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Adjuvant radiotherapy and local recurrence in vulvar cancer – a subset analysis of the AGO-CaRE-1 study

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HIGHLIGHTS

- Local recurrence occurred significantly more often in N+ pts without adjuvant radiotherapy to the vulva (HR 1.79; p=0.019).
- The effect of RT on local recurrence was independent of the resection status.
- 50% disease free survival time (DFST) indicated a stronger impact of adjuvant RT to the vulva in HPV + pts.

ARTICLE INFO

ABSTRACT

Background. The impact of adjuvant radiotherapy (RT) to the vulva with regard to prognosis and local recurrence in patients with vulvar squamous cell cancer (VSCC) is poorly described.

Patients and methods. In the AGO-CaRE-1 study 1618 patients with primary VSCC FIGO stage ≥ IB, treated between 1998-2008, were documented. In this retrospective subanalysis, 360 patients were included based on the following criteria: nodal involvement (pN+), known RT treatment and known radiation fields.

Results. The majority had pT1b/pT2 tumors (n=299; 83.1%). In 76.7%, R0 resection was achieved. 57/360 (15.8%) N+ patients were treated with adjuvant RT to the groins/pelvis and 146/360 (40.5%) received adjuvant RT to the vulva and groins/pelvis. 157/360 (43.6%) patients did not receive any adjuvant RT. HPV status was available in 162/360 patients (45.0%), 75/162 tumors were HPV+(46.3%), 87/162 (53.7%) HPV-. During a median follow-up of 17.2 months, recurrence at the vulva only occurred in 25.5% of patients without adjuvant RT, in 22.8% of patients with adjuvant RT to groins/pelvis and in 15.8% of patients with adjuvant RT to the vulva and groins/pelvis respectively. The risk reducing effect of local RT was independent of the resection margin status. 50% disease free survival time (50% DFST) indicated a stronger impact of adjuvant RT to the vulva in HPV+ compared to HPV- patients (50% DFST 20.7 months vs. 17.8 months).

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Conclusion. Adjuvant RT to the vulva was associated with a lower risk for local recurrence in N+ VSCC independent of the resection margin status. This observation was more pronounced in patients with HPV+ tumors in comparison to HPV− tumors.

1. Introduction

Due to rising incidence there has been an increased interest in improved treatment strategies for patients with vulvar squamous cell cancer (VSCC) over the last decades [1]. VSCC can be divided into (at least) two subgroups: HPV independent and HPV dependent carcinomas [2,3]: HPV independent VSCCs arise more frequently and are thought to be associated with higher recurrence rates as well as shorter OS in comparison to HPV dependent VSCC [4]. In case of early-stage VSCC, current state-of-the-art treatment consists of radical excision of the primary tumor and groin staging performed by sentinel node (SN) biopsy or elective inguino-femoral lymphadenectomy depending on tumor size, focality and clinical evaluation of the groin nodes. Adjuvant radiotherapy (RT) to groins and pelvis is applied in case of advanced nodal involvement [5,6]. However, indication criteria for adjuvant RT of the vulva beyond R1/R2 resection remain currently unclear. Common histopathological parameters as well as clinical factors provide insufficient predictive information regarding the individual risk of local recurrences or the question if local radiotherapy can decrease this risk [7–11]. In the overall cohort of the AGO-CaRE 1 study (Arbeitsgemeinschaft Gynäkologische Onkologie - Chemo and Radiotherapy in Epithelial Vulvar Cancer-1), prognosis was significantly better for node positive (N+) patients with adjuvant RT to the groin (+/- other fields) compared to node positive (N+) patients without RT (3-year PFS of the RT group 39.6% vs. 25.8% without RT) [12]. However, whether and in which cases adjuvant RT can effectively reduce the risk for local recurrence is still an open question.

In the past, local recurrence was considered of low significance with regard to overall survival (OS) in patients with VSCC. However, data from the long-term follow-up of the GRoningen INternational Study of Sentinel nodes in Vulvar Cancer (GROINSS)-VI study demonstrated a high 10-year local recurrence rate of 39.5% and a significantly reduced disease-specific survival (DSS) after local recurrence (10-year DSS: 68.7% vs. 90.4%), as patients often develop further recurrences, including distant metastases (5.1%) [5,11,13,14]. In this context, prognostic factors for the prediction of local recurrences are becoming increasingly important for therapy planning.

In addition to groin lymph node status, different tumor characteristics such as size, invasion depth, grading [15] and especially underlying skin diseases like lichen sclerosus (LS) or pre-invasive lesions (dVIN) in the tumor free margin have been subject of controversial discussions for years. It has become common ground that patients with LS dependent tumors based on *TP53* mutations have a higher risk for recurrence [16], however the benefit of radiotherapy in prevention of these recurrences is unclear and has to be weighted with its morbidity.

The aim of the current subanalysis of the AGO - CaRE-1 study was to evaluate the association between adjuvant RT and the prevalence of local recurrence in patients with VSCC. Furthermore the prognostic impact of adjuvant RT to the vulva depending on the tumor`s human papilloma virus (HPV) status was investigated.

