Recurrence patterns identify aggressive form of human papillomavirus-dependent vulvar cancer

Rebekah E. McWhirter1,2,3, Petr Otahal3, Debbie Taylor-Thomson1, Elaine Lawurrpa Maypilama1, Alice R. Rumbold4,5, Joanne L. Dickinson3, Jane C. Thorn6, Jacqueline A. Boyle1,7 and John R. Condon1

Background: Vulvar cancer is rare and, as a result, is understudied. Treatment is predominantly surgery, irrespective of the type of vulvar cancer, and is associated with physical, emotional and sexual complications. A cluster of human papillomavirus (HPV)-dependent vulvar cancer patients was identified in Arnhem Land Northern Territory (NT), Australia, in which young Indigenous women were diagnosed at 70 times the national incidence rate.

Aims: To assess whether women from the Arnhem Land cluster differ from women with vulvar squamous cell carcinoma (VSCC) and vulvar intraepithelial neoplasia (VIN) resident elsewhere in the NT in recurrence after treatment, disease progression and mortality.

Materials and methods: A retrospective cohort study of NT-resident women diagnosed with VIN or invasive vulvar cancer (VSCC) between 1 January 1993 and 30 June 2015 was undertaken. Time to recurrence was assessed using cumulative incidence plots and Fine and Gray competing risk regression models. Mean cumulative count was used to estimate the burden of recurrent events.

Results: Indigenous women from Arnhem Land experienced more recurrences after treatment than non-Indigenous women, the cancers recurred faster, and Indigenous women have worse survival at five years.

Conclusions: In characterising the epidemiological features of this cluster, we have identified a particularly aggressive form of vulvar cancer. This provides a unique opportunity for elucidating the aetipathological pathways driving vulvar cancer development that may ultimately lead to preventive and therapeutic targets for this neglected malignancy. Further, these findings have important implications for clinical practice and HPV vaccination policy in the affected population.

Keywords: human papillomavirus, Indigenous women, recurrence, vulvar cancer, vulvar intraepithelial neoplasia, vulvar neoplasms
INTRODUCTION

In 2009, a cluster of vulvar cancer, an otherwise rare disease, was identified in Arnhem Land, a remote and sparsely populated region of the Northern Territory (NT), Australia. Indigenous women aged <50 years had an age-adjusted incidence rate of vulvar cancer of 31.1 per 100 000 (95% CI 13.1–49.1), or 70 times the national Australian rate of 0.4 per 100 000 (95% CI 0.4–0.5) in this age group. Investigation of this cluster found all tested cases to be positive for human papillomavirus (HPV), but that the increased incidence could not be explained by increased infection with high-risk HPV types or infection with a particularly virulent variant of HPV16. This suggests the involvement of another cofactor, such as an environmental exposure or genetic predisposition. While a preliminary genetic investigation found no effect of genome-wide homozygosity or any individual region of homozygosity on vulvar squamous cell carcinoma (VSCC) and vulvar intraepithelial neoplasia (VIN) in the East Arnhem cluster, the possibility of a genetic risk factor has yet to be eliminated.

Vulvar cancer has received sparse attention in the research literature, in part because it is rare (3–5% of all gynaecological cancers). VSCC comprises the majority (>90%) of vulvar cancers. There are two distinct aetiological pathways for VSCC, resulting in separate forms of the disease. One is associated with infection with HPV, usually affects younger women, arises from vulvar high-grade squamous intraepithelial lesions (HSIL) (previously called usual type VIN (uVIN)) and results in basaloid or warty carcinoma. The other variant is HPV-independent, usually affects postmenopausal women, is associated with differentiated VIN (dVIN) arising in an area affected by vulvar dermatoses such as lichen sclerosus, and leads to keratinising VSCC. Evidence to date indicates that dVIN progresses to invasive VSCC more frequently and faster than HSIL, and is more likely to recur after treatment.

Vulvar neoplasms are predominantly treated with surgery, irrespective of whether the disease is HPV-dependent or independent. Treatment for VSCC and VIN (both HSIL and dVIN) has evolved only marginally and continues to be associated with substantial physical morbidity and psychosexual dysfunction. A trend toward less radical surgery and an increase in the use of sentinel lymph node biopsies has gone some way toward reducing morbidity for patients with localised disease without reducing survival. Options for treating advanced or recurrent VSCC remain limited, contributing to higher mortality rates in these patients.

