Clinical Oncology 34 (2022) 3–10

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Lichen Sclerosis is Associated With a High Rate of Local Failure After Radio(chemo)therapy for Vulvar Cancer

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Abstract

Aims: Radio(chemo)therapy plays an important role in the treatment of vulvar cancer, either as postoperative treatment or as definitive treatment in patients who present with inoperable disease. Only limited data are available regarding outcome after modern state of the art radio(chemo)therapy and more information regarding prognostic factors are warranted. The aim of this study was to evaluate disease outcomes after radio(chemo)therapy in patients with vulvar cancer with special emphasis on the impact of lichen sclerosis on local control.

Materials and methods: All consecutive patients ($n = 109$) from the western half of Denmark who were treated with definitive ($n = 52$) or postoperative ($n = 57$) radio(chemo)therapy between January 2013 and January 2020 were included. Local control, cause-specific survival and overall survival, as well as morbidity, were analysed using Kaplan–Meier statistics. Prognostic factors for local control were analysed in univariate and multivariate analysis.

Results: At a median follow-up of 35 (4–95) months, 46 (42.0%) patients were diagnosed with recurrence. Eighty per cent of the recurrences were located to the vulva region, leading to a 5-year local control of 58.9% (confidence interval 47.9–69.9). Cause-specific survival was 62.9% (confidence interval 53.1–72.7), whereas overall survival was 58.0% (confidence interval 47.6–68.5). Grade 3–4 morbidity was diagnosed in 10 (9%) patients. Lichen sclerosis (hazard ratio 3.89; confidence interval 1.93–7.79) was an independent risk factors for local recurrence. Patients without lichen sclerosis had a 5-year local control rate of 83.6% (confidence interval 67.2–99.0) and 62.6% (confidence interval 43.2–82.0) after postoperative and definitive radio(chemo)therapy, respectively. In patients with lichen sclerosis, the local control rate was 44.0% (confidence interval 19.3–69.0) and 17.6% (confidence interval 0–30.0) after postoperative and definitive radio(chemo)therapy, respectively.

Conclusion: Radio(chemo)therapy plays an important role in the treatment of vulvar cancer. However, despite dose escalation, a substantial proportion of patients experienced local relapse. Pre-existing lichen sclerosis seems to have a significant impact on the risk of recurrence. This should influence surveillance programmes for these patients.

Key words: Definitive radiotherapy; lichen sclerosis; postoperative radiotherapy; vulvar cancer

Introduction

Vulvar cancer is an uncommon cancer that account for about 5% of all gynaecological malignancies. The peak incidence of vulva cancer is 65–70 years and most tumours are squamous cell carcinomas [1]. There are two main aetiological pathways for vulvar cancer. One pathway is related to previous human papillomavirus (HPV) infection, whereas the other and non-HPV-related pathway is associated with chronic inflammatory disease (lichen sclerosis) and the precursor differentiated vulvar intraepithelial lesions pathway [2–4].

The surgical treatment of vulvar cancer includes a wide local excision in operable patients. Due to the risk of regional lymph node metastases in patients with >1 mm invasion depth, sentinel lymph node dissection is recommended in clinical and radiologically node-negative patients with tumour size <4 cm. In patients with tumour size ≥4 cm, multifocality or pathological groin lymph nodes including sentinel lymph node macrometastasis (>2 mm) inguino-femoral lymph node dissection is recommended

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https://doi.org/10.1016/j.clon.2021.07.014

[5,6]. The role of adjuvant radio(chemo)therapy has been established in several large retrospective studies showing improved survival in patients with lymph node-positive disease [6–8]. In contrast, the benefit of postoperative radio(chemo)therapy in cases with non-radical resection margin is less clear and no consensus guideline is available [9,10].

Patients who are inoperable due to locally advanced disease with tumour invasion into neighbouring organs (urethra, anus, bladder) are selected for definitive radio(-chemo)therapy. The literature on definitive radio(chemo) therapy in advanced vulvar cancer is limited [11–13]. Moreover, recurrence and survival outcomes after modern radio(chemo)therapy using state of the art imaging and highly conformal radiotherapy techniques such as intensity-modulated radiotherapy/volumetric-modulated arc therapy (IMRT/VMAT) have only been investigated in small retrospective studies [14–19]. More knowledge regarding the impact of clinical and pathological factors on recurrence and survival outcomes is warranted. The aim of the present study is to investigate disease outcomes in terms of local control, cause-specific survival and overall survival after definitive or postoperative radio(chemo) therapy. Furthermore, morbidity related to radio(chemo) therapy as well as prognostic factors for local control were investigated.