2. Methods

The current analysis is evaluating a subgroup of the AGO-CaRE -1 study [12]. Aim of this large retrospective study was to investigate treatment patterns and prognostic factors in patients with VSCC. 1618 patients with primary VSCC FIGO stage IB and higher (UICC-TNM-classification and stage-groupings version 6) treated at 29 gynecologic cancer centers in Germany between 1998-2008 were documented [12]. The study was approved by each local Ethics Committee (leading vote: Hamburg, reference number PV3658, and registered with ClinialTrials.gov (NCT01304667)). Results of the main analysis have been published before [12]. Within a translational subproject available formalin fixed paraffin embedded (FFPE) tissue of the CaRE-1 patients (n=652) was collected centrally and analyzed for HPV- DNA via polymerase chain reaction (PCR) [17].

In the current subanalysis, n=360 patients were included based on the following selection criteria: nodal involvement detected in surgical groin staging (pN+), known RT treatment status (RT, chemoradiation, no RT), intention of RT (adjuvant) and known RT target volumes (groins/pelvis alone, vulva and groin/pelvis). In total, n=360 node positive patients (no RT: n= 157, RT of the groin/pelvis alone: n=57, RT vulva and groin/pelvis: n=146) were identified and analyzed with regard to prognosis and local recurrences. Also, the association between HPV status and prognosis was investigated. Data of HPV status was available in 162/360 patients (45.0%) (HPV + 46.3%, HPV – 53.7%) as tumor material could only be collected from n= 652 patients within the AGO CaRE translational subanalysis [17].

2.1. Statistical analysis

Analysis was performed using Stata (StataCorp LP, Version 16). Variables are described as median and range or count and percentage, respectively. The best evidence for the comparison of treatment options results from randomized controlled trials. Since randomization was not performed in this study, but in contrast, treatment was administered with respect to certain clinical characteristics, a statistical propensity score technique was applied to mimic randomization and to uncorrelate treatment from baseline characteristics. Inverse-probability-of-treatment-weighting (IPTW) is an established method to estimate causal treatment effects from observational data [18]. In short, individual patient data is weighed inverse-proportional to the patient's likelihood to receive the treatment. This technique was applied to achieve balance regarding the baseline variables across the three treatment groups (see Tables 1a/b before/after IPTW weighting). Variables included in the IPTW algorithm were age (continuous), number of nodes affected (1, 2, 3, >3), pT status (T1a, T1b, T2, T3/4) and resection status (R0, R1). HPV was not included in the first algorithm due to the missing data. Balancing was challenging in this data set. Therefore, a standardized difference below 0.2 was considered as sufficiently balanced (see Fig. 1a-c, supplement). Furthermore, since IPTW did not fully balance the three groups (ECOG and resection margin status remained imbalanced), additional adjustment for age (continuous), nodes affected (1, 2, 3, >3), resection margin status (0, 1, missing), pT status (T1a, T1b, T2, T3/4) and ECOG (0,1,2,3/4, missing) was modelled to obtain double-robust estimates. IPTW was furthermore performed for HPV subgroups separately, taking age (continuous), number of nodes affected (1, 2, 3, >3), pT (T1a, T1b, T2, T3/4) and resection status (R1, R0) into account. Disease-free survival (DFS) was calculated as the time interval between primary diagnosis and disease recurrence or death of any cause or censoring, and overall survival (OS) was the period resulting from primary diagnosis to death of any cause or censoring. Local-recurrence free survival was calculated as the time interval between primary diagnosis and vulva-recurrence or death of any cause or censoring. Multivariate Cox regression analysis was applied on the weighted data to determine significant differences at a level of 5%.

Table 1a

Patient characteristics (n=360) before IPT weighting with regard to adjuvant treatment (p-values from a-ANOVA, b- Pearson Chi-square test, and d- logrank test. 'Missing' and 'unknown' categories excludEd.) A standardized difference below 0.2 was considered as balanced.