Mortality rates have remained steady, or increased in some regions, and women suffer from associated morbidities that reduce quality of life. Greater understanding of the development of VSCC and its precursor lesions, VIN, is needed to improve preventive or therapeutic strategies.

Recurrence of VSCC occurs in 12–37% of patients, with most recurrences (40–80%) occurring within two years of treatment. Rates of recurrence have remained steady over the past 30 years, and the causes of local recurrences are poorly understood, contributing to a lack of preventive and therapeutic options. Risk factors previously identified as associated with recurrence include smoking, larger lesion size, inadequate surgical excision margins, stromal invasion, and treatment with laser ablation. However, more recent studies indicate that these risk factors, and especially positive margins, are less influential in determining recurrence than the presence of tumour-adjacent epithelium already molecularly altered by inflammation (eg chronic lichen sclerosus) or infection (ie high-risk HPV), and the small numbers involved in most studies mean that current evidence of risk factors for recurrence remains equivocal.

Gynaecologists treating vulvar cancer in the NT over the past 20 years have noted that women from East Arnhem are more likely to suffer recurrences than other women with vulvar cancer. This study therefore assesses whether women from the Arnhem Land cluster differ from women with VSCC and VIN resident elsewhere in the NT in recurrence after treatment, disease progression and mortality.

MATERIALS AND METHODS

A retrospective cohort study of NT-resident women diagnosed with VIN or invasive vulvar cancer (VSCC) between 1 January 1993 and 30 June 2015 was undertaken. Ethics approval for this study was received from the Human Research Ethics Committee of NT Department of Health and Menzies School of Health Research (HREC-2011-1569).

Data sources

Cases and recurrences were ascertained from the Colposcopy Database maintained by the Gynaecology Outreach Service (GOS) and the Royal Darwin Hospital, which comprises records of all colposcopies performed by the GOS and public gynaecology services since 1996. This was supplemented by the NT Cancer Registry and information from client medical records in the NT public hospitals’ clinical information system, allowing the dataset to be extended back to January 1993.

Definitions

Women were included if they were NT residents diagnosed with VIN or VSCC between 1 January 1993 and 30 June 2015; women were excluded if they were diagnosed with VIN or VSCC but had no record of treatment, recurrence, or any further information. The data sources used do not distinguish between HSIL and dVIN; consequently, VIN is used to refer to all high-grade vulvar intraepithelial neoplasias.
TABLE 1 Characteristics of women diagnosed with VIN or VSCC by recurrence status, Northern Territory, January 1993 to June 2015

|                  | No recurrence | Recurrence |
|------------------|---------------|------------|
| Age at diagnosis | 48.5 (13.0)   | 41.5 (15.0) |
| Indigenous status|               |            |
| Indigenous       | 36 (40.0%)    | 54 (60.0%) |
| Non-Indigenous   | 40 (69.0%)    | 18 (31.0%) |
| Index neoplasm   |               |            |
| VSCC             | 40 (58.8%)    | 28 (41.2%) |
| VIN              | 36 (45.0%)    | 44 (55.0%) |
| Year of diagnosis|               |            |
| <2000            | 15 (35.7%)    | 27 (64.3%) |
| 2000+            | 61 (57.5%)    | 45 (42.5%) |
| District         |               |            |
| TE               | 52 (57.8%)    | 38 (42.2%) |
| CA               | 10 (83.3%)    | 2 (16.7%)  |
| EA               | 14 (30.4%)    | 32 (69.6%) |

Percentages based on row totals.

CA, Central Australia; EA, East Arnhem; TE, Top End; VIN, vulvar intraepithelial neoplasia; VSCC, vulvar squamous cell carcinoma.

Indigenous: an individual’s self-reported status as an Aboriginal, Torres Strait Islander, or Aboriginal and Torres Strait Islander person.

Non-Indigenous: an individual’s self-reported status as a non-Indigenous person.

The index diagnosis for cohort inclusion was histologically confirmed high-grade VIN (equivalent to former classifications of VIN II and III) or VSCC. Recurrence was defined as the first subsequent diagnosis of VIN, VSCC, perianal intraepithelial neoplasia, or anal intraepithelial neoplasia.