Materials and Methods

In total, 136 consecutive patients with vulvar cancer were referred for radio(chemo)therapy between January 2013 and January 2019 at Aarhus University Hospital in Denmark. Twenty-seven patients underwent palliative radiotherapy, leaving 109 patients as candidates for the present study. These patients included 52 inoperable patients who underwent definitive radio(chemo)therapy (39 patients with primary disease and 13 patients with recurrent disease) and 57 patients who underwent postoperative radio(chemo)therapy (50 patients with primary disease and seven patients with recurrent disease).

All patients were assessed with a clinical examination under general anaesthesia, positron emission tomography-computed tomography (PET-CT) and magnetic resonance imaging (MRI) scans at diagnosis and were discussed at a multidisciplinary team conference with participation of specialists within oncogynaecology, radiology, pathology and clinical oncology.

Surgery was carried out according to national guidelines [20]. Postoperative radio(chemo)therapy was given in case of one or more lymph node metastases or insufficient tumour margin. Patients with disease extension that would require resection of the vagina, anus or >1 cm of the urethra to achieve negative margins were referred for definitive radio(chemo)therapy.

Radio(chemo)therapy was planned with the patient in the frog leg position and based on PET-CT and MRI scans with image fusion according to the bony anatomy. In patients with a visible tumour, an individualised bolus consisting of a 5 mm super flap and gauge with saline was applied. All patients were treated with IMRT or VMAT.

Concomitant weekly cisplatin (40 mg/mm^2, maximum 70 mg) was given if feasible. In total, 55 (50%) patients were selected for cisplatin. The median number of cycles given was five (one to six). In four (4%) patients, neoadjuvant platinum-based combination chemotherapy was used in an attempt to downsize large tumours prior to definitive radio(chemo)therapy.

Definitive Radio(chemo)therapy

In patients allocated to definitive radio(chemo)therapy, a gross tumour volume of the primary (GTV-T) and pathological lymph node volumes (GTV-N) was defined. The clinical target volumes (CTV-T and CTV-N) were defined by adding a 5–10 mm margin around the GTV-T and 3–5 mm to each individual GTV-N and cropping for anatomical normal structures and skin. All patients had an elective target volume defined that always included the vulva region and the groins. In cases with groin lymph node metastases, the external iliac region was also included in the elective target.

The prescribed dose to the elective target volume was 51.2 Gy in 1.6 Gy/fraction. Tumour and lymph node boost were delivered as a simultaneous integrated boost (SIB) with 64 Gy in 2 Gy/fraction to all patients, with the exception of six patients who were selected for a brachytherapy boost. These patients were treated with an elective dose to the tumour, followed by a pulse dose rate brachytherapy tumour boost of 19–30 Gy in 30–50 hourly pulses.

Postoperative Radio(chemo)therapy

Postoperative radio(chemo)therapy was delivered to an elective target that included the vulva region alone in 22 (39%) patients with insufficient surgical margin and no evidence of groin metastases after surgery, to the vulva, groins and external iliac regions in 25 (44%) patients with insufficient surgical margin and groin metastases and to the groins alone in 10 (18%) patients with groin metastases and adequate tumour-free margin. The dose to the elective target was 50 Gy in 1.67 Gy/fraction. Fourteen patients (24%) with a positive tumour margin and five (9%) patients with perinodal lymphatic growth had a SIB to 60 Gy in 2 Gy/fraction.

During the scheduling of postoperative radio(chemo) therapy, residual tumour was identified in one (2%) patient and another 11 patients (19%) had additional PET-positive lymph nodes. These patients had a GTV-T or GTV-N defined using the same methodology as for definitive radio(chemo)therapy. The prescribed dose was also changed to 51.2 Gy in 1.6 Gy/fraction to the elective target and a SIB of 64 Gy in 2 Gy/fraction to the residual disease.

Post-treatment Follow-up

Follow-up after radio(chemo)therapy was carried out every 3 months in the first year, every 6 months for the next

3 years and annually thereafter. In patients treated for macroscopic tumour, the treatment response was assessed with routine PET-CT, MRI and a clinical examination at 3 months of follow-up.

Clinically relevant patient- and treatment-related factors were extracted from medical records (Table 1). Furthermore, disease outcome (local control, cause-specific survival and overall survival) and late morbidity were recorded.

Disease outcome was analysed with Kaplan–Meier statistics. Follow-up was calculated as the time from diagnosis until an event (recurrence or death) or last follow-up, whichever came first. Patients were censored at last follow-up or at the time of disease recurrence during follow-up.

Morbidity was scored according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE, V3.0) and analysed in crude numbers.

Univariate analysis of relevant prognostic variables for local control was conducted by Cox regression analysis. Statistically significant independent variables ($P \leq 0.05$) from the univariate analysis were entered in a multivariate model.

The SPSS statistical software system v.20 (IBM SPSS Statistics for Windows, Version 20.0 Armonk; NY: IBM Corp.) was used for statistical analysis.

Results

Baseline characteristics for the 109 patients are listed in Table 1. Briefly, the median age was 69 (33–86) years and 59% had comorbidity, but with 89% of the patients in performance status ≤1. A high proportion of the patients had advanced disease, with tumour stage II–III (36%) and lymph node metastases (65%). Lichen sclerosis was present in 38 (35%) patients and was more common among the elderly half of the patients (26/56; 46%) compared with the younger half of the patients (12/53; 23%).

At 3 months of follow-up, a complete clinical response was obtained in 39/52 (75%) patients after definitive radio(chemo)therapy.

Table 1
Patient characteristics (no grading was available in three patients with adenocarcinoma)

Variable		All patients (n = 109)	Definitive radiotherapy (n =52)	Postoperative radiotherapy (n = 57)
Age (median)		69 (33–86)	68 (43–85)	70 (33–86)
Performance status	0–1	60 (55%)	29 (56%)	31 (55%)
	1	38 (35%)	19 (36%)	19 (33%)
	2	11 (10%)	4 (8%)	7 (12%)
Comorbidity	Yes	84 (59%)	29 (56%)	35 (61%)
Smoking	Yes	40 (37%)	19 (37%)	21 (37%)
Primary disease	Yes	89 (82%)	39 (75%)	50 (88%)
Tumour size (mm)	≤2 cm	30 (28%)	9 (17%)	21 (37%)
	>2–4 cm	56 (51%)	28 (54%)	28 (49%)
	>4 cm	23 (21%)	15 (29%)	8 (14%)
Lymph nodes	0	38 (35%)	18 (35%)	20 (35%)
	1	31 (28%)	12 (23%)	19 (33%)
	2	20 (18%)	8 (15%)	12 (21%)
	≥3	20 (18%)	14 (27%)	6 (11%)
Multifocality	Yes	3 (3%)	0 (0%)	3 (5%)
T-stage (TNM)	0	4 (4%)	3 (6%)	1 (2%)
	1	65 (60%)	13 (25%)	52 (91%)
	2	33 (30%)	30 (58%)	3 (5%)
	3	7 (6%)	6 (12%)	1 (2%)
N-stage (TNM)	0	38 (35%)	18 (35%)	20 (35%)
	1	52 (48%)	22 (42%)	30 (53%)
	2	17 (16%)	10 (19%)	7 (12%)
	3	2 (2%)	2 (4%)	0 (0%)
Squamous cell carcinoma	Yes	106 (97%)	52 (100%)	54 (95%)
Differentiation grade	Well	44 (40%)	23 (44%)	21 (37%)
	Moderate	35 (32%)	17 (33%)	18 (32%)
	Poor	27 (25%)	12 (23%)	15 (26%)
	No grade	3 (3%)	0 (0%)	3 (5%)
Lichen sclerosis	Yes	38 (35%)	20 (39%)	18 (32%)

At a median follow-up of 35 (4–95) months, 46 recurrences were diagnosed in 19 (33%) and 27 (52%) patients treated with postoperative and definitive radio(chemo) therapy, respectively. The recurrences mainly involved the vulvar region, with a total of 37 local recurrences diagnosed in 13 (23%) and 24 (46%) patients after postoperative and definitive radio(chemo)therapy, respectively.

