Phase II study of definitive chemoradiation for locally advanced squamous cell cancer of the vulva

van Triest, Baukelien; Rasing, Marnix; van der Velden, Jacobus; de Hullu, Joanne A.; Witteveen, Petronella O; Beukema, Jannet C; van der Steen-Banasik, Elsbieta; Westerveld, Henrike; Snyers, An; Peters, Max

Published in:
Gynecologic Oncology

DOI:
10.1016/j.ygyno.2021.07.020

Publication date:
2021

Gynecologic Oncology 163 (2021) 117–124

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Phase II study of definitive chemoradiation for locally advanced squamous cell cancer of the vulva: An efficacy study

Baukelien van Triest [a,*,1], Marnix Rasing [b,1], Jacobus van der Velden [d], Joanne de Hullu [f], Petronella O. Witteveen [c], Jannet C. Beukema [i], Elsbieta van der Steen-Banasik [h], Henrike Westerveld [e], An Snyers [g], Max Peters [b], Carien L. Creutzberg [k], Remi A. Nout [j], Ludy Lutgens [l], Ina Jürgenliemk-Schulz [b]

[a] Netherlands Cancer institute, Department of Radiotherapy, Amsterdam, Netherlands
[b] University Medical Center Utrecht, Department of Radiation Oncology Utrecht, Netherlands
[c] University Medical Center Utrecht, Department of Medical Oncology, Utrecht, Netherlands
[d] Amsterdam University Medical Center, Department of Gynaecology, Amsterdam, Netherlands
[e] Amsterdam University Medical Center, Department of Radiotherapy, Amsterdam, Netherlands
[f] Radboud University Medical Center, Department of Gynaecology, Nijmegen, Netherlands
[g] Radboud University Medical Center, Department of Radiation Oncology, Nijmegen, Netherlands
[h] Radiotherapie Groep, Deventer/Arnhem, Netherlands
[i] University Medical Center Groningen, Department of Radiotherapy, Groningen, Netherlands
[j] Erasmus University Medical Center, Department of Radiotherapy, Rotterdam, Netherlands
[k] Leiden University Medical Center, Department of Radiotherapy, Leiden, Netherlands
[l] Maastricht Radiation Therapy and Oncology clinic (Maastro), Maastricht, Netherlands

HIGHLIGHTS

- Surgery for locally advanced vulvar cancer is often extensive with stoma formation or need for reconstructive surgery.
- Definitive capecitabine-based chemoradiation is feasible with acceptable acute and late toxicity.
- Local clinical complete response of 62% after 12 weeks and persistent local control of 42% after 2 years
- Need for subsequent stoma formation in only 17% of patients.
- Definitive chemoradiation can serve as alternative for extensive surgery in locally advanced vulvar cancer.

ARTICLE INFO

Article history:
Received 6 May 2021
Received in revised form 6 July 2021
Accepted 11 July 2021
Available online 21 July 2021

Keywords:
Locally advanced
Vulvar cancer
Definitive chemoradiotherapy
Organ-sparing
Toxicity

ABSTRACT

Objective. To evaluate feasibility of chemoradiation as alternative for extensive surgery in patients with locally advanced vulvar cancer and to report on locoregional control, toxicity and survival.

Methods. In a multicenter, prospective phase II trial patients with locally advanced vulvar cancer were treated with locoregional radiotherapy combined with sensitizing chemotherapy (capecitabine). Treatment feasibility, percentage locoregional control, survival and toxicity were evaluated.

Results. 52 patients with mainly T2/T3 disease were treated according to the study protocol in 10 centers in the Netherlands from 2007 to 2019. Full dose radiotherapy (tumor dose of 64.8Gy) was delivered in 92% and full dose capecitabine in 69% of patients. Most prevalent acute ≥ grade 3 toxicities were regarding skin/mucosa and pain (54% and 37%). Late ≥grade 3 toxicity was reported for skin/mucosa (10%), fibrosis (4%), GI incontinence (4%) and stress fracture or osteoradionecrosis (4%). Twelve weeks after treatment, local clinical complete response (cCR) and regional control (RC) rates were 62% and 75%, respectively. After 2 years, local cCR persisted in 22 patients (42%) and RC was 58%. Thirty patients (58%) had no evidence of disease at end of follow-up (median 35 months). In 9 patients (17%) extensive surgery with stoma formation was needed. Progression free survival was 58%, 51% and 45% and overall survival was 76%, 66%, 52% at 1,2, and 5 years.

* Corresponding author.
E-mail address: b.v.triest@nki.nl (B. van Triest).
[1] Both authors contributed equally to the work

https://doi.org/10.1016/j.ygyno.2021.07.020

Conclusions. Definitive capecitabine-based chemoradiation as alternative for extensive surgery is feasible in locally advanced vulvar cancer and results in considerable locoregional control with acceptable survival rates with manageable acute and late toxicity.

1. Introduction

Vulvar cancer is a rare disease with an annual incidence of 2–3 per 100.000 women. About 70% of patients with squamous cell cancer (SCC) of the vulva present with a local tumor confined to the vulva (cT1). Standard treatment consists of a radical local excision of the primary tumor and either lymph node evaluation by sentinel lymph node biopsy or primary inguinal femoral lymphadenectomy (IFL) [1,2]. Treatment of more advanced stages with either extension of the tumor to the vagina, urethra, anus, bladder- or rectal mucosa, or fixation to the pubic bone (cT2/3) is challenging. Positive lymph nodes (LN) are present in 50–60% of patients with T3 tumors.

Surgery for locally advanced vulvar cancer especially when central structures are involved, such as the anal sphincter or the upper two-thirds of the urethra, often requires extensive surgery with colo- and/or urostomy as a consequence, or the need for extensive reconstructive surgery. Other than stoma formation, postoperative morbidity and mortality are a significant problem in these patients. Morbidity such as serious wound breakdown, infection and leg edema is frequently observed after extensive surgery for advanced vulvar cancer. In selected patients with advanced vulvar cancer treated with pelvic exenteration 5-year survival is about 60% [3]. This extensive surgical treatment results in a decrease in postoperative physical, psychological and sexual functioning [4].

In anal cancer, radiotherapy combined with chemotherapy (CRT) as sphincter sparing therapy is very efficacious in preventing colostomies [5–7]. Studies with a moderate dose of neoadjuvant chemoradiation (40-50Gy) showed that organ-sparing was also possible in vulvar cancer patients with extensive disease [8–10].