For the primary recurrence analysis, follow-up time was defined as the time from initial diagnosis to first recurrence, death, last contact date, or the end of the study. Date of treatment was not available for all women. To examine the potential for bias arising from differences in the time to first treatment (reflecting different disease states at diagnosis), sensitivity analyses were undertaken with follow-up time defined as the time from first treatment to first recurrence, death, last contact date, or the end of the study. Last contact date was the most recent date, prior to the end of the study period, in which there was a record of contact with any health service in the clinical information system. Additionally, for the secondary analysis examining the number of recurrence events, multiple recurrence events per individual were recorded.

Women’s usual place of residence was grouped by NT government administrative health districts: Top End (comprising Darwin Urban, Darwin Rural, and Katherine), Central Australia (comprising Alice Springs Urban, Alice Springs Rural, and Barkly), and East Arnhem.

Statistical methods

Data for the cohort are summarised as: for categorical variables, frequency and percentage; for continuous variables, mean and standard deviation or median and interquartile range. Differences between groups for categorical variables were analysed using χ² or Fisher’s exact test, where applicable. Time to recurrence is summarised for Indigenous and non-Indigenous women using cumulative incidence plots; these are preferred over Kaplan–Meier when there is the presence of a non-negligible competing risk, in this case mortality. Fine and Gray competing risk regression models were therefore employed to account for this competing risk in estimating the sub-distribution hazard of recurrence for Indigenous versus non-Indigenous women adjusted for age at diagnosis (as a proxy for possible differences in aetiology), year of diagnosis (pre-2000/post-2000) and type of index neoplasm (VIN/VSCC). District was not entered into the final adjusted model because all women in East Arnhem identified as Indigenous and it was not possible to separate the effects of Indigenous status and District. Analysis of District was performed in a subset of the data containing only Indigenous women. Mean cumulative count was used to estimate the burden of recurrent events in the presence of competing risks. All analyses were performed in R 3.3.3 using the cmprsk package and the MCC function.

RESULTS

Data were available for 152 women; one woman was excluded because she was not an Australian resident and three because of incomplete ascertainment of recurrence. The total follow-up period for the 148 women in this study period is from 1 January 1993 to 30 June 2015.

A greater proportion of Indigenous than non-Indigenous women had invasive disease (VSCC) at first diagnosis (51.1% (n = 46) compared with 37.9% (n = 22)), although this difference is non-significant (P = 0.16). Non-Indigenous women were older at initial diagnosis than Indigenous women (mean age of 50.2 years (SD = 14.0) compared to 41.8 years (SD = 13.7)). A total of 72 (48.6%) women, 54 Indigenous and 18 non-Indigenous had at least one recorded recurrence (Table 1). Recurrence was more likely in younger women, those initially diagnosed with VIN, and women from East Arnhem. The rate of recurrence in women from Central Australia was comparatively low.

The cumulative incidence of recurrence (Fig. 1) after five years was 48.8% for Indigenous women compared with 30.2% for non-Indigenous women, rising to 64.1% compared with 36.6% after 10 years. The cumulative mortality for Indigenous women was 17.9% compared with 3.7% for non-Indigenous women after 5 years, rising to 19.5% compared with 19.6% after 10 years. Recurrence is more frequent in Indigenous women, compared to non-Indigenous women (Fig. 2). At five years after diagnosis, Indigenous women have had on average one recurrence per woman, and non-Indigenous women have had 0.5. The results were not substantively different in the sensitivity analyses utilising time from first treatment as the starting point for follow up (data not shown).
Recurrence in vulvar cancer

In univariate analyses (Table 2), Indigenous women had two-fold higher risk of recurrence compared with non-Indigenous women; this risk remained after adjustment for age at diagnosis, type of index neoplasm, and year of diagnosis. Women with an index VIN had a slightly elevated risk compared with women initially diagnosed with VSCC in both univariate (subdistribution hazard ratio (SHR) = 1.49) and adjusted (SHR = 1.44) analyses. Women from East Arnhem had an elevated risk of recurrence in univariate analysis (SHR = 1.64) because all East Arnhem cases were Indigenous women, who have a high incidence of recurrence. In the subset model containing only Indigenous women, incidence of recurrence was similar for residents of East Arnhem and other districts (East Arnhem SHR = 1.01, 95% CI: 0.55, 1.86), adjusted for age, type of index neoplasm and year of diagnosis.

It was not possible to discern a difference between Indigenous and non-Indigenous women for progression from VIN to VSCC, as only four women (two of each Indigenous status) were diagnosed with an VSCC recurrence following an initial VIN diagnosis. Data on type of treatment received was available for 100 women. Treatment was predominantly surgical in nature and did not differ by Indigenous status (Table 3, P = 0.654). Time to treatment following diagnosis did not differ substantively by Indigenous status (data not shown).

DISCUSSION

In this study, we found that Indigenous women in the NT had a two-fold higher risk of recurrence of VSCC and VIN. This was apparent for Indigenous women living in East Arnhem as well as the surrounding district and was robust to adjustment for age at diagnosis. Indigenous women experienced a shorter time to recurrence, a greater number of recurrences, and a higher mortality rate within five years of treatment.

The differences in the natural history of HSIL and dVIN have resulted in different approaches to treatment. HPV-dependent HSIL has classically been known to develop slowly, occasionally spontaneously regress, and be less likely to progress to invasive cancer than HPV-independent dVIN. Thus, HPV-independent lesions have demanded immediate surgical treatment, whereas HPV-dependent HSIL could be treated with topical immune modulators (eg imiquimod) and monitored for longer periods, avoiding surgical treatment for many.

However, in the Arnhem Land cluster we have evidence of a cluster of unusually aggressive HPV-dependent vulvar neoplasia. The more conservative treatment normally used for HPV-dependent lesions is inappropriate in this population.

The underlying cause of this cluster of aggressive HPV-dependent vulvar neoplasia is not clear. HPV infection, while an essential precondition, is insufficient to explain the cluster on its own. Smoking, while very common among Arnhem Land residents, is equally prevalent in other remote Aboriginal communities in

FIGURE 1 Cumulative incidence plot showing recurrence and mortality stratified by Indigenous status.

FIGURE 2 Mean cumulative count of recurrences by Indigenous status.

TABLE 2 Univariate and multivariate competing risks regression models for time to recurrence

|                        | Univariate models | Multivariate model |
|------------------------|-------------------|--------------------|
|                        | SHR    | 95% CI | SHR    | 95% CI |
| Indigenous status      |        |        |        |        |
| Non-Indigenous         | –      | –      | –      | –      |
| Indigenous             | 2.00   | 1.16   | 3.46   | 1.94   |
| Age at diagnosis (per year) | 0.98 | 0.96   | 1.00   | 0.99   |
| Index neoplasia        |        |        |        |        |
| VSCC                   | –      | –      | –      | –      |
| VIN                    | 1.49   | 0.93   | 2.38   | 1.44   |
| Year diagnosis         |        |        |        |        |
| <2000                  | –      | –      | –      | –      |
| 2000+                  | 0.84   | 0.53   | 1.33   | 0.97   |
| District               |        |        |        |        |
| CA                     | 0.29   | 0.07   | 1.25   |       |
| EA                     | 1.64   | 1.06   | 2.56   |       |

CA, Central Australia; CI, confidence interval; EA, East Arnhem; SHR, subdistribution hazard ratio; TE, Top End; VIN, vulvar intraepithelial neoplasia; VSCC, vulvar squamous cell carcinoma.
the Top End that do not experience similar rates of vulvar disease and recurrence.\textsuperscript{4,29} Further, it appears that time to treatment and treatment type are similar between Indigenous and non-Indigenous patients, which is unsurprising given the small pool of gynaecologists in the NT.

It might be expected that Indigenous women present with more advanced disease, given the sense of shame associated with the disease and the limited access to healthcare in these remote communities. With no choice of doctor in many remote communities, women in Arnhem Land would, for instance, have difficulty talking to a male clinician about an issue deemed to be ‘women’s business’. This may be a contributing factor to the high proportion of Indigenous women with invasive disease at first diagnosis, although this difference is not statistically significant. Further, since it was first suspected that a cluster of vulvar disease was present in Arnhem Land, concerted efforts have been made to raise community and clinical awareness of the issue and to increase screening efforts as part of Well Women Checks. While a tendency to present with more advanced disease may contribute to the higher mortality rate observed in affected Arnhem Land women in the years immediately following treatment, it is notable that those women diagnosed initially with VIN were more likely to experience recurrence after treatment than women diagnosed with cancer.

The higher mortality rate observed in Indigenous women compared to non-Indigenous women at five years disappears by 10 years. This is explained by the fact that this is all-cause mortality (data were not available for cause-specific mortality) and non-Indigenous women are on average almost 10 years older than Indigenous women at age of diagnosis. It is therefore likely that difference in mortality between the two groups is eliminated by 10 years because all-cause mortality increases in non-Indigenous women due to older age.

