

^{iv} Poynten IM, Stein AN, Conway EL, Prestage G, Regan DG, Jin F, et al. Geographical clustering of anal cancer incidence in Australia. *Sex Health* 2012 2012, 9: 509-512.

^v Madeddu D, Grulich A, Richters J, Ferris J Grierson J, Smith A, et al. estimating population distribution and HIV prevalence among homosexual and bisexual men. *Sex Health* 2006, 3: 37-43

^{vi} Machalek DA PI, Jin F, Fairley CK, Farnsworth A, Garland SM, Hillman RJ, Petoumenos K, Roberts J, Tabrizi SN, Templeton DJ, Grulich AE. Anal Human Papillomavirus Infection and associated Neoplastic Lesions in Homosexual Men: Systemic Review and Meta-Analysis. *Lancet Oncology* 2012, 13: 487-500.

^{vii} Wilson D, Mapping HIV outcomes: geographical and clinical forecasts of number of people living with HIV in Australia. Number of people living with diagnosed HIV by statistical region and year, 2010, p21

^{viii} De Pokomandy et al. HAART and progression to high-grade anal intraepithelial neoplasia in men who have sex with men and are infected with HIV. *Clinical Infectious Diseases* 2011; 52: 1174-1181.

^{ix} Wilson D. Mapping HIV outcomes: geographical and clinical forecasts of number of people living with HIV in Australia. Monograph, 2010, p49.

^x Grulich AE, Poynton IM, Machalek DA, Fengyi J, Templeton DJ, Hillman RJ. The epidemiology of anal cancer. *Sexual health* 2012, 9, 504-508.

^{xi} Australian Institute of Health and Welfare 2011, 2010 National Drug Strategy Household Survey, Drug statistics series no. 25, no. PHE 145, AIHW, Canberra

^{xii} Pitts M et al. Private Lives: A report on the health and wellbeing of GLBTI Australians, Monograph series no 57, The Australian Research Centre in Sex, Health and Society, La Trobe University, Gay and Lesbian Health Victoria, Melbourne, 2006.

^{xiii} Mooney SJ, Deacon RM, Comfort J, Richters J, Parkhill N, Women in Contact with the Sydney Gay and Lesbian Community: Report to the Sydney Women and Sexual Health (SWASH) Survey 2006, 2008, 2010 and 2012, ACON and Centre for Values, Ethics and the Law in Medicine (VELiM), University of Sydney.

^{xiv} A large scale NHMRC and Cancer Council NSW-funded study. The Study of Prevention of Anal Cancer (SPANMC) has been underway at St Vincent's Hospital for more than three years. The study has recruited more than 420 participants, and more than 1,000 high resolution anoscopies have been performed. Recruitment will close in mid-2015 when 600 homosexual men (approximately 250 HIV-positive) will have been enrolled, and the final participants will complete the study in mid-2018.

^{xv} Email correspondence; 5% of HIV positive gay men in Sydney over the age of 35 years. This is a conservative estimate based on the frequencies of HSIL seen in SPANC