The 2- and 5-year local control rates were 69.6% (confidence interval 60.2–78.4) and 58.9% (confidence interval 47.9–69.9), respectively. The cause-specific survival at 2 and 5 years was 69.6% (confidence interval 60.8–78.4) and 62.9% (confidence interval 53.1–72.7), respectively, whereas overall survival was 64.3% (confidence interval 55.3–73.3) and 58.0% (confidence interval 47.6–68.4) at 2 and 5 years, respectively (Figure 1).

Patients treated with postoperative radio(chemo)therapy had a better local control compared with patients treated with definitive radio(chemo)therapy ($P = 0.004$). No difference in cause-specific survival ($P = 0.362$) and overall survival ($P = 0.492$) was found between the two cohorts of patients (Figure 2).

Treatment of residual ($n = 6$) and recurrent disease ($n = 13$) after radio(chemo)therapy included salvage surgery in 19 patients (eight patients underwent exenteration and 11 patients underwent vulvar resections). After salvage surgery, 10 patients developed a second recurrence. The remaining nine patients were without signs of recurrence at the time of last follow-up.

Univariate analysis of factors associated with local control showed that increasing age ($P = 0.023$), presence of lichen sclerosis ($P < 0.001$), treatment strategy (definitive radiotherapy versus postoperative radiotherapy) ($P = 0.006$) and clinical tumour size ($P = 0.006$) were associated with local failure. In the multivariate analysis, the presence of lichen sclerosis ($P < 0.001$), treatment strategy ($P = 0.024$) and tumour size ($P = 0.026$) remained as independent risk factors for local failure (Table 2).

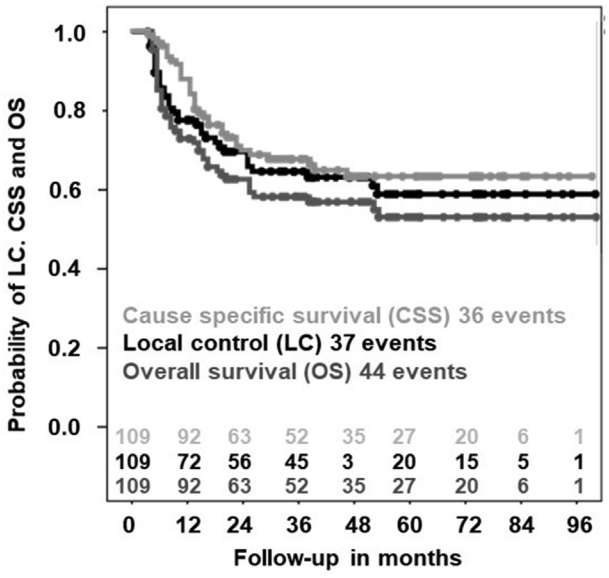

Fig 1. Local control, cause-specific survival and overall survival in 109 vulvar cancer patients treated with definitive or postoperative radio(chemo)therapy.

The impact of lichen sclerosis on local control was analysed for all patients and in stratified analyses according to treatment strategy. Independent of treatment strategy, lichen sclerosis was associated with a significantly increased risk for local failure in both groups of patients. In patients without lichen sclerosis, the 5-year local control rate was 83.6% (confidence interval 67.2–99.0) and 62.6% (confidence interval 43.2–82.0) after postoperative and definitive radio(chemo)therapy, respectively. In patients with lichen sclerosis, the 5-year local control rate was 44.0% (confidence interval 19.3–69.0) and 17.6% (confidence interval 0–30.0) after postoperative and definitive radio(-chemo)therapy, respectively (Figure 3).

Moderate grade 2 late morbidity (53 events) was found in 30 (27%) patients and included 24 (22%) patients with fibrosis (skin), 12 (11%) patients with vaginal stenosis, nine (8%) patients with urinary incontinence, five (5%) patients with fecal incontinence, one (1%) patient with renal insufficiency, one (1%) patient with rectal bleeding and one (1%) patient with neuropathy. Severe grade 3–4 late morbidity was found in 10 patients and included six (6%) patients with skin/soft tissue necrosis with delayed wound healing requiring surgical intervention ($n = 4$) or hyberbaric oxygen therapy ($n = 2$), three (3%) patients with complete vaginal stenosis and one (1%) patient with anal incontinence.