	Total: N+ with and without RT n=360 (100%)	N + without adj. RT n= 157 (43.6%)	N + with RT Groins/Pelvis n= 57 (15.8%)	N+ with RT Vulva and Groins /Pelvis n= 146 (40.5%)	p-value
Age (median, range)	68.9 (20-94)	71.74 (20.3-94.3)	65.65 (32.16-82.82)	68.24 (30.42-87.48)	0.052 a
HPV status					0.811 b
HPV positive	75 (20.8%)	33 (47.8%)	12 (50.0%)	30 (43.5%)	
HPV negative	87 (24.2%)	36 (52.2%)	12 (50.0%)	39 (56.5%)	
Unknown	198 (55%)	88	33	77	
pT Stadium					0.507 b
p T1b	62 (17.2%)	30 (19.1%)	11 (19.3%)	21 (14.4%)	
p T2	237 (65.8%)	106 (67.5%)	35 (61.4%)	96 (65.8%)	
p T3/4	60 (16.6%)	21 (13.4%)	10 (17.5%)	29 (19.8%)	
Missings	1 (2.7%)	-	1 (1.75%)	-	
Tumor diameter mm (median, range)	35 (2-200)	32 (2-140)	35 (5-110)	35 (2.8-200)	0.242 a
Depth of invasion mm (median, range)	7 (0.25-110)	6.5 (0.25-80)	6 (1.5-35)	8 (1.1-110)	0.33 a
Minimal path res section margmm (median, range)	4 (0.25-25)	3 (1-16)	3.5 (2-15)	4 (0.25-25)	0.284 a
Lymph nodes affected					0.002 c
1	148 (41.1%)	84 (53.5%)	23 (40.4%)	41 (28.1%)	
2	83 (23.1%)	32 (20.4%)	12 (21.1%)	39 (26.8%)	
3	48 (13.3%)	16 (10.2%)	9 (15.8%)	23 (15.7%)	
> 3	65 (18.1%)	20 (12.8%)	10 (17.5%)	35 (23.9%)	
Missings	16 (4.4%)	5 (3.1%)	3 (5.2%)	8 (5.5%)	
Grading					0.807 c
G 1	19 (5.2%)	8 (5.1%)	4 (7%)	7 (4.8%)	
G 2	214 (59.4%)	93 (59.2%)	31 (54.4%)	90 (61.6%)	
G 3	119 (33.1%)	52 (33.2%)	22 (38.6%)	45 (30.8%)	
Unknown	8 (2.2%)	4 (2.5%)	0 (0.00%)	4 (2.8%)	
ECOG status					0.027 c
ECOG 0	100 (27.7%)	36 (22.9%)	18 (31.6%)	46 (31.5%)	
ECOG 1	68 (18.9%)	19 (12.1%)	13 (22.8%)	36 (24.6%)	
ECOG 2	48 (13.3%)	20 (12.7%)	7 (12.3%)	21 (14.4%)	
ECOG 3+4	21 (5.9%)	15 (9.55%)	3 (5.2%)	3 (2.1%)	
Missings	123 (34.2%)	67 (42.7%)	16 (28.1%)	40 (27.4%)	
Surgical therapy vulva					0.191 c
1 = wide excision	27 (7.5%)	18 (11.4%)	4 (7%)	5 (3.4%)	
2 = partial vulv	95 (26.4%)	40 (25.5%)	15 (26.3%)	39 (26.7%)	
3 = complete vul	235 (65.2%)	98 (62.5%)	37 (64.9%)	100 (68.5%)	
4 = exenteration	3 (0.9%)	1 (0.6%)	1 (1.8%)	2 (1.4%)	
Resection status					0.003 c
R 0	276 (76.7%)	125 (79.6%)	49 (85.9%)	102 (69.9%)	
R 1	51 (14.1%)	15 (9.6%)	4 (7.02%)	32 (21.9%)	
R Missing	33 (9.2%)	17 (10.8%)	4 (7.02%)	12 (8.2%)	
Radiotherapy performed					<0.001 c
RT only	177 (49.2%)	0	52 (91.2%)	125 (85.6%)	
RCTX	26 (7.2%)	0	5 (8.8%)	21 (14.4%)	
No	157 (43.6%)	157 (100%)	0	0	
Recurrence site					
No rec	143 (39.7%)	56 (35.7%)	21 (36.8%)	66 (45.2%)	
Vulva only	76 (21.1%)	40 (25.5%)	13 (22.8%)	23 (15.9%)	
Groins only	15 (4.2%)	7 (4.5%)	3 (5.2%)	5 (3.4%)	
Vulva + Groins	17 (4.7%)	8 (5.1%)	4 (7%)	5 (3.4%)	
Including pelvis	19 (5.3%)	7 (4.5%)	3 (5.3%)	9 (6.1%)	
Including dist	36 (10%)	13 (8.2%)	4 (7%)	19 (13%)	
Unknown	2 (0.5%)	0	2 (3.5%)	0	
Death before rec	52 (14.4%)	26 (16.5%)	7 (12.4%)	19 (13%)	
Median DFS (months)	15.9	12.7	15.3	18.3	0.077 d
Median OS (months)	53.6	42.7	53.6	57.9	0.707 d

3. Results

3.1. Patients

Of 360 N+ patients with stage IB-IV VSCC, 177(49.2%) received adjuvant RT only while 26/360 patients (7.2%) were treated with concomitant chemoradiation (mainly with cisplatin), and 157/360 patients (43.6%) did not undergo any adjuvant RT treatment. 57/360 patients (15.8%) received adjuvant RT to the groins/pelvis alone and 146/360 patients (40.5%) were treated with adjuvant RT to the vulva, groins and pelvis. The median total dose applied in all N+ patients with adjuvant RT irrespective of the fields irradiated was 50.4 Gy.

Patient characteristics are displayed in Table 1a. Median age was 68.9 years (20-94) and median follow-up was 17.2 months (range 0.0-163.5). The majority had locally early stage tumors (T1b/T2; TNM staging system Version 6; 299/360, 83.1%) with a median diameter of 35mm (2-200mm). Overall, 330/360 patients (91.6%) were treated with a partial or complete vulvectomy (26.4% partial and 65.2% complete vulvectomy), further surgical therapy consisted of wide excision (27/360 patients, 7.5%) and exenteration (3/360 patients, 0.9%). Median minimal pathological resection margin was 4mm (0.25-25mm) and tumor-free margins were achieved in 276/360 patients (76.7% R0). In 33/360 patients (9.2%) the resection status was missing, while in 51/360 patients (14.1%) R1 status was present (9.6% R1 within the N+

without RT subgroup, 7% R1 in the N+ with RT groins/pelvis cohort and 21.9% R1 within the N+ with RT vulva and groins/pelvis subgroup). In the total cohort, 148/360 patients (41.1%) had one positive lymph node (LN), while 65/360 patients (18.1%) had more than 3 positive inguinal LNs. As assumed, the majority of N+ patients in whom adjuvant RT was omitted, had only one positive LN (53.5%, 84/157 patients), while N+ patients with adjuvant RT to the vulva and groins/pelvis had an increased nodal involvement represented by 3 or more positive LNs in 39.7% (58/146 patients). HPV status was available for 162/360 tumors (45%), thereof 75/162 tumors were found to be HPV positive (46.3%), and 87/162 (53.7%) negative. Table 1a shows the observed distribution of variables before IPTW and Table 1b shows the distribution after IPTW. IPTW did improve balancing but did not fully balance the three groups with respect to ECOG and resection margin status (Figs 1a-c, supplement), therefore additional adjustment for age (continuous), nodes affected (1, 2, 3, >3), resection margin status (0,1, missing), pT status (T1a, T1b, T2, T3/4) and ECOG (0,1,2,3/4, missing) was modelled to obtain double-robust estimates. In order to sufficiently compare the impact of adjuvant RT to the vulva in HPV + and HPV - patients, 50% disease-free-survival time (50% DFST, in months) before and after propensity weighting was statistically evaluated (Table 2).

3.2. Recurrence

Within a median follow-up of 17.2 months (range 0.0-163.5 months), a total of 60.2% of patients (217/360) experienced any kind of disease recurrence or death, 39.7% (143/360 patients) remained free of recurrences and/or death at all, and death before recurrence occurred in 14.4% (52/360 patients). Table 3 describes the localization of the disease recurrence with regard to the applied adjuvant RT. Of note, 23/146 patients (15.8%) experienced a local recurrence at the vulva only although adjuvant RT was previously applied to vulva and groins/pelvis. Furthermore, within the group of patients with adjuvant RT of the vulva and groins/pelvis, 13.0% (19/146 patients) suffered from distant recurrences as the second most frequent site of recurrence after isolated local recurrences at the vulva (15.8%). IPTW analysis with multivariate adjustment yielded a significantly increased local recurrence risk in N+ patients without adjuvant RT compared to N+ patients with adjuvant RT to the vulva and groins/pelvis (HR 1.79, 95%CI 1.09; 2.91, p= 0.019) independent of the resection margin status (Fig. 1). To further describe the effect of RT on disease free survival time, 50% DFST were calculated in HPV + and HPV – patients (Table 2). The results indicate a stronger effect of local radiotherapy in HPV+ patients compared to HPV - patients (50% DFST 20.7 months vs. 17.8 months): Hazard Ratio HPV + patients: a) without RT 2.28 (p= 0.21), b) with RT vulva and groins/pelvis: 1, c) with RT groins/pelvis 6.35, (p= 0.01) vs.

Hazard Ratio HPV – patients a) without RT 1.89 (p= 0.30), b) with RT vulva and groins/pelvis: 1 and c) with RT groins/pelvis 1.68, (p= 0.35, respectively). The risk for local recurrence with regard to HPV status is displayed in Fig. 2.

3.3. Prognosis

In case of patients without adjuvant RT prognosis was significantly impaired in comparison to patients with adjuvant RT to the groins/pelvis and to the vulva (HR 1.53, 95%CI 1.10; 2.13, p=0.010) (Fig. 3).

Median DFS for N+ patients without adjuvant RT was 12.7 months; for N+ patients with adjuvant RT to the groins/pelvis 15.3 months and DFS for N+ patients with RT to the vulva and groins/pelvis 18.3 months (HR without RT 1.53, 95%CI 1.10; 2.13, p=0.010 HR with RT groins/pelvis 1.10 (95%CI 0.73; 1.65, p= 0.64). Also median OS was shorter in the N+ patients without RT compared to N+ patients with RT to the groins/pelvis and to the vulva and groin/pelvis (median OS 42.7 months vs. 53.6 months vs. 57.9 months), but no significant association was observed (HR without RT 1.34, 95% CI: 0.85; 2.12, p= 0.19, HR with RT groins/pelvis 1.09, 95%CI 0.66; 1.80, p=0.73) (Fig. 3).

4. Discussion

The impact of adjuvant RT to the vulva in N+ patients has been poorly described. Currently indication criteria for adjuvant RT beyond R1 and R2 resection remain unclear. In contrast to te Grootenhuis et al. who did not observe any difference in local recurrences between patients with and without adjuvant RT to the vulva [19], our results provide evidence that the local recurrence rate is significantly reduced from 25.5% in N+ patients without adjuvant RT to 15.8% in N+ with adjuvant RT to the vulva and groins/pelvis. Adjuvant RT to the groins/pelvis alone did not influence the local recurrence rate [13].

The question when to reasonably recommend local RT to the vulva – especially in view of the often considerable side effects – is still insufficiently answered. Despite (radical) primary treatment, the overall local recurrence rate (LRR) even in patients with early-stage VSCC remains high with 27.2% at 5 years, and 39.5% at 10 years [13]. 43-72% of these patients will suffer from a second local recurrence and another 57% will develop a third or even more local recurrences [13]. While previous studies revealed higher local recurrences rates for node positive patients, it was recently observed that also sentinel node (SN) negative patients seem to experience local recurrences to a relevant amount of the cases: 5-year LRR was 24.6% and 10-year LRR was 36.4% for SN node negative patients, while SN node positive patients developed local recurrences in 33.2% (5-year LRR) and 46.4% (10-year LRR) (p=0.003) [13]. As mentioned above, vulvar radiation is often associated with substantial side effects such as vaginal stenosis (VS), dryness and sexual dysfunction [20–24]. The incidence of VS reported varies between 1.25-88% [23], however, according to patient-reported outcomes (PROs), sexual dysfunction as a consequence of vaginal morbidity is most likely underreported [25]. VS most commonly occurs within the first year posttreatment and is reported to gradually increase with time [23]. Moreover, VS and sexual dysfunction negatively impact the patients quality of life and represent long-term source of psychological and physical distress [23]. Especially in these often younger patients, preservation of sexual functioning, is essential. Patients should therefore be advised at the beginning of the treatment about the potential side effects and its consequences [23]. Vaginal dilatation continues to be the internationally accepted and recommended prevention - and treatment strategy of choice for VS induced by radiation. However, there is a lack of high-level evidence regarding the use of dilatators and further clinical trials are needed [23]. In view of these considerable and often long-term side effects caused by vulvar radiation, indication for RT to the vulva should therefore be carefully considered as the benefit of RT should (always) be weighted with its morbidity.

Table 2
50% disease free survival time with regard to HPV status and adjuvant RT (a standardized difference below 0.2 was considered as balanced).

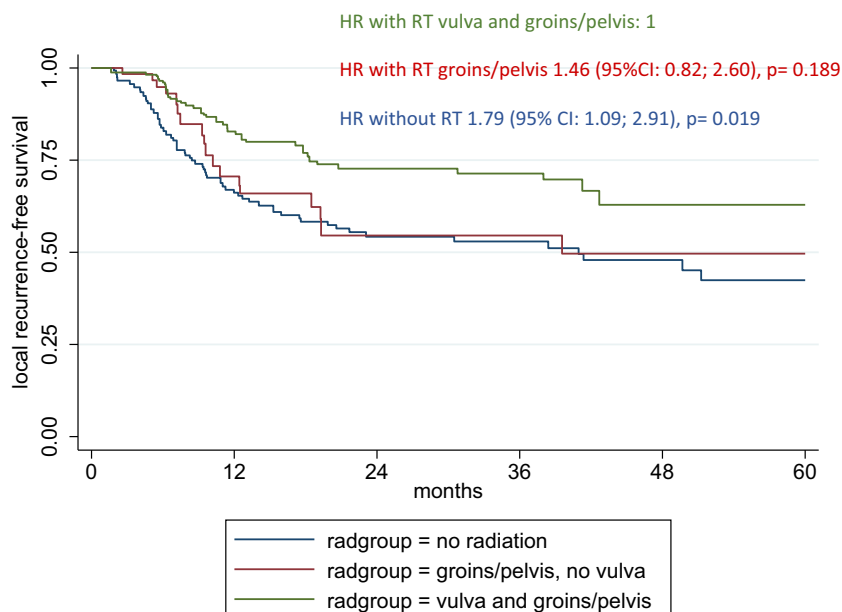| 50% disease free survival time (months)	No adjuvant RT to the vulvaHPV – pts	No adjuvant RT to the vulvaHPV + pts	Adjuvant RT to the vulvaHPV – pts	Adjuvant RT to the vulvaHPV + pts
As observed	15.2	9.7	14.6	20.7
After PS (propensity) weighting	10.8	9.6	17.8	20.7

Table 3

Site of disease recurrence with regard to the applied adjuvant RT (a standardized difference below 0.2 was considered as balancEd.)