When combining chemotherapy and radiotherapy several chemotherapeutic regimens have been reported for a variety of cancer types. In vulvar cancer 5-FU has been used in combination with cisplatin or Mitomycin C with acceptable toxicity, but the studies are small and median age is lower than might be expected in the general population with vulvar cancer [11–15]. Especially in an older patient population, nephrotoxicity of cisplatin might be of concern. Therefore, low dose weekly carboplatin has been considered instead, based on cervical cancer data [16]. Translational data on carboplatin as radiosensitizer are variable and prospective clinical data on direct comparison are not available in gynecological cancers. Mitomycin C is not introduced in newer chemoradiation studies in rectal, cervical or head- and neck cancer, because of its toxicity profile. Oral fluoropyrimidines, because of their ease of administration, constitute an attractive alternative for fluorouracil. Capecitabine, an oral fluoropyrimidine carbamate, has been designed with the aim of delivering 5-FU predominantly to the tumor cells [17–19]. The combination of capecitabine with radiotherapy has been studied in several phase I studies. A dosage of 825–1000 mg/sqm bid administered continuously during a radiotherapy period of 6 weeks has been shown a feasible and well-tolerated regimen [20–23]. Because of the intensive radiotherapy regimen in this relatively older patient population, monotherapy with capecitabine with a treatment interruption was chosen as combined modality approach in the present study.

The aim of this national prospective multi-centre study was to investigate the feasibility of definitive CRT with high-dose RT in combination with capecitabine-based chemotherapy in patients with locally advanced vulvar carcinoma. The alternative treatment for all patients would have been extensive surgery with at least one stoma as a consequence or the need for extensive reconstructive procedures. Data will be presented regarding locoregional treatment response including any need for additional surgery, acute and long-term toxicity and survival.

2. Materials and methods

2.1. Patient population

Patients were eligible if the following inclusion criteria were met: SCC of the vulva with locally advanced disease (initial diagnosis or (since 2009) extensive recurrence after previous local surgery) not curable without extensive reconstructive surgery, and/or colostomy and/or urostomy; amenable to curative treatment; performance status WHO 0–2; fit for salvage surgery if needed; measurable disease at least locally (vulvar area); pretreatment laboratory values in normal range, being able mentally, physically and geographically to undergo treatment and follow-up; age > 18 years. The following exclusion criteria were applicable: pathological LN outside the pelvis, distant metastases, concomitant or previous malignancy other than basal cell carcinoma of the skin or CIN of the cervix. The institutional review board at the AUMC approved this prospective non-randomized multi-center phase II study. Written informed consent was obtained.

2.2. Treatment

In this study, definitive CRT was the main treatment. Surgery for the primary vulvar tumor was to be performed according to protocol in case of histologically proven residual disease twelve weeks after CRT, or as salvage treatment in case of progressive disease (PD). Patients with cN0 groin LN and no enlarged/suspicious LN on imaging (ultrasound/CT/MRI) were treated with CRT only. Intended treatment approach for patients with cN1/2 groin LN was upfront nodal debulking or a bilateral IFL eight to twelve weeks after the end of radiotherapy. However, based on response evaluation and patient's condition nodal approach was individualized.

Concerning radiotherapy, a planning CT scan was acquired for all patients in supine treatment position with full bladder instruction. External beam radiotherapy (EBRT) definition of target and organs at risk were according to ICRU-62. Gross tumor volume (GTV) of the primary tumor was based on clinical examination and/or CT/MR imaging. For the clinical target volume (CTV) a minimal margin of 1 cm was applied to the GTV of the primary tumor and LN. The CTV of the elective LN field encompassed the mons veneris, obturator fossa, inguinal-, external and internal iliac- and femoral LN region, and a margin of 0.5 cm around the corresponding vascular structures, any visible LN in this area with a margin of 0.5 cm. All planning target volume (PTV) margins were ≥ 1 cm. A 3D treatment plan was calculated with dose specification and homogeneity requirements according to the ICRU-50 report (i.e. the dose delivered to the PTV should be ≥95% and ≤ 107% of the dose prescribed to the ICRU-point). All patients were treated with radiotherapy using photons with or without electrons according to local guidelines. Any treatment planning technique was allowed. Bolus was used for superficial parts of the PTV. The prescribed dose to areas of macroscopic disease was 64.8 Gy and 50.4 Gy for the elective nodal regions (1.8Gy/fraction). Treatment was given initially with 3D-conformal therapy and IMRT was allowed after 2010. Radiotherapy was delivered in a planned overall treatment time of seven weeks without a planned treatment break. Treatment started with radiation on the primary tumor only (boost), for eight days. From day eight until end of treatment, the total target

volume was irradiated, which means that patients had two fractions on day eight, separated by at least 6, preferably 8 h. This treatment setup enabled that radiation on macroscopic disease and elective regions ended on the same day and made evaluation of both local and regional status possible 12 weeks after end of treatment.

Chemotherapy consisted of capecitabine twice daily with a prescribed dose of 825 mg/m^2 bid and was given concomitantly during days 1–14, 22–35 and 43–49 of treatment. In case of chemotherapy related acute grade 2 toxicity or higher, interruption or dose reduction of capecitabine was allowed according to local standard.

2.3. Response assessment and follow-up

Patients were evaluated at least four and eight weeks after treatment, in order to monitor acute toxicity and rule out disease progression. Response assessment took place at 12 weeks and 2 years after CRT. A radiation oncologist and gynecologic oncologist performed clinical and gynecological evaluation together. Imaging studies were optional during follow-up. Lesions suspicious for recurrence had to be biopsied. In case of residual disease in the vulva 12 weeks after treatment, a local resection with a clinical tumor free resection margin of ≥1 cm had to be performed. Data on disease recurrence, salvage surgery, need for stoma surgery and serious adverse events (SAE) were collected. Short-term or acute toxicity was defined as any treatment related morbidity within 90 days after initiation of CRT and was scored using CTCAE version 3 [24]. Late toxicity was defined as all morbidity that persisted or newly developed after ≥90 days after the initiation of CRT or discharge from the hospital and was reported according to the RTOG/EORTC guidelines [25,26]. Follow-up visits were three-monthly in the first two years and six-monthly until five years after treatment. The database was closed on June 01, 2020.

