

# Reducing the morbidity associated with treatment of vulvar cancer

## Predicting groin lymph node metastases in primary vulvar cancer and local recurrences

Met steun van Ruby&Rose is onze onderzoeksgroep bezig met de uitvoering van een onderzoek op het gebied van vulvakanker (schaamlipkanker). Het doel betreft 2 onderzoeksvragen; met beide onderdelen zijn we nog druk bezig en hopen dit rond de zomer 2021 af te ronden.

Onderstaand een kort overzicht:

1 Helaas gebeurt het vaak dat vulvakanker na een uitgebreide behandeling toch opnieuw ontstaat. Het is niet goed bekend hoe vaak en bij wie er dan lymfklieruitzaaiingen ontstaan. Daarom is het doel om landelijk alle patiënten te verzamelen waar de vulvakanker is teruggekomen om te weten hoe vaak deze uitzaaiingen vóórkomen. Dit kan helpen in het samen met de patiënt beslissen wat de beste behandeling is. In een recente posterpresentatie hebben we de resultaten gepresenteerd van 4 gynaecologisch oncologische centra en zagen dat ongeveer 15% van de patiënten lymfklieruitzaaiingen had; de grootte en diepte van de tumoren speelden hierbij een belangrijke rol. Momenteel zijn we het onderzoek aan het afronden. We hebben nu de gegevens van alle 8 Nederlandse centra en we verwachten in de zomer van 2021 dit onderzoek en artikel af te ronden.

2 Het tweede deel van ons onderzoek richt zich meer op basaal onderzoek. Tot nu toe is het zo dat patiënten met vulvakanker vrijwel altijd een operatie nodig hebben van de liezen om te weten of er uitzaaiingen zijn. Er is echter behoefte aan een niet-invasieve (zonder operatie) methode om patiënten met lymfeklieruitzaaiingen te selecteren. Kennis van de tumor-aandrijvende signaaltransductieroutes bij patiënten met en zonder liesklieruitzaaiingen zou nuttig kunnen zijn bij het voorspellen van de aan- of afwezigheid hiervan. Bovendien komt vulvakanker het vaakst voor bij postmenopauzale patiënten (na de overgang) met lage bloedspiegels van het vrouwelijk hormoon oestrogeen, wat suggereert dat hormonale factoren daadwerkelijk een rol kunnen spelen bij het ontstaan van kanker. Een nieuwe benadering om de activiteit van tumor-aanstormende signaaltransductieroutes te bepalen gebeurt in samenwerking met Philips. Dit is in vulvakanker nog nooit verricht. Na een pilot zijn we nu bezig met een groter aantal samples. De analyse en uitwerking zal in de loop van 2021 worden afgerond.

# Incidence and prognostic factors for inguinofemoral lymph node metastases in patients with a first local recurrence of vulvar squamous cell carcinoma

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## Introduction

- Local recurrences of vulvar squamous cell carcinoma (VSCC) are reported in up to 40% of patients at 10 year follow-up
- In all these patients an inguinofemoral lymphadenectomy is indicated, if not performed during primary treatment. This treatment is associated with significant morbidity.
- Knowledge of the risk of inguinofemoral lymph node metastases in local recurrences is necessary to optimally counsel patients concerning treatment of the groins, and to explore alternative treatment regimens

### Objective

To determine the incidence and prognostic factors of lymph node metastases in women with a first local recurrence of VSCC.

## Methods

- A nation-wide multicenter retrospective study was performed. All patients with a first local recurrence of VSCC, after primary surgical treatment with curative intent between 2000-2015, were included.
- Lymph node status at time of first local recurrence was considered *positive* when histologically or radiologically confirmed, or positive nodes were found <18 months after treatment. *Negative* when ruled out by histology or imaging, or after follow-up ≥18 months without groin recurrences. *Unknown* if no histology or imaging was available or follow-up <18months.
- Interim analysis was conducted on the results of 4 participating gynecologic oncology centers (Academic Medical Center, Amsterdam; Erasmus Medical Center, Rotterdam; University Medical Center Groningen and Radboud University Medical Center Nijmegen)