|	Total n= 360	N+ without adj. RT n= 157	N+ with RT groins/pelvis n= 57	N+ with RT vulva and groins/pelvis n= 146
Localization of disease recurrence				
No recurrence	143 (39.7%)	56 (35.67%)	21 (36.84%)	66 (45.21%)
Vulva only	76 (21.1%)	40 (25.48%)	13 (22.81%)	23 (15.75%)
Groins only	15 (4.2%)	7 (4.46%)	3 (5.26%)	5 (3.42%)
Vulva + Groins	17 (4.7%)	8 (5.1%)	4 (7.02%)	5 (3.42%)
Including pelvis	19 (5.3%)	7 (4.46%)	3 (5.26%)	9 (6.16%)
Including distant	36 (10%)	13 (8.28%)	4 (7.02%)	19 (13.01%)
Unknown	2 (0.5%)	0	2 (3.5%)	0
Death before rec	52 (14.4%)	26 (16.56%)	7 (12.28%)	19 (13.01%)
Recurrences in total	217/360	101/157 **64.3%**	36/57	80/146
	60.2%		**63.1%**	**54.79%**

In the past, the impact of appropriately treated local recurrence on survival was thought to be of subordinated relevance [26]. In contrast, te Grootenhuis et al. recently detected a significant decrease of 10-year DSS from 96.1% to 80.8% (p<0.001) in case of local recurrence for SN node negative patients, while 10-year DSS for SN positive patients was even worse reflected by a decrease from 77.7% to 44.6% (p= 0.0042) [13]. Despite the fact that inguinal nodal involvement is the most important prognostic factor for both, PFS and OS (3-year PFS rate of 35.2% and OS rate of 56.2% in node positive patients vs. 75.2% and 90.2% in node negative patients) [12,27–30], a variety of prognostic and risk factors must be taken into account when it comes to prediction of local recurrences. Univariate risk factors for local recurrence beyond nodal involvement were reported to be higher age (>75 years), greater tumor size, a multifocal tumor growth, depth of invasion > 2mm and lymphovascular space invasion [9,31–34]. Nonetheless, prognostic relevance of these clinico-pathological factors remained equivocal according to a recently published review and so does the indication of adjuvant local radiotherapy [7]. Most importantly, the role of the tumor free resection margin distance has been discussed intensively due to controversial study results reflected by local recurrences rates varying from 0-50% [26,35–38]. A tumor free margin is essential for locoregional control of the disease [36,39], however, the pathological margin distance is controversial. Until recently, a tumor-free resection

margin of at least 8 mm was considered state of the art [3]. However, several more recent publications including those of our own group provided evidence that there is no correlation between disease recurrence and pathological margin distance > 8mm [19,38]. Adjuvant RT is supposed to be a major confounder when it comes to adequately evaluate margin status and local recurrence risk. However, even in N- patients treated only surgically no beneficial effect of wider margins could be observed (vulvar local recurrence rate was 12.6% in the < 8mm resection margin group compared to 10.2% in the > 8mm resection margin group). These findings were supported by data from te Grootenhuis et al. who could also demonstrate that pathological tumor free margin distance had no significant effect on the local recurrence rate (continuous HR 1.93, 95% CI 0.98-1.06) [19]. Tumor biology is most likely the reason for the previous inhomogeneous results as of utmost importance for local recurrence. In this context, another multivariate analysis by te Grootenhuis et al. observed a significantly higher local recurrence rates in patients with dVIN and LS in the margin after excision of VSCC (HR 2.76 95%CI 1.62-4.71) [19].

Two studies recently investigated the occurrence of local recurrences after adjuvant RT in relation to the tumor's HPV status using immunostaining for p16 expression as a surrogate parameter [40,41]. Results from these studies indicate less local recurrences in patients with HPV positive tumors: Yap et al. described more loco regional

HR with RT vulva and groins/pelvis: 1

HR with RT groins/pelvis 1.46 (95%CI: 0.82; 2.60), p= 0.189

HR without RT 1.79 (95% CI: 1.09; 2.91), p= 0.019

radgroup = no radiation
radgroup = groins/pelvis, no vulva
radgroup = vulva and groins/pelvis

Fig. 1. Local recurrence free survival with regard to the applied adjuvant RT (a standardized difference below 0.2 was considered as balanced.)