2.4. Study design and statistical methods

Primary endpoint was locoregional control defined as clinical complete response (cCR) in the vulvar area (local response) and clinically or pathologically proven absence of tumor in the groins (regional control) 12 weeks after completion of CRT and (if indicated) groin dissection/LN debulking in cN1,2 patients. Secondary endpoints were morbidity and treatment related toxicity, incidence of fecal and/or urinary incontinence and/or reconstructive surgery performed and locoregional recurrence rate at 24 months after CRT. A cCR in at least 50% of patients was considered sufficient to warrant further investigation because it would approach the local control rate of extensive surgery with 100% stoma formation. If fewer than 14 responses would be observed among the first 42 patients, the trial would be terminated. Otherwise, the trial would continue to accrue up to 68 patients. With α set at 0.05 and β at 0.2, the minimax design suggests 42 patients for the first stage. After inclusion of 56 patients, the trial management group decided to close the trial because of slow accrual and need for optimized modern treatment techniques.

For a comparison between groups with and without PD, we used Fisher's exact test for independent variables with 2 groups, chi-square test for independent variables with >2 groups and simple logistic regression for quantitative variables. Progression free survival (PFS) was defined as survival without local and/or regional and/or distant recurrence. Disease specific survival (DSS) was defined as the percentage of patients who have not died from vulvar cancer. Overall survival (OS) was defined as the time until date of death due to any cause. Survival was calculated from start of CRT until death. Patients still alive were censored at the last date of follow-up. Kaplan-Meier estimates were created for PFS, DSS and OS with and without stratification for cCR after 12 weeks and cN-stage. Univariable and multivariable regression analyses were performed for PFS, DSS and OS. Analyses were performed using SPSS version 25.0 (IBM Corp, IBM SPSS Statistics for Windows, Armonk, NY) and R version 3.6.3 ('rms', 'survminer' packages). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Patient and treatment characteristics

Fifty-six patients with SCC of the vulva and a median age of 64 years (range 25–88) were included from March 2007 until April 2017 by a total of 10 Dutch radiation oncology centers specialized in the treatment of gynecological cancers. Four patients were excluded from the analysis because they did not meet inclusion criteria ($n = 3$) or had treatment cessation after 12 radiation fractions, related to pre-existent comorbidity ($n = 1$), leaving 52 patients for the final analysis. Most patients had unifocal disease and midline tumors were more prevalent than lateralized lesions. Forty-eight patients had no prior treatments, while four patients had an extensive local recurrence after primary surgery. Additional information of baseline patient- and treatment-related

Table 1
Patient characteristics ($n = 52$).

Variable	
Age	
Median ± interquartile range	64 (56–73)
Range	25–88
Charlson comorbidity index	
0	32 (62)
1	9 (17)
2 or more	2 (4)
Unknown	9 (17)
Differentiation	
Well	11 (21)
Moderate	23 (44)
Poor	4 (8)
Unknown	14 (27)
Lateralization	
Lateral	11 (21)
Midline	41 (79)
Multifocality	
Unifocal	45 (87)
Multifocal	7 (13)
Distance to other structures	
< 10 mm distance to anus	28 (54)
< 10 mm distance to clitoris	18 (35)
< 10 mm distance to urethra	24 (46)
Tumor diameter (millimeter)	
Median	50
Range	15–150
cT-stage	
1	3 (6)
2	29 (56)
3	12 (23)
4[a]	4 (8)
Recurrence	4 (8)
cN-stage	
0	32 (62)
1	10 (19)
2	9 (17)
3	1 (2)
pN-stage	
0	15 (29)
1	7 (13)
2	6 (12)
3	1 (2)
Unknown	23 (44)
Full dose radiotherapy	
Yes	48 (92)
No	4 (8)
Full dose capecitabine	
Yes	36 (69)
No	16 (31)

Data are presented as numbers with percentages in parentheses.
[a] According to TNM 6th edition; in current TNM this would be classified as T3.

Table 2
Treatment related toxicity and serious adverse events (n = 52).

Acute toxicity	
Skin/mucosa ≥ grade 3	28 (54)
Pain ≥ grade 3	19 (37)
Gastro-intestinal ≥ grade 3	4 (8)
Bladder ≥ grade 3	5 (10)
Nausea ≥ grade 3	2 (4)
Total ≥ grade 3	38 (73)
Serious adverse events[a]	
Total	16 (31)
Admission for pain	7
Admission for diarrhea/dehydration	4
Admission for malaise	1
Admission for coronary spasm	1
Bowel perforation (grade 5)	1
Late grade 4 bone toxicity	2
Late toxicity	
Skin/mucosa ≥ grade 2	8 (15)
Skin/mucosa ≥ grade 3	5 (10)
Fibrosis ≥ grade 2	4 (8)
Fibrosis ≥ grade 3	2 (4)
GI incontinence ≥ grade 3	2 (4)
Stress fracture + osteoradionecrosis ≥ grade 3	2 (4)
Pain ≥ grade 3	1 (2)
Stenosis ≥ grade 3	1 (2)
Edema ≥ grade 3	0 (0)
GU incontinence ≥ grade 3	0 (0)
Total ≥ grade 3	11 (21)

Data are presented as numbers with percentages in parentheses.
[a] In case of admission the main reason for admission is mentioned.

characteristics can be found in Table 1. Before initiation of CRT, 9 patients underwent a nodal debulking and 4 patients had a sentinel node procedure. In 14 patients suspicious nodes were cytologically confirmed. Two patients underwent a bilateral IFL eight to twelve weeks after the end of the radiotherapy. The mean radiotherapy dose to the primary tumor was 64.1 Gy and 90% of patients received the planned dose of 64.8 Gy. The mean elective dose to the nodal regions was 49.0 Gy (range 27.0–52.2 Gy) and 2 patients received a sequential boost on remaining LN (61.2 and 64.8 Gy).

3.2. Treatment compliance and toxicity

Regarding compliance, 92% of patients ($n = 48$) received the intended radiotherapy dose and 69% patients ($n = 36$) received the full dose of chemotherapy. Reasons for receiving lower radiotherapy dose were: discontinuation during treatment ($n = 1$), severe skin toxicity ($n = 2$) and refusal of further treatment (n = 1). Sixteen patients (33%) did not receive full dose chemotherapy as planned, i.e. on every planned day ($n = 10$, mostly discontinuation after week 5), had a dose reduction (n = 2) or both ($n = 4$), all for reasons of toxicity. Notably, the incidence of cardiovascular comorbidity (including hypertension, myocardial infarction, pulmonary embolism and diabetes mellitus) was 75% in patients with a lower chemotherapy dose compared to 38% in the whole study population ($p < 0.001$). One patient died during treatment due to cardiac arrest, treatment relatedness was unlikely. Another patient died of sepsis after surgery for bowel perforation two months after CRT, this was considered as treatment related.