No grade 5 morbidity was observed.

Discussion

Multidisciplinary management of vulvar cancer has been centralised in two university hospitals in Denmark. This study investigated disease outcomes and risk factors for local recurrence in 109 consecutive patients from the western half of the country after state-of-the-art postoperative or definitive radio(chemo)therapy.

In our analyses, most treatment failures included a local failure. This is in agreement with previous studies reporting high locoregional failure rates between 27 and 47% after postoperative or definitive radio(chemo)therapy for vulvar cancer [14,16–18]. Our findings, with a 5-year cause-specific survival and overall survival of 62.9% and 58.0%, respectively, are also in line with a previous study reporting a 5-year cause-specific survival and overall survival of 70.4% and 50.8% in 61 patients treated with postoperative or definitive radiotherapy [13] and two other studies reporting 5-year overall survival rates of 44.2% and 51.6% [14,21].

Different clinicopathological risk factors have been suggested as prognostic factors for radio(chemo)therapy in vulvar cancer, e.g. tumour stage and size, lymph node metastases and increasing age have been found to impact negatively on the local control rate and survival outcomes [17,22]. Moreover, lichen sclerosis and HPV-negative tumours have been associated with poor outcomes [3,4,16].

A history of lichen sclerosis was found in one third of all patients in our study. This number is in agreement with

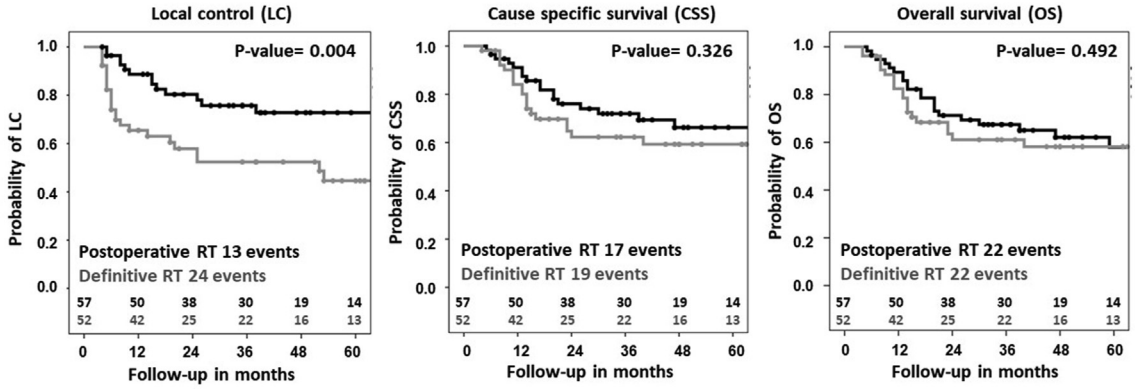

Fig 2. Local control, cause-specific survival and overall survival in 109 vulvar cancer patients after definitive ($n = 52$) and postoperative ($n = 57$) radio(chemo)therapy.

previous studies reporting lichen sclerosis in 31–39% of all patients with vulvar cancer [3,4,16].

In our study, lichen sclerosis was identified as the most important risk factor for local recurrence. The association between lichen sclerosis and local recurrence was not only found in the total population but also in the stratified analysis of patients treated with postoperative or definitive radio(chemo)therapy.

The impact of lichen sclerosis on outcome after radio(-chemo)therapy has not been well investigated and most studies have not included this risk factor in their analysis [11–14,17,18,23]. In one study, lichen sclerosis was associated with an increased risk for recurrence among 49 patients treated with radio(chemo)therapy in the univariate analysis. The finding was not confirmed in a multivariate analysis [16]. In another study including 201 patients with vulva cancer primarily treated with surgery, lichen sclerosis was identified as the primary risk factor for local failure, with a three-fold increase in local failure after surgery among patients with pre-existing lichen sclerosis [3]. These data, together with our data, suggest that the underlying damage of the epithelium in patients with lichen sclerosis not only predisposes to the development of malignant transformation but also increases the risk of recurrent or persistent disease following curative treatment [24].