This study is limited by its reliance on a dataset collected for clinical rather than research purposes, with corresponding limitations in data range and quality. It includes only colposcopies performed in the public healthcare system and fails to account for those few patients treated by private gynaecologists in Darwin. While this may result in an underestimate of VIN in non-Indigenous women, there is no reason to believe that patients treated privately differed systematically in rates of recurrence compared to those in the public system.

A second limitation is sample size; while this study includes relatively large numbers given the rarity of vulvar cancer and VIN, it is too small to permit the inclusion of large numbers of covariates in the model. To increase the precision of our estimates, vulvar cancer and VIN have been combined in the analyses, on the basis that they are on the same spectrum of disease and an index diagnosis of either may be followed by a recurrence of the other. While it would be optimal to report these separately, the numbers available do not permit this. Similarly, it would be ideal if the time to recurrence model could be adjusted for known risk factors, such as stage of disease, size of initial lesion, margin status, and nodal status. However, these data were incomplete in the dataset available, and therefore including them as covariates would unacceptably reduce the sample size, in addition to introducing risks associated with multiple testing.

The findings reported here have implications for clinical practice. Women from East Arnhem treated for vulvar neoplasia require regular clinical follow up and may be less suitable for conservative surgical methods. Given the remote locations of the affected communities, follow up by GOS teams can be delayed and/or incomplete; they typically spend one or two days in each community every four months. Increasing awareness of vulvar disease within communities and the resident health service staff may help to increase appointment attendance, although the high turnover of health staff, the high levels of movement between communities and outstations, and frequent cultural ceremonies (particularly funerals) halting other community business all represent ongoing challenges for effective patient follow up.

In Australia, the National Cervical Screening Program guidelines changed on 1 December 2017 from a Pap test every two years, to an HPV test every five years. Although this Program is not directed toward identifying cases of vulvar cancer or its precursor lesions, the administration of this test represents an obvious chance for the opportunistic identification of such lesions. However, our findings indicate that five years is too long an interval for vulvar checks in East Arnhem Indigenous women, given their high-risk status. Vulvar checks, consisting of vulvar examination by experienced clinicians trained in vulvar disease,\textsuperscript{30} should

| Treatment category | Indigenous patients | Non-Indigenous patients |
|--------------------|---------------------|-------------------------|
| Vulvectomy\textsuperscript{†} | 14 (23%) | 6 (16%) |
| Excision\textsuperscript{‡} | 39 (63%) | 24 (63%) |
| Non-specific surgery\textsuperscript{§} | 7 (11%) | 5 (13%) |
| Other\textsuperscript{¶} | 2 (3%) | 3 (8%) |
| Totals | 62 (100%) | 38 (100%) |

\textsuperscript{†}Includes: radical vulvectomy, simple vulvectomy, hemi-vulvectomy, partial vulvectomy, vulvectomy ± radiotherapy, vulvectomy ± groin (node) dissection.
\textsuperscript{‡}Includes: excision, excision biopsy, wide local excision.
\textsuperscript{§}Includes: surgery ± chemoradiation, surgery ± radiotherapy.
\textsuperscript{¶}Includes: imiquimod, radiotherapy only, refused treatment.
be disassociated from cervical screening in this population, and undertaken every two years, or every year for first-degree relatives of known cases of VSCC or VIN (given the familial clustering observed by clinicians).4

A national HPV vaccination program was implemented in Australia in 2007 for females, and extended to included males in 2013.31,32 In 2012, coverage for areas classified as Very Remote (including East Arnhem) was comparable to elsewhere for Dose 1, but by Dose 3 was around 10% lower than other areas in Australia.33 It is therefore expected that the incidence of VIN and VSCC will decrease commensurately in coming decades, although eradication may be hampered by lower three-dose coverage and by the prevalence of a broader range of oncogenic HPV strains in Arnhem Land.2

Women aged over 26 years when the vaccine was introduced remain unprotected, and many will have already experienced HPV infection. While there is no evidence that HPV vaccination improves clearance where HPV infection or lesions are pre-existing, there is evidence that women vaccinated irrespective of initial HPV status, who were subsequently treated for cervical lesions, had a lower risk of recurrent lesions.34,35 There may, therefore, be value in extending HPV vaccination coverage to include older women at risk of developing vulvar neoplasias to mitigate the longer-term effects as well as those already affected. Such an approach may be valuable given that little progress has been made toward improving treatment for recurrent disease.36

Our findings provide support for: increased resources for HPV vaccination in Arnhem Land, to ensure maximal three-dose coverage; consideration of the extension of free vaccination to women aged up to 45; and consideration of the provision of HPV vaccines to unvaccinated or incompletely vaccinated women diagnosed with HSIL or VSCC.