Reasons for discontinuation of therapy were: progression during treatment, request by patient or unacceptable toxicity, intercurrent illness with implications for safety or treatment delivery.

Table 2 gives an overview of treatment related toxicity and serious adverse events. The most common grade ≥ 3 acute toxicity was radiation dermatitis/vulvar mucositis (54%) and pain (37%). Lower grades of dermatitis/vulvar mucositis were seen in all patients. A total of 16 SAE's were documented with hospital admission predominantly for

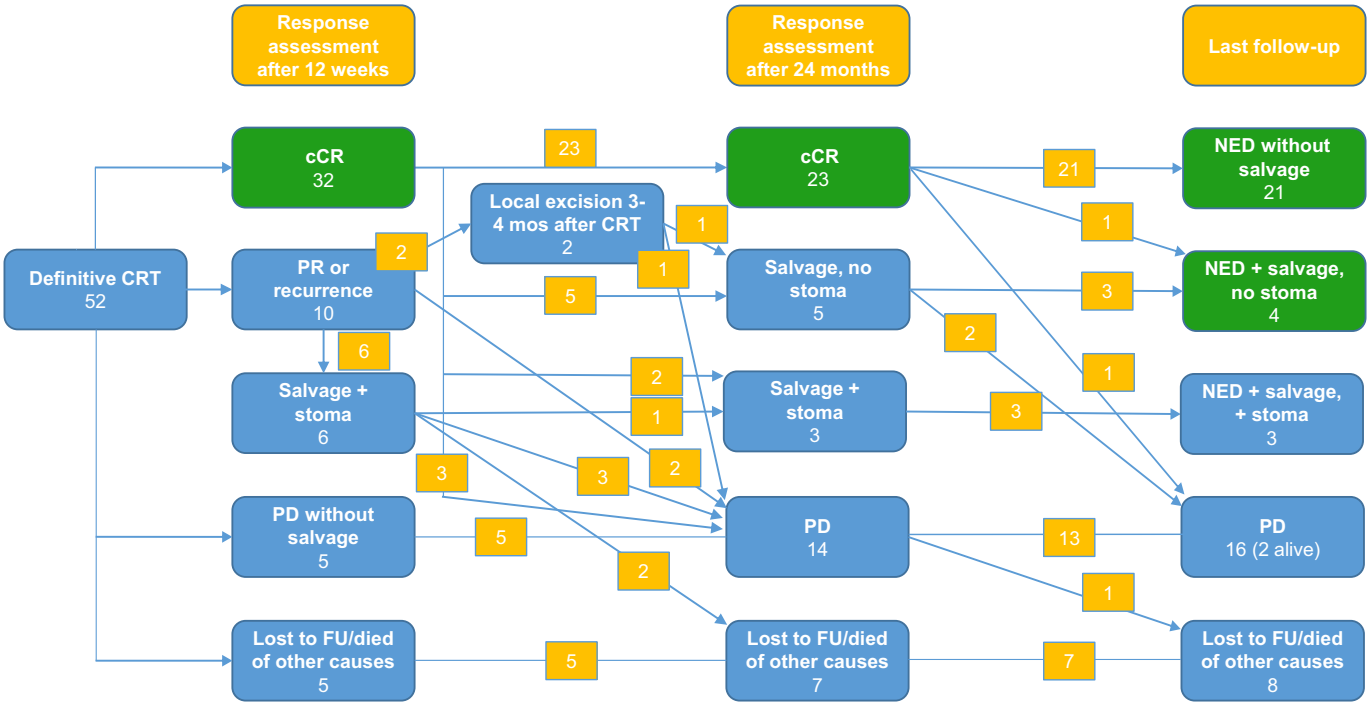

Fig. 1. Flowchart displaying the outcome for all patients at the response assessment after 12 weeks and 24 months and at last follow-up, in the blue boxes. All patients are counted only once on the 3 moments of outcome evaluation. The arrows show the treatment outcome route patients followed; numbers in orange boxes correspond with numbers of patients who move from a previous outcome status to a subsequent outcome status. CRT: chemoradiotherapy, cCR: complete response (persistent complete response for assessment after 24 months), PR: partial response, salvage: salvage surgery, PD: progressive disease, FU: follow-up, NED: no evidence of disease.

Table 3
Description of treatment related outcomes (n = 52).

Control rate after 12 weeks		
Local	cCR	32 (62)
	cPR	9 (17)
	PD/recurrence	8 (15)
	Lost to FU/died of other causes	3 (6)
Regional	Regional control	39 (75)
	cPR	3 (6)
	PD/recurrence	7 (14)
	Lost to FU/died of other causes	3 (6)
Control rate after 24 months		
Local	cCR	22 (42)
	PD	15 (29)
	Salvaged	8 (15)
	Lost to FU/died of other causes	6 (12)
Regional	Regional control	30 (58)
	PD	14 (27)
	Salvaged	1 (2)
	Lost to FU/died of other causes	6 (12)
Disease progression		
Total		26 (50)
Local		22 (42)
Regional		10 (19)
Distant		9 (17)
Surgical treatment		
Rate of surgical treatments		17 (33)
Wide local excision +3–4 months		2 (4)
Rate of salvage treatments		16 (31)
With stoma formation		9 (17)
Without stoma formation + > 4 months		6 (12)
Median time until salvage in months (range)[a]		6 (1–70)
Rate of 2nd or 3rd salvage treatments		5 (10)
Stoma surgery		9 (17)
Colostomy		5* (10)
Urostomy		5 (10)
Median time until stoma in months (range)[a]		3 (−2–17)
NED[b] at end of follow-up		30 (58)
Alive with NED		26 (50)
Colostomy-free survival		24 (46)
Progression free survival[c]		
1 year		58%
2 years		51%
5 years		45%
Disease specific mortality		
Locoregional		7
Distant		8
Disease specific survival		
1 year		83%
2 years		72%
5 years		68%
Overall survival		
1 year		76%
2 years		66%
5 years		52%

Data are presented as numbers with percentages in parentheses.
[a] Measured from end of CRT.
[b] 1 patient had colostomy 1 month prior to CRT.
[c] Progression was defined as local and/or regional and/or distant recurrence.

pain relief or diarrhea/dehydration. One patient died of sepsis after surgery for bowel perforation 2 months after treatment, which was classified as treatment-related. The most common late grade ≥ 3 toxicity was skin/mucosal toxicity with 2 patients experiencing grade 3 and 3 experiencing grade 4 toxicity. Two patients developed grade 4 late bone toxicity: one had osteomyelitis following salvage surgery, and the other patient had a sacral bone fracture and osteoradionecrosis 16 months after treatment. No evident cause could be found when evaluating these cases (no radiation dose irregularities).