A

B
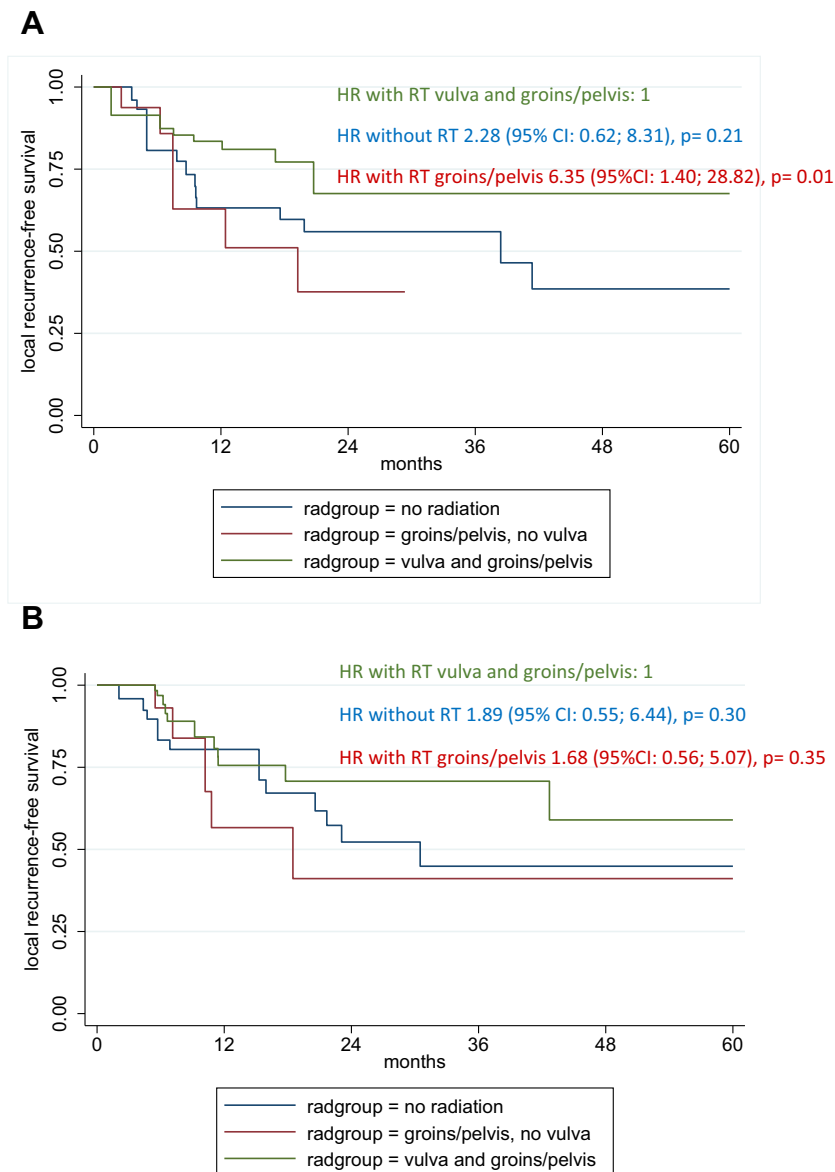
Fig. 2. Radiation fields and local recurrence risk by HPV status in the IPT weighted sample.
a: Local recurrences in HPV positive patients with regard to the applied adjuvant RT
b: Local recurrences in HPV negative patients with regard to the applied adjuvant RT

relapses in patients with HPV negative tumors (HR 2.38 (95%CI 1.15-4.93)), whereas Lee at al. observed less local recurrences in HPV positive patients (HR 0.2, 95%CI 0.06-0.6) [40,41]. Dohopolski et al. confirmed these results within a cohort of patients with known p16 status treated with adjuvant RT (n=39) [42]. Herein, infield relapse rate at 3 years was lower in p16 positive patients (32.5%) compared to p16 negative patients (59.1%, p= 0.072) – a benefit which could be translated into prolonged PFS (p= 0.062), but, however, not into longer OS.
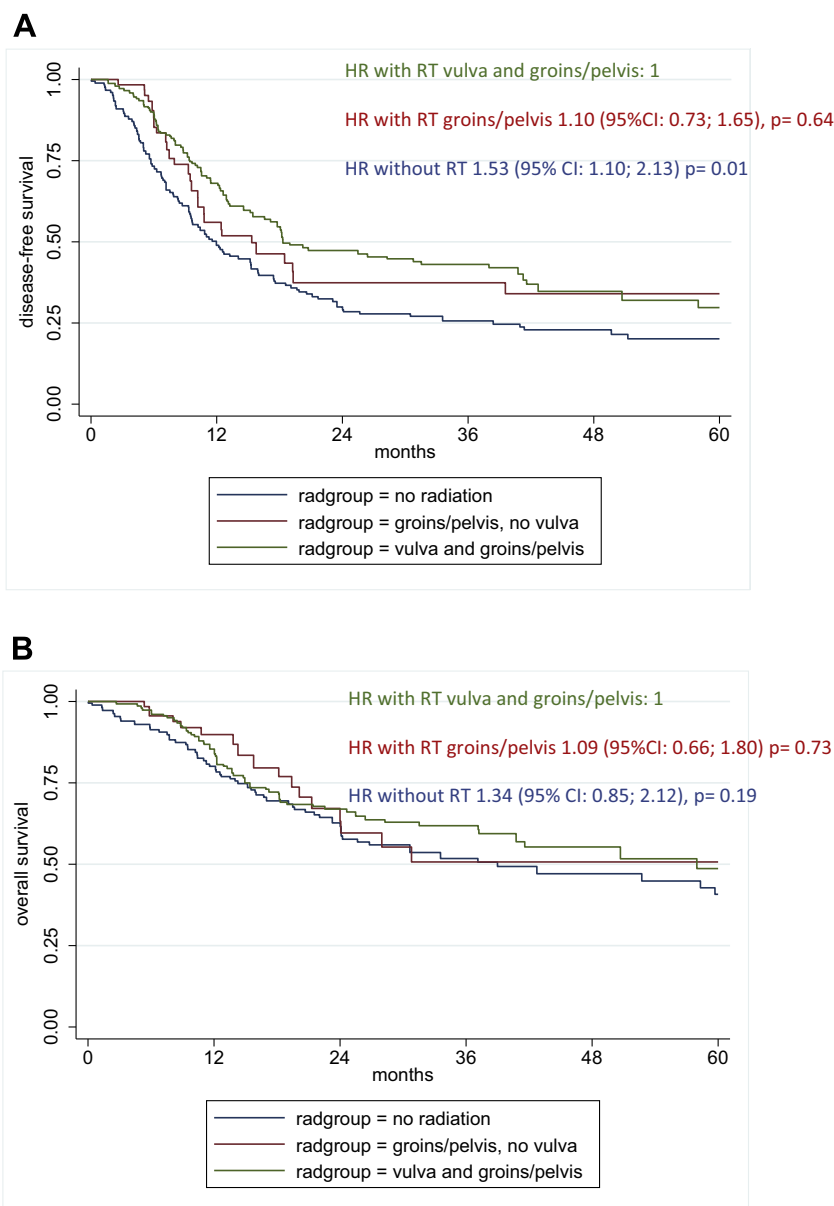
Our results are in line with previously reported data as the LRR in HPV positive patients was lower in comparison to HPV negative patients. Furthermore, our results indicate a stronger effect size of adjuvant RT to the vulva in HPV positive patients compared to HPV negative patients with regard to the appearance of local recurrences. As the other groups we could not demonstrate an impact of local RT on OS.

The main limitation of our subgroup analysis is the retrospective character possibly including selection bias and incomplete data. Although IPTW weighting was statistically applied in order to achieve comparable

subgroups and minimise selection bias, a potential imbalance especially with regard to the resection has to be taken into account. As a second step, additional adjustment including resection margin status was therefore performed (see Fig. 1-3 in Tbl 1c, supplement) – however, results should ideally be confirmed in prospectively designed studies. Based on previous experiences, this will in fact be a challenging project to realize given the small numbers of cases and the inhomogenously treated patients subgroups. Taken these circumstances into account, our analysis appears to be of even higher relevance.

Although our median FU period with 17.2 months (range 0.0-163.5) was comparatively short, it nevertheless underlines the beneficial/risk-reducing impact of adjuvant RT on the occurence of local recurrences – especially when arising early during the course of the disease.

In conclusion, our results provide evidence that adjuvant RT to the vulva significantly reduces the risk for local recurrence in N+ patients. This effect was mainly observed in the HPV+ group with the limitation of missing data and the dilemma of a generally higher risk for local

A

HR with RT vulva and groins/pelvis: 1

HR with RT groins/pelvis 1.10 (95%CI: 0.73; 1.65), p= 0.64

HR without RT 1.53 (95% CI: 1.10; 2.13) p= 0.01

(y-axis: disease-free survival; x-axis: months)

radgroup = no radiation
radgroup = groins/pelvis, no vulva
radgroup = vulva and groins/pelvis

B

HR with RT vulva and groins/pelvis: 1

HR with RT groins/pelvis 1.09 (95%CI: 0.66; 1.80) p= 0.73

HR without RT 1.34 (95% CI: 0.85; 2.12), p= 0.19

(y-axis: overall survival; x-axis: months)

radgroup = no radiation
radgroup = groins/pelvis, no vulva
radgroup = vulva and groins/pelvis

Fig. 3. DFS and OS with regard to adjuvant RT (a standardized difference below 0.2 was considered as balancEd.)
a: Disease free survival with regard to the applied adjuvant RT
b: Overall survival with regard to the applied adjuvant RT

recurrence in patients with HPV negative tumors. No relevant impact on OS was observed. Consequently, determination of HPV – status is of great relevance for therapeutic decision making and should be part of the standard pathological workup.

Authors' contributions

All authors have made substantial intellectual contributions to the article, provided critical feedback and given approval of the final manuscript to be published. L.W. and S.M. initially designed and coordinated the multicenter AGO-CaRE-1 Study and the subprojects. In the current subanalysis, L.W. and A.J. took the lead in writing the manuscript, were responsible for the conception/design of the article as well as for data collection and interpretation. C.E.: statistically analyzed and interpreted the data of the patients, C.P. and S.C interpreted the data as well as helped to draft the manuscript. K.P., M.B., T.B., F.H., N.G, S.I., J.S., A.I., P.H., J.J., H-G.S., K.B., M.B., A.M. supervised the project by providing substantial feedback and revising it critically for intellectual content.

Declaration of Competing Interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.11.004.

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