This cluster of aggressive HPV-dependent vulvar cancer represents a unique opportunity to further elucidate the aetiology of this poorly understood malignancy. The demographic features of the cluster are suggestive of the involvement of genetic risk factors predisposing Indigenous Arnhem Land women to the effects of HPV. While research into the genetic basis of vulvar cancer is relatively sparse, elucidation of the biological pathways may provide potential targets for preventive and therapeutic interventions that are both more targeted and associated with less morbidity and mortality than current treatments.37

ACKNOWLEDGEMENTS

Our thanks to GOS nurses Lesley Stewart and Emma Noonan, for invaluable assistance in data extraction. We also wish to thank our long-standing Indigenous Reference Group, for their guidance and support. This work was supported by National Health and Medical Research Council (NHMRC) Project Grant 1060187. AR and JB are supported by Career Development Fellowships from the NHMRC (APP1022996 and APP1122540, respectively). JD is supported by an Australian Research Council Future Fellowship.

REFERENCES

1. Condon JR, Rumbold AR, Thorn JC et al. A cluster of vulvar cancer and vulvar intraepithelial neoplasia in young Australian Indigenous women. Cancer Causes Control 2009; 20: 67–74.
2. Rumbold AR, Tan SE, Condon JR et al. Investigating a cluster of vulvar cancer in young women: a cross-sectional study of genital human papillomavirus prevalence. BMC Infect Dis 2012; 12: 243.
3. Tan SE, Garland SM, Rumbold AR et al. Investigating a cluster of vulvar cancers in young women: distribution of human papillomavirus and HPV-16 variants in vulvar dysplastic or neoplastic biopsies. Sex Health 2013; 10: 18–25.
4. McWhirter RE, Thomson RJ, Martellick JR et al. Runs of homozygos- ity and a cluster of vulvar cancer in young Australian Aboriginal women. Gynecol Oncol 2014; 133: 421–426.
5. Forman D, Bray F, Brewster DH et al., eds. Cancer Incidence in Five Continents Vol X. Lyon: IARC Scientific Publications; 2014, 164.
6. Hales G, Aleymany L, Quiros B et al. Biological relevance of human papillomaviruses in vulvar cancer. Mod Pathol 2017; 30: 549–562.
7. de Sanjose S, Alemany L, Ordi J et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. Eur J Cancer 2013; 49: 3450–3461.
8. del Pino M, Rodriguez-Carunchio L, Ordi J. Pathways of vulvar intraepithelial neoplasia and squamous cell carcinoma. Histopathology 2013; 62: 161–175.
9. Reyes MC, Cooper K. An update on vulvar intraepithelial neo- plasia: terminology and a practical approach to diagnosis. J Clin Pathol 2014; 67: 290–294.
10. Bornstein J, Bogliatto F, Haeftner HK et al. The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) terminology of vulvar squamous intraepithelial lesions. J Low Genit Tract Dis 2016; 20: 11–14.
11. Eva LJ, Ganesan R, Chan KK et al. Vulval squamous cell carcinoma occurring on a background of differentiated vulval intraepithelial neoplasia is more likely to recur: a review of 154 cases. J Reprod Med 2008; 53: 397–401.
12. Wills A, Obermair A. A review of complications associated with the surgical treatment of vulvar cancer. Gynecol Oncol 2013; 131: 467–479.
13. Hinten F, Van den Einden L, Hendriks J et al. Risk factors for short- and long-term complications after groin surgery in vulvar cancer. Br J Cancer 2011; 105: 1279–1287.
14. Rottmann M, Beck T, Burges A et al. Trends in surgery and outcomes of squamous cell vulvar cancer patients over a 16-year period (1998–2013): a population-based analysis. J Cancer Res Clin Oncol 2016; 142: 1331–1341.
15. Clancy A, Spaans J, Weberpals J. The forgotten woman’s cancer: vulvar squamous cell carcinoma (VSCC) and a targeted approach to therapy. Ann Oncol 2016; 27: 1696–1705.
16. Hennes S, Nijboer JM, Reinisch A et al. Abdominoperineal excisions in the treatment regimen for advanced and recurrent vul- var cancers—analysis of a single-centre experience. Indian J Surg 2015; 77: 1270–1274.
17. Akhtar-Danesh N, Elt L, Lytwyn A. Trends in incidence and sur- vival of women with invasive vulvar cancer in the United States and Canada: a population-based study. Gynecol Oncol 2014; 134: 314–318.
18. Barlow EL, Kang Y-J, Hacker NF, Canfell K. Changing trends in vul- var cancer incidence and mortality rates in Australia since 1982. Int J Gynecol Cancer 2015; 25: 1683–1689.
19. Meltzer-Gunnes C, Småstuen MC, Kristensen GB et al. Vulvar carcinoma in Norway: a 50-year perspective on trends in incidence, treatment and survival. Gynecol Oncol 2017; 145: 543–548.
20. Nooij L, Brand F, Gaarenstroom K et al. Risk factors and treatment for recurrent vulvar squamous cell carcinoma. Crit Rev Oncol Hematol 2016; 106: 1–13.
21. Yap J, O’Neill D, Nagenthiran S et al. Current insights into the aetiology, pathobiology and management of local disease recurrence in squamous cell carcinoma of the vulva: a review paper. BJOG 2017; 124: 346–954.