3.3. Treatment response and salvage surgery

Treatment outcome is displayed in Fig. 1 and Table 3. Response assessment at 12 weeks after treatment showed a clinical complete response (cCR) for the primary tumor in 32 patients (62%) and regional control in 39 patients (75%), respectively (Table 3). After 2 years, 22 patients (42%) had persistent local cCR, additionally 8 patients had been successfully salvaged of whom one had a local and regional salvage. Regional control was 58% after 2 years. Overall, 17/52 (33%) patients had a surgical treatment because of residual or recurring local or regional disease without distant metastases, with a median time between CRT and surgery of 6 months (range 1–70). Regarding the surgical procedures: 2 comprised a wide local excision after 3–4 months according to protocol, 6 were salvage treatments without stoma formation after >4 months and 9 were salvage treatments with stoma formation (17%). There was no case of a regional salvage without local salvage. Of all 17 patients who had additional surgery at some point during follow-up, 9 patients had a cCR at 12 weeks after CRT, with a median time to recurrence of 7 months. The remainder had a partial response ($n = 6$) or local recurrence ($n = 2$) after 12 weeks. Five patients had more than one salvage surgery, because of new recurrences or incomplete resection. Of the 2 patients who had a wide local excision 12 weeks after CRT, 1 died of locoregional PD after 11 months and the other developed 2 subsequent locoregional recurrences that were successfully salvaged. In 8 patients, stoma surgery was necessary after all, with a total of 5 urostomy and 4 colostomy placements. All of these patients had a midline localization of the primary tumor and 5 had a primary tumor localization <10 mm adjacent to urethra and/or anus. One additional patient had a (disease related) colostomy before CRT started. Salvage surgery was successful in 9/16 patients with no evidence of disease at last follow-up (of whom 2 patients were lost to follow-up) and 7 patients died of PD. In a total of 25 patients (48%) long-lasting locoregional control was achieved without stoma formation.

S1 and S2 respectively display clinical and treatment characteristics of patients who died within 6 months after treatment and of all patients with PD after CRT treatment (locoregional and/or distant). No significant differences were seen between patients with or without PD concerning the variables age, lateral versus midline localization, uni- versus multifocality, distance towards anus, clitoris and urethra, differentiation grade, tumor size, cT- and cN-stage and full dose radiotherapy and chemotherapy. Tumor size, advanced nodal disease and recurrent disease at time of inclusion may have influenced the detrimental outcome, although differences were not significant (S3).Tumor size and receiving full dose radiotherapy were not significantly correlated with response after 12 weeks and 24 months.

3.4. Overall oncologic outcome

Fig. 1 displays a flowchart with oncologic outcome for all patients 12 weeks and 24 months after CRT and at last follow-up. At time of analysis, median follow-up was 35 months (1–131 months) for all patients and 49 months for the patients alive (range 3–131). Overall, at time of last follow-up 28 patients were alive without evidence of disease, 7 of them needed salvage surgery with stoma formation in 3 of them. Sixteen patients had PD with 2 of them being alive. Eight patients were either lost to follow-up of died of other courses. For detailed information regarding the different treatment related outcome measures, see Figs. 1, 2 and Fig. S2.

PFS was 58%, 51% and 45% after 1,2 and 5 years, DSS was 83%, 72% and 68% after 1,2 and 5 years and OS was 76%, 66% and 52% after 1,2 and 5 years (Fig. 3). PFS, DSS and OS were significantly better in patients with cCR 12 weeks after treatment, while nodal status (cN0 versus cN1/2) had no impact (S4 + S5). S6 shows univariable regression analyses for possible interactions between PFS, DSS, OS and various patient-, tumor- and treatment related factors. Multivariable Cox regression analysis was performed with variables lateral versus midline

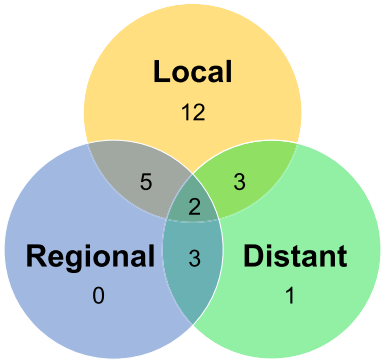

Fig. 2. Venn diagram showing the occurrence of local and/or regional and/or distant recurrences since CRT treatment.

localization, cT3–4 stage, cN-stage, recurrence at time of inclusion (instead of primary tumor), full RT dose and cCR after 12 weeks. PFS, DSS and OS were significantly correlated with cCR after 12 weeks, DSS and OS were significantly correlated with full radiotherapy dose. PFS was also significantly correlated with cT3–4 stage and both PFS and OS were significantly correlated with cN-stage.

4. Discussion

The results of this multi-center phase II study show that capecitabine-based CRT for patients with locally advanced vulvar cancer is feasible, resulting in 62% locoregional control 12 weeks after treatment, 42% persistent local control and 58% regional control 24 months after treatment. Surgical salvage treatment and stoma formation were necessary in 33% and 17% of patients and colostomy-free survival was 46%. We conclude that definitive CRT in patients with locally advanced vulvar cancer is a good alternative for patients otherwise in need of extensive surgery, with acceptable acute and late toxicity.