Due to the pattern of treatment failure, with mainly local recurrences, continuous surveillance after radio(chemo)therapy for vulva cancer is important; especially among patients with lichen sclerosis, who seem to have the highest risk for local recurrence. This is due to salvage surgery, which has curative potential in locally recurrent disease and in our study resulted in subsequent local control in half of the patients with repeated recurrence after radio(chemo)therapy [25].

Previous investigations have considered increasing age as a risk factor for local recurrence [14,17]. In our study, this was also the case in the univariate analysis, but not in the

Table 2
Univariable and multivariable analysis of prognostic factors for local control in 109 patients treated with definitive ($n = 52$) or postoperative ($n = 57$) radio(chemo)therapy

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	*P*	Hazard ratio	95% confidence interval	*P*
Age	1.035	1.005–1.066	0.023	1.020	0.987–1.054	0.243
Lichen sclerosis yes versus no	4.407	2.257–8.606	<0.001	3.879	1.931–7.793	<0.001
Primary versus recurrent disease	1.590	0.749–3.375	0.227			
Definitive versus postoperative radiotherapy	2.579	1.311–5.074	0.006	2.214	1.112–4.410	0.024
Smoking yes versus no	0.736	0.369–1.465	0.383			
Cisplatin yes versus no	0.548	0.284–1.058	0.073			
Comorbidity yes versus no	0.946	0.495–1.808	0.867			
Performance status 0 versus 1–2	1.897	0.989–3.639	0.054			
Tumour size	1.023	1.007–1.039	0.050	1.018	1.002–1.034	0.026
T-stage T0–1 versus 2–3	1.654	0.865–3.163	0.128			
N-stage N0 versus N1–2	0.913	0.513–1.625	0.757			
Differentiation grade	1.012	0.673–1.524	0.953			

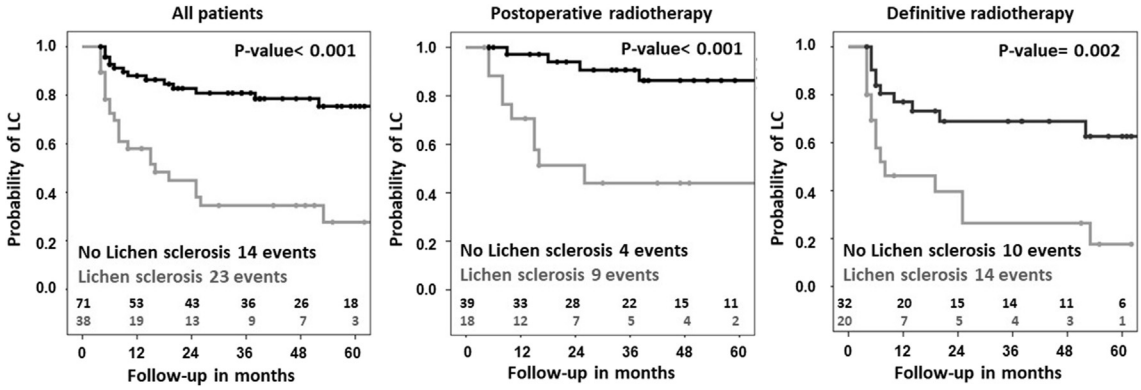

Fig 3. Local control in 109 vulvar cancer patients after definitive (n = 52) and postoperative (n = 57) radio(chemo)therapy according to the presence of lichen sclerosis.

multivariable analysis. As lichen sclerosis is more common in elderly women, age and the presence of lichen sclerosis probably interacted in the multivariate analysis.