22. Iacoponi S, Zapardiel I, Diestro MD et al. Prognostic factors associated with local recurrence in squamous cell carcinoma of the vulva. J Gynecol Oncol 2013; 24: 242–248.

23. Wallbillich J, Rhodes H, Milbourne A et al. Vulvar intraepithelial neoplasia (VIN 2/3): comparing clinical outcomes and evaluating risk factors for recurrence. Gynecol Oncol 2012; 127: 312–315.

24. te Grootenhuis NC, Pouwer A-FW, de Bock GH et al. Prognostic factors for local recurrence of squamous cell carcinoma of the vulva: a systematic review. Gynecol Oncol 2018; 148: 622–31.

25. Austin P, Lee D, Fine J. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016; 133: 601–609.

26. Dong H, Robison LL, Leisenring WM et al. Estimating the burden of recurrent events in the presence of competing risks: the method of mean cumulative count. Am J Epidemiol 2015; 181: 532–540.

27. Core R, Team R. A Language and Environment for Statistical Computing, Vienna, Austria: R Foundation for Statistical Computing, 2017.

28. van Seters M, van Beurden M, ten Kate Fj et al. Treatment of vulvar intraepithelial neoplasia with topical imiquimod. N Engl J Med 2008; 358: 1465–1473.

29. Australian Bureau of Statistics. Australian Aboriginal and Torres Strait Islander Health Survey: First Results, Australia, 2012-13, vol. cat. no. 4727.055.001, 2013.

30. Eva LJ. Screening and follow up of vulval skin disorders. Best Pract Res Clin Obstet Gynaecol 2012; 26: 175–188.

31. Brotherton JML, Fridman M, May CL et al. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet 2011; 377: 2085–2092.

32. Korostil IA, Ali H, Guy RJ et al. Near elimination of genital warts in Australia predicted with extension of human papillomavirus vaccination to males. Sex Transm Dis 2013; 40: 833–835.

33. National HPV Vaccination Program Register. HPV Vaccination Coverage by Remoteness of area of residence for females aged 12–13 years in 2012 2015. Available from URL: http://www.hpvregister.org.au/research/coverage-data/HPV-Vaccination-Coverage-Remoteness-2012.

34. Garland SM, Paavonen J, Jaisamrarn U et al. Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: Post-hoc analysis from a randomized controlled trial. Int J Cancer 2016; 139: 2812–2826.

35. Brotherton JML, Wrede CDH. Offering HPV vaccination to women treated for high-grade cervical intraepithelial neoplasia: what do you need to know? ANZJOG 2014; 54: 393–394.

36. Weberpals JJ, Lo B, Duciaume MM et al. Vulvar squamous cell carcinoma (VSCC) as two diseases: HPV status identifies distinct mutational profiles including oncogenic fibroblast growth factor receptor 3. Clin Cancer Res 2017; 23: 4501–4510.

37. McWhirter RE, Marthick JR, Boyle JA, Dickinson JL. Genetics and epigenetic variation in vulvar cancer: current research and future clinical practice. ANZJOG 2014; 54: 406–411.