The development of new therapeutic strategies in vulvar cancer is challenging because the disease is rare and has a quite diverse initial presentation. Randomized data are lacking and we therefore have to rely predominantly on reports on small observational studies. This study did not compare capecitabine alone to weekly platinum alone. Therefore, the efficacy of capecitabine remains unknown in comparison to a platinum regimen. Two studies with 26 and 28 patients included, reported on definitive chemoradiation, using chemotherapy schedules of 5FU/MMC and weekly cisplatin and high dose radiation with 60 Gy and 65.4 Gy, respectively [27,28]. The outcome data showed a cCR in 72% and locoregional control of 75% at 4 years [27] compared to a cCR in 80.7% and a 1-year local control rate of 72.4% [28]. Differences in locoregional control seem to be in favor of these two studies. However, our study represents a large multi-center approach with a uniform treatment schedule and high dose 64.8Gy radiation. Two GOG studies, GOG101 and GOG205, reported on a neoadjuvant strategy in vulvar cancer with the aim of converting the unresectable primary vulvar tumor into a resectable one [8,29]. Comparing different studies of neoadjuvant treatment we can appreciate that an increase of pathologic CR related to the RT dose is observed; GOG101 pCR 31% (47.6Gy), G0G205 pCR 50% (57.6 Gy) and Beriwal pCR 48.5% (46.4 Gy with IMRT technique) [8,10,29]. It is tempting to conclude that the higher RT dose in the GOG 205 and the use of modern RT techniques could have attributed to this difference [9,10,29]. Although the percentage of pCR is encouraging, post-operative toxicity such as wound infections of 24.2% [10] is not negligible.

Our acute toxicity data showed skin/dermatitis as the major type of toxicity with grade ≥ 3 toxicity in 54%. Pain was the second most prevalent type of toxicity in 37% of patients, predominantly related to dermatitis complaints. Other studies also reported a high percentage of dermatitis, which is to be expected with CRT in this area. Gastrointestinal toxicity (≥ grade 3) was present in 8% of patients. Previous studies reported on acute GI grade 2 toxicity in about 30% (grade 3 was not reported, not mentioned or not observed) [27,30]. We reported grade 3 GI toxicity in 4 patients (8%). This difference can be related to the retrospective manner of the data collection of the other studies. Reported low-grade toxicity often is less reliable from retrospective series, while serious toxicity will be more reliable. Another difference can be the type of chemotherapy. In most studies chemotherapy is cisplatin-based [28,30], cisplatin-5FU-based [9,29] or 5FU-based chemotherapy [27]. Our study is the first to report on oral-5FU (capecitabine) based chemotherapy in combination with radiotherapy. Only 68% of patients completed capecitabine as planned. Several dose adaptions of capecitabine in combination with radiotherapy have been studied in small studies. In a review by Glynne-Jones it was concluded that continuous capecitabine (825 mg/m2 twice daily for 7 days a week) is the most effective regimen and has very similar tolerability to the less dose-intensive intermittent regimens of capecitabine given 5 days/week followed by 2 days of rest [31]. Perhaps for this elderly patient group the less dose-intensive intermittent regimen might be a better option, but more robust data on toxicity of the different regimens are warranted. Alternatively, one could opt for concurrent chemoradiotherapy with cisplatin, or carboplatin if treatment with cisplatin is not feasible [15,16], as is recommended in current guidelines [2,32].

Our study is one out of few that prospectively collected data on treatment related late toxicity with ≥ grade 3 seen in 11 out of 52 patients (21%). Skin/mucosa related grade ≥ 3 toxicity was most common (10%). Tans et al. report grade 3 radiation ulcers in 4 patients, skin

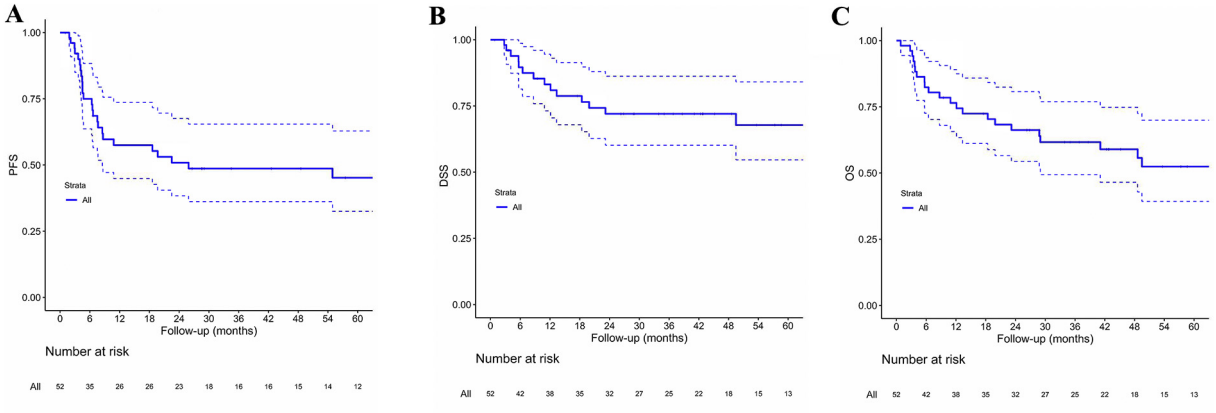

Fig. 3. Kaplan-Meier estimates showing progression free survival (A), disease specific survival (B) and overall survival (C) for the total group.

changes such as atrophy and fibrosis in 6 patients and a total percentage of long-term toxicity in 7 out of 28 patients (25%) [27]. Rishi et al. [28] reported on grade 3–4 late toxicity in 5 out of 26 patients, with high-grade soft tissue toxicity in 3 patients. All four studies show a prevalence of toxicity that could really have impact on the quality of life of this patient group after this treatment. So far, quality of life (QoL) data are limited for the extensive schedules of definitive CRT in this vulnerable patient group [33]. For next generation studies, QoL questionnaires or patient reported outcome should be implemented.

Unfortunately, data on HPV status were unavailable. The long duration of the current study can also be mentioned as a limitation. The study results were strengthened by presenting data on both acute and late toxicity, recurrence characteristics, stoma formation and survival in a large prospective series in patients with this rare disease.

In conclusion, we present prospective data on 52 patients with locally advanced vulvar cancer treated with high dose definitive chemoradiation with 64.8 Gy tumor dose combined with capecitabine 825 mg/m2 BID. Complete response 12 weeks after CRT was predictive for persistent control after 24 months. With a colostomy-free-survival of 46% this treatment approach is a good alternative for patients who are in need of extensive surgery. Shared-decision making should be used to discuss pros and cons related to an organ preserving approach versus extensive surgical procedures.

For next generation definitive chemoradiation protocols for patients with locally advanced vulvar cancer, emphasis should be put on integrating modern radiation (boost) techniques, delineation and treatment planning guidelines in order to derive optimal dose distributions aiming at increased effectivity with less toxicity. Biology-driven trial designs can be used to include e.g. HPV-status [34], patient reported outcomes on toxicity and quality of life should be incorporated and platinum-based CRT could be further explored.