Improvements in radio(chemo)therapy for vulvar cancer have until now used dose-escalation to the vulvar region and increasing use of concomitant cisplatin. The Gynecologic Oncology Group (GOG) 205 study investigated the impact of increasing the dose from 47.5 Gy in a split course (as given in the GOG 101 study) to 57.6 Gy with daily treatment and concomitant cisplatin in 58 patients selected for preoperative radio(chemo)therapy. This resulted in improved clinical and pathological complete response rates from 48% and 31%, respectively, in the GOG 101 study to 64% and 50% in GOG 205 [11,12]. Since the publication of GOG 101 and 205, which used two-dimensional/three-dimensional radiotherapy primarily with an anterior to posterior/posterior to anterior field technique, the introduction of IMRT has enabled delivery of highly conformal radiotherapy with steep dose gradients and the elimination of dose modulation across overlapping target regions, thus reducing the dose to the bladder, rectum and small bowel [26]. Furthermore, consensus contouring guidelines for target delineation for IMRT treatment planning have been published [27]. Dose escalation using IMRT has been investigated in two recent retrospective studies. In the first study, 49 patients were treated with preoperative or definitive radio(chemo)therapy with 59.4–66.0 Gy. In the preoperative patients, complete clinical and pathological response rates of 76% and 70%, respectively, were obtained [16]. In the second study, 26 patients were treated with definitive radio(chemo)therapy and they obtained a complete clinical response rate of 80% [18]. These results are in agreement with our study and together with GOG 101 and 205 suggest a dose–response relationship for vulvar cancer. Based on our data, it could be argued that further improvement in local control may be guided by dose-escalation. However, in our study, severe late morbidity with soft tissue necrosis resulting in surgery or hyperbaric oxygen treatment was reported in 6/52 (12%) patients, treated to a median tumour dose of 64 Gy. This is in agreement with a previous study investigating toxicity in 26 patients treated with definitive radio(chemo)therapy using a high-dose IMRT technique. In that study, five (19%) patients presented with soft tissue injury requiring surgical interventions, including debridement and grafting, after a median tumour dose of 66 Gy [18]. Based on these findings, it could be argued that the application of 64–66 Gy represents an upper limit of external beam radiation doses that are safely delivered even with conformal radiotherapy using an IMRT technique and that further dose escalation will substantially increase the risk of severe late morbidity.

In our study, regional control was excellent, with no isolated groin recurrences among the 52 patients who underwent definitive radio(chemo)therapy. Two previous studies investigated groin recurrences after definitive radio(chemo)therapy. One study, included 22 clinically node-negative patients who received 45–50 Gy to the groin. No isolated groin recurrences were observed in this subgroup. In the remaining 27 patients with image-positive lymph node metastases, a mean dose of 60 Gy was prescribed and one (4%) patient developed an isolated groin recurrence [16]. In the other study, 33 patients with lymph-node positive inguinal metastases were treated with a median dose 66 Gy and one (3%) patient developed a recurrence [28]. These data suggest that 50 Gy to the groins, with a boost to 60–64 Gy for clinically positive nodes, is adequate in definitive radio(chemo)therapy.

In our study, isolated groin recurrences were found in three (5%) of 59 radiologically node-negative patients after postoperative radio(chemo)therapy with 50 Gy. The GROINNS-V II study has shown that postoperative radio(-chemo)therapy with 50 Gy to the groin is a safe alternative to inguino-femoral lymph node dissection in patients with squamous cell carcinoma of the vulva, tumour size <4 cm and one sentinel node micro-metastasis ≤ 2 mm. For patients with sentinel node metastasis >2 mm, radiotherapy with a total dose of 50 Gy was not as safe compared with radical inguino-femoral lymph node dissection, and it was speculated that a higher dose was needed to maintain regional control [6]. To draw firm conclusions regarding the optimal dose in patients with macro-metastases or more than one micro-metastasis in the sentinel lymph nodes in the groin(s), we believe that dose escalation should be investigated in a future study.

The present study included a comparatively large number of patients with vulvar cancer who underwent modern conformal radio(chemo)therapy according to common guidelines. The study was limited by its retrospective nature and heterogenous sample regarding treatment indication. Future prospective multi-institutional studies will gain more knowledge regarding radio(chemo)therapy in this rare disease.

Conclusion

Image-based radio(chemo)therapy plays an important role in definitive and postoperative treatment of vulvar cancer. Despite dose-escalated radiotherapy, a substantial proportion of the patients experience a local recurrence. Pre-existing lichen sclerosis has a significant impact on the risk of recurrence. This should influence the surveillance programmes after radio(chemo)therapy in order to detect local recurrence early for salvage surgery.

Conflicts of interest

The authors declare no conflict of interest.

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