Phase II study of definitive radiochemotherapy for locally advanced squamous cell cancer of the vulva: an efficacy study

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Protocol after CKTO review
May, 2006

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