Conflicts of interest statement

The authors have no conflicts of interest relevant to this work.

Author contribution section

Designing trial: BvT, JvdV, JdH, POW, LL, IJS.
Patient inclusion: BvT, JvdV, JdH, POW, JCB, EvdSB, HW, AS, CLC, RAN, LL, IJS.
Data collection and analyses: BvT, MR, JvdV, MR, MP, IJS.
Writing of manuscript: BvT, MR, JvdV, JdH, LL, IJS.

Acknowledgements

This study was supported by a grant from the Dutch Cancer Society (CKTO 2005-25).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.07.020.

References

[1] L.J. Rogers, M.A. Cuello, Cancer of the vulva, Int.J.Gynaecol.Obstet. 143 (Suppl. 2) (2018) 4–13, https://doi.org/10.1002/ijgo.12609.
[2] M.H.M. Oonk, F. Planchamp, P. Baldwin, M. Bidzinski, M. Brännström, F. Landoni, S. Mahner, U. Mahantshetty, M. Mirza, C. Petersen, D. Querleu, S. Regauer, L. Rob, R. Rouzier, E. Ulrikh, J. van der Velden, I. Vergote, L. Woelber, A.G.J. van der Zee, European society of gynaecological oncology guidelines for the management of patients with vulvar cancer, Int.J.Gynecol.Cancer 27 (2017) 832–837, https://doi.org/10.1097/IGC.0000000000000975.
[3] D.M. Forner, B. Lampe, Exenteration in the treatment of Stage III/IV vulvar cancer, Gynecol.Oncol. 124 (2012) 87–91, https://doi.org/10.1016/j.ygyno.2011.09.014.
[4] M. Janda, A. Obermair, D. Cella, A.J. Crandon, M. Trimmel, Vulvar cancer patients' quality of life: a qualitative assessment, Int.J.Gynecol.Cancer. 14 (2004) 875–881 (IJG14524 [pii].
[5] H. Bartelink, F. Roelofsen, F. Eschwege, P. Rougier, J.F. Bosset, D.G. Gonzalez, D. Peiffert, M. van Glabbeke, M. Pierart, Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups, J. Clin.Oncol. 15 (1997) 2040–2049, https://doi.org/10.1200/JCO.1997.15.5.2040.
[6] L.L. Gunderson, K.A. Winter, J.A. Ajani, J.E. Pedersen, J. Moughan, A.B. Benson 3rd, C.R. Thomas Jr., R.J. Mayer, M.G. Haddock, T.A. Rich, C.G. Willett, Long-term update of US GI intergroup RTOG 98–11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin, J.Clin.Oncol. 30 (2012) 4344–4351, https://doi.org/10.1200/JCO.2012.43.8085.
[7] N.B. Tomasoa, D. Meulendijks, J. Nijkamp, A. Cats, L. Dewit, Clinical outcome in patients treated with simultaneous integrated boost - intensity modulated radiation therapy (SIB-IMRT) with and without concurrent chemotherapy for squamous cell carcinoma of the anal canal, Acta Oncol. 55 (2016) 760–766, https://doi.org/10.3109/0284186X.2015.1124141.
[8] D.H. Moore, G.M. Thomas, G.S. Montana, A. Saxer, D.G. Gallup, G. Olt, Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group, Int.J.Radiat.Oncol.Biol.Phys. 42 (1998) 79–85 (S0360–3016(98)00193-X pii).
[9] G.S. Montana, G.M. Thomas, D.H. Moore, A. Saxer, C.E. Mangan, S.S. Lentz, H.E. Averette, Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: a gynecologic oncology group study, Int.J.Radiat.Oncol.Biol.Phys. 48 (2000) 1007–1013 (S0360–3016(00)00762–8 pii).
[10] S. Beriwal, G. Shukla, A. Shinde, D.E. Heron, J.L. Kelley, R.P. Edwards, P. Sukumvanich, S. Richards, A.B. Olawaiye, T.C. Krivak, Preoperative intensity modulated radiation therapy and chemotherapy for locally advanced vulvar carcinoma: analysis of pattern of relapse, Int.J.Radiat.Oncol.Biol.Phys. 85 (2013) 1269–1274 (S0360–3016(12)03770–4 pii).
[11] S.C. Han, D.H. Kim, S.A. Higgins, M.L. Carcangiu, B.M. Kacinski, Chemoradiation as primary or adjuvant treatment for locally advanced carcinoma of the vulva, Int.J.Radiat.Oncol.Biol.Phys. 47 (2000) 1235–1244 (S0360–3016(00)00569–1 pii).
[12] F. Landoni, A. Maneo, G. Zanetta, A. Colombo, S. Nava, F. Placa, G. Tancini, C. Mangioni, Concurrent preoperative chemotherapy with 5-fluorouracil and mitomycin C and radiotherapy (FUMIR) followed by limited surgery in locally advanced and recurrent vulvar carcinoma, Gynecol.Oncol. 61 (1996) 321–327 (S0090–8258(96)90150-X pii).
[13] G. Lupi, F. Raspagliesi, R. Zucali, R. Fontanelli, D. Paladini, R. Kenda, F. di Re, Combined preoperative chemoradiotherapy followed by radical surgery in locally advanced vulvar carcinoma. A pilot study, Cancer 77 (1996) 1472–1478 (10.1002/(SICI)1097-0142(19960415)77:8<1472::AID-CNCR8>3.0.CO;2-E pii).
[14] D.P. Ryan, C.C. Compton, R.J. Mayer, Carcinoma of the anal canal, N.Engl.J.Med. 342 (2000) 792–800, https://doi.org/10.1056/NEJM200003163421107.
[15] R.H. Mak, L.M. Halasz, C.K. Tanaka, M. Ancukiewicz, D.J. Schultz, A.H. Russell, A.N. Viswanathan, Outcomes after radiation therapy with concurrent weekly platinum-based chemotherapy or every-3-4-week 5-fluorouracil-containing regimens for squamous cell carcinoma of the vulva, Gynecol.Oncol. 120 (2011) 101–107, https://doi.org/10.1016/j.ygyno.2010.09.004.
[16] K. Katanyoo, S. Tangjitgamol, M. Chongthanakorn, T. Tantivatana, S. Manusirivithaya, K. Rongsriyam, A. Cholpaisal, Treatment outcomes of concurrent weekly carboplatin with radiation therapy in locally advanced cervical cancer patients, Gynecol.Oncol. 123 (2011) 571–576, https://doi.org/10.1016/j.ygyno.2011.09.001.
[17] T. Ishikawa, M. Utoh, N. Sawada, M. Nishida, Y. Fukase, F. Sekiguchi, H. Ishitsuka, Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts, Biochem.Pharmacol. 55 (1998) 1091–1097 (S0006–2952(97)00682–5 pii).
[18] M. Miwa, M. Ura, M. Nishida, N. Sawada, T. Ishikawa, K. Mori, N. Shimma, I. Umeda, H. Ishitsuka, Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue, Eur.J.Cancer. 34 (1998) 1274–1281 (S0959804998000586 [pii).
[19] E. Bajetta, C. Carnaghi, L. Somma, C.G. Stampino, A pilot safety study of capecitabine, a new oral fluoropyrimidine, in patients with advanced neoplastic disease, Tumori. 82 (1996) 450–452.
[20] B. Patel, J. Forman, J. Fontana, A. Frazier, E. Pontes, U. Vaishampayan, A single institution experience with concurrent capecitabine and radiation therapy in weak and/or elderly patients with urothelial cancer, Int.J.Radiat.Oncol.Biol.Phys. 62 (2005) 1332–1338 (S0360–3016(05)00092–1 pii).
[21] J.C. Kim, T.W. Kim, J.H. Kim, C.S. Yu, H.C. Kim, H.M. Chang, M.H. Ryu, J.H. Park, S.D. Ahn, S.W. Lee, S.S. Shin, J.S. Kim, E.K. Choi, Preoperative concurrent radiotherapy with capecitabine before total mesorectal excision in locally advanced rectal cancer, Int. J. Radiat. Oncol. Biol. Phys. 63 (2005) 346–353 (S0360–3016(05)00407–4 pii).
[22] S.Y. Ngan, M. Michael, J. Mackay, J. McKendrick, T. Leong, D. Lim Joon, J.R. Zalcberg, A phase I trial of preoperative radiotherapy and capecitabine for locally advanced, potentially resectable rectal cancer, Br.J.Cancer. 91 (2004) 1019–1024 (6602106 [pii).
[23] J. Dunst, T. Reese, T. Sutter, H. Zühlke, A. Hinke, K. Kölling-Schlebusch, S. Frings, Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer, J.Clin.Oncol. 20 (2002) 3983–3991, https://doi.org/10.1200/JCO.2002.02.049.
[24] A. Trotti, A.D. Colevas, A. Setser, V. Rusch, D. Jaques, V. Budach, C. Langer, B. Murphy, R. Cumberlin, C.N. Coleman, P. Rubin, CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment, Semin.Radiat.Oncol. 13 (2003) 176–181 (S1053–4296(03)00031–6 pii).