## Results

- 292 patients with a macro-invasive local recurrence of VSCC were included. Median follow-up after local recurrence was 61 months, the median interval time between primary VSCC and first local recurrence 27 months.
- Positive inguinofemoral lymph nodes were present in 15.8% patients with a first local recurrence of VSCC.
- Significant differences for tumor size (median 25mm vs 14mm,  $p < 0.01$ ) and depth of invasion (4.8mm vs 3.1mm,  $p = 0.01$ ) were found in relation to the lymph node status

**Table 1.** Tumor characteristics first local recurrence in relation to lymph node status in patients with known lymph node status (N=235)

	Negative lymph node status (N=189)	Positive lymph node status (N=46)	p-value
	Median (range) or N(%)		
Focality			0.251 <sup>a</sup>
- Unifocal	167 (88.8)	38 (82.6)	
- Multifocal	21 (11.3)	8 (17.4)	
- Unknown	1	0	
Tumor size (mm)	14.0 (0.7-80.0)	25.0 (3.9-80.0)	0.000 <sup>b</sup>
Depth of invasion	3.1 (1.1-37.0)	4.8 (1.9-39.0)	0.001 <sup>b</sup>
Differentiation			0.062 <sup>b</sup>
- Well	52 (32.3)	8 (20.0)	
- Moderately	88 (54.7)	23 (57.5)	
- Poor	21 (13.0)	9 (22.5)	
- Unknown	28	6	
LVSI	17 (11.6)	6 (17.6)	0.337 <sup>a</sup>

<sup>a</sup> Pearson Chi-Square, <sup>b</sup> Mann-Whitney U test

## Conclusion

In 15.8% of patients with a first local recurrence of VSCC inguinofemoral lymph node metastases were detected. A larger tumor size and depth of invasion were significant prognostic factors for the presence of positive lymph nodes at the time of recurrent disease. Data of the other 4 participating centers will be added in order identify subgroups with low risk on lymph node metastases, to individualize treatment and follow-up.

# Signal transduction analysis in vulvar squamous cell carcinoma

## Abstract:

Vulvar squamous cell carcinoma (SCC) has two etiologic mechanisms: non-human papilloma virus (HPV) related, often in a background of lichen sclerosus (LS)/differentiated vulvar intraepithelial neoplasia (dVIN), and HPV-related in the underlying premalignancy high grade squamous cell intraepithelial lesion (HSIL). A novel approach to determine tumor signal transduction pathway activity (STA) by using knowledge-based Bayesian computational models, infers pathway activity from mRNA expression levels of target genes.

*Aims.* The primary aim is to explore differences in STA between non HPV-related and HPV-related vulvar SCC. The secondary aim is to assess the differences in STA between vulvar SCC with and without metastases in the inguinofemoral lymph nodes and lastly, to assess the correlation between ER STA and immunohistochemical (IHC) expression.

*Methods.* STA analyses was performed on mRNA (after microdissection) of formalin fixed paraffin embedded (FFPE) tissue samples: vulvar SCC without lymph node metastases and HPV-related (n=5), and non HPV-related (n=10), and with lymph node metastases (n=3), lichen sclerosus (n=5) and normal vulvar tissue (n=2). STA of the estrogen receptor (ER), androgen receptor (AR), transforming growth factor beta (TGF $\beta$ ), hedgehog (HH) and Wnt pathways was measured. IHC analysis of ER, PR, AR and Ki67 was performed and interpreted by an expert gynecopathologist.

*Results.* ER STA activity was significantly higher in non HPV-related compared to HPV-related vulvar SCC (p=0.027). There was no significant difference in AR, HH and TGF $\beta$  STA between non HPV-related and HPV-related vulvar SCC. ER, PR and AR IHC expression was not detected in vulvar SCC. A higher AR expression was observed in LS compared to normal vulvar tissue. No correlation between STA and IHC was observed.

*Conclusion.* We showed significantly higher ER STA in non HPV-related compared to HPV-related vulvar SCC but this was not correlated with IHC ER expression. At this point the metastases could not yet be defined in vulvar SCC. These findings are currently validated in larger series.

**Keywords:** Vulvar squamous cell carcinoma | Signaling pathway activity | Estrogen receptor | Immunohistochemical expression |

Extension of data:

