Title: Recurrence patterns identify aggressive form of HPV-dependent vulvar cancer

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Abstract

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 HPV-dependent vulvar cancer patients was identified in Arnhem Land, 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 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. 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 characterizing the epidemiological features of this cluster, we have identified a particularly aggressive form of vulvar cancer. This provides a unique opportunity for elucidating the aetiopathological 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 human papillomavirus vaccination policy in the affected population.

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.[1] Indigenous women aged less then 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.[2, 3] 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 VSCC and VIN in the East Arnhem cluster, the possibility of a genetic risk factor has yet to be eliminated.[4]

Vulvar cancer has received sparse attention in the research literature, in part because it is rare (3-5% of all gynaecological cancers).[5, 6] Vulvar squamous cell carcinoma (VSCC) comprises the majority (>90%) of vulvar cancers.[7] There are two distinct aetiological pathways for VSCC, resulting in separate forms of the disease.[7-9] 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))[10] 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 keratinizing 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.[9, 11]

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.[12, 13] A trend towards less radical surgery and an increase in the use of sentinel lymph node biopsies has gone some way towards reducing morbidity for patients with localized disease without reducing survival.[12, 14] Options for treating advanced or recurrent VSCC remain limited, contributing to higher mortality rates in these patients.[15, 16]

Mortality rates have remained steady, or increased in some regions, and women suffer from associated morbidities that reduce quality of life.[17-19] Greater understanding of the development of VSCC and its precursor lesions, vulvar intraepithelial neoplasia (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 2 years of treatment.[20] 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.[21] Risk factors previously identified as associated with recurrence include smoking, larger lesion size, inadequate surgical excision margins, stromal invasion, and treatment with laser ablation.[20, 22, 23] 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 (e.g. chronic lichen sclerosus) or infection (i.e. high-risk HPV),[21] and

the small numbers involved in most studies means that current evidence of risk factors for recurrence remains equivocal.[24]

Gynaecologists treating vulvar cancer in the NT over the past twenty 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.

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. Ethical approval for this study was received from the Human Research Ethics Committee of Northern Territory 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 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 neoplasia.

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 Chi-squared or Fishers 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.[25] 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 vs 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.[26] All analyses were performed in R 3.3.3 using the cmprsk package and the MCC function.[26, 27]

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 (Figure 1) after 5 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 (Figure 2). At 5 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).

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 (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 Northern Territory 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.[6] Thus, HPV-independent lesions have demanded immediate surgical treatment, whereas HPV-dependent HSIL could be treated with topical immune modulators (e.g. imiquimod) and monitored for longer periods, avoiding surgical treatment for many.[6, 28]

In the Arnhem Land cluster, however, 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 the Top End that do not experience similar rates of vulvar disease and recurrence.[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 fatality 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 ten 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 ten years older than Indigenous women at age of diagnosis. It is therefore likely that difference in mortality between the two groups is eliminated by ten 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 reduce the sample size unacceptably, 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 Gynaecology Outreach Service 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 towards 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,[30] should 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 neoplasia 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 towards 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]

Tables

Figures

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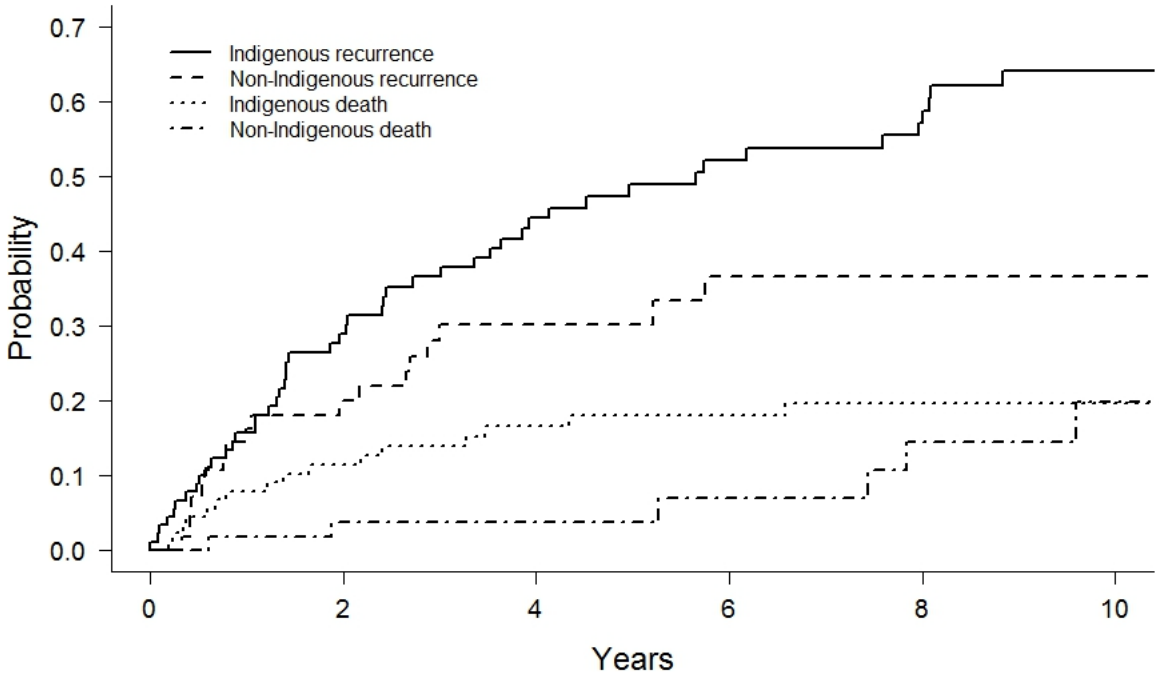

Figure 1

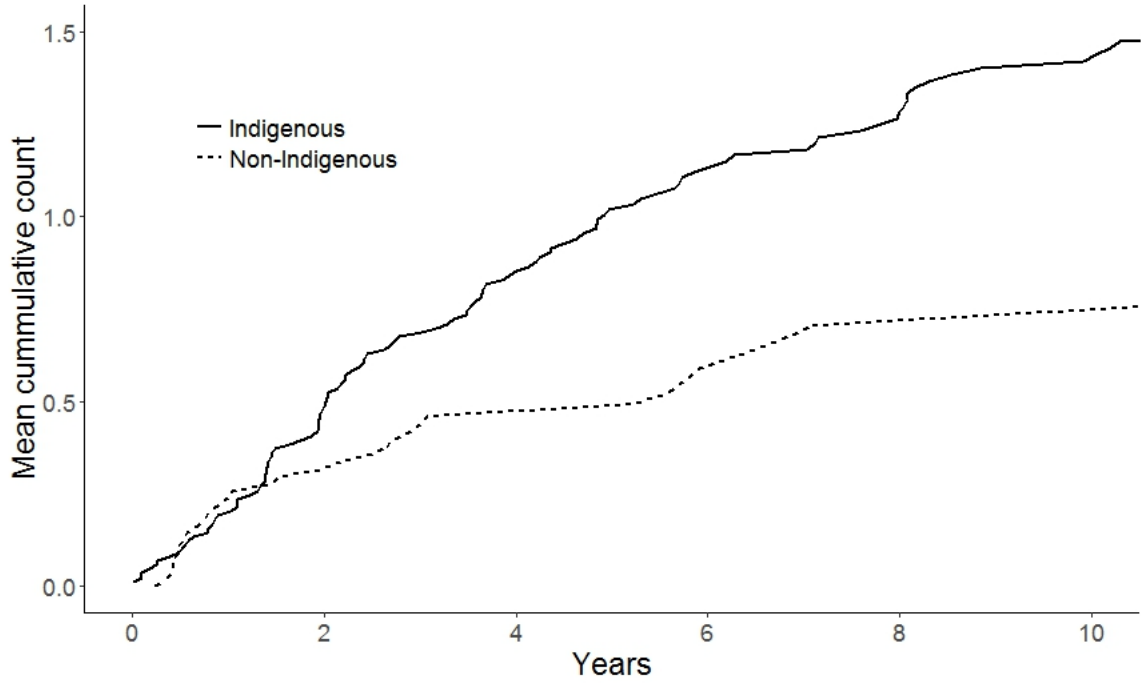

Figure 2

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

Abbreviations: Vulvar Squamous Cell Carcinoma (VSCC); Vulvar Intraepithelial Neoplasia (VIN); Top End (TE); Central Australia (CA); East Arnhem (EA)

Table 2: Univariate and multivariable competing risks regression models for time to recurrence

		Univariate models			Multivariable model		
		SHR	95% CI		SHR	95% CI	
Indigenous status	Non-Indigenous		-			-	
	Indigenous	2.00	1.16	3.46	1.94	1.12	3.34
Age at diagnosis	(per year)	0.98	0.96	1.00	0.99	0.97	1.01
Index neoplasia	VSCC		-			-	
	VIN	1.49	0.93	2.38	1.44	0.87	2.38
Year diagnosis	<2000		-			-	
	2000+	0.84	0.53	1.33	0.97	0.61	1.54
District	TE		-				
	CA	0.29	0.07	1.25			
	EA	1.64	1.06	2.56			

Abbreviations: Subdistribution Hazard Ratio (SHR); Confidence Interval (CI); Vulvar Squamous Cell Carcinoma (VSCC); Vulvar Intraepithelial Neoplasia (VIN); Top End (TE); Central Australia (CA); East Arnhem (EA)