[25] J.D. Cox, J. Stetz, T.F. Pajak, Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC), Int.J.Radiat.Oncol.Biol.Phys. 31 (1995) 1341–1346 (0360–3016(95)00060-C pii).
[26] A. Trotti, R. Byhardt, J. Stetz, C. Gwede, B. Corn, K. Fu, L. Gunderson, B. McCormick, M. Morrisintegral, T. Rich, W. Shipley, W. Curran, Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy, Int. J. Radiat. Oncol. Biol. Phys. 47 (2000) 13–47 (S0360301699005593 [pii).
[27] L. Tans, A.C. Ansink, P.H. van Rooij, C. Kleijnen, J.W. Mens, The role of chemo-radiotherapy in the management of locally advanced carcinoma of the vulva: single institutional experience and review of literature, Am.J.Clin.Oncol. 34 (2011) 22–26, https://doi.org/10.1097/COC.0b013e3181cae6a1.
[28] A. Rishi, M. Rollins, K.A. Ahmed, D.C. Hunt, P. Sarkar, D.C. Fernandez, M.S. Hoffman, S.M. Apte, M.M.K. Shahzad, H.S. Chon, J.Y. Chern, R.M. Wenham, M.E. Montejo, High-dose intensity-modulated chemoradiotherapy in vulvar squamous cell carcinoma: Outcome and toxicity, Gynecol.Oncol. 156 (2020) 349–356 (S0090–8258(19)31678–6 pii).
[29] D.H. Moore, S. Ali, W.J. Koh, H. Michael, M.N. Barnes, C.K. McCourt, H.D. Homesley, J.L. Walker, A phase II trial of radiation therapy and weekly cisplatin chemotherapy for the treatment of locally-advanced squamous cell carcinoma of the vulva: a gynecologic oncology group study, Gynecol.Oncol. 124 (2012) 529–533, https://doi.org/10.1016/j.ygyno.2011.11.003.
[30] Y.J. Rao, A. Chundury, J.K. Schwarz, C. Hassanzadeh, T. DeWees, D. Mullen, M.A. Powell, D.G. Mutch, P.W. Grigsby, Intensity modulated radiation therapy for squamous cell carcinoma of the vulva: Treatment technique and outcomes, Adv.Radiat. Oncol. 2 (2017) 148–158, https://doi.org/10.1016/j.adro.2017.02.006.
[31] R. Glynne-Jones, J. Dunst, D. Sebag-Montefiore, The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: how successful have we been? Ann.Oncol. 17 (2006) 361–371 (S0923–7534(19)43521–7 pii).
[32] N.R. Abu-Rustum, NCCN Clinical Practice Guidelines in Oncology. Vulcar Cancer (Squamous Cell Carcinoma) Version 3.2021 - April 26, 2021, 2021.
[33] K.L. Mirabeau-Beale, A.N. Viswanathan, Quality of life (QOL) in women treated for gynecologic malignancies with radiation therapy: a literature review of patient-reported outcomes, Gynecol.Oncol. 134 (2014) 403–409 (S0090–8258(14)00963–9 pii).
[34] L.J. Lee, B. Howitt, P. Catalano, C. Tanaka, R. Murphy, N. Cimbak, R. DeMaria, P. Bu, C. Crum, N. Horowitz, U. Matulonis, A.N. Viswanathan, Prognostic importance of human papillomavirus (HPV) and p16 positivity in squamous cell carcinoma of the vulva treated with radiotherapy, Gynecol.Oncol. 142 (2016) 293–298 (S0090–8258(16)30743–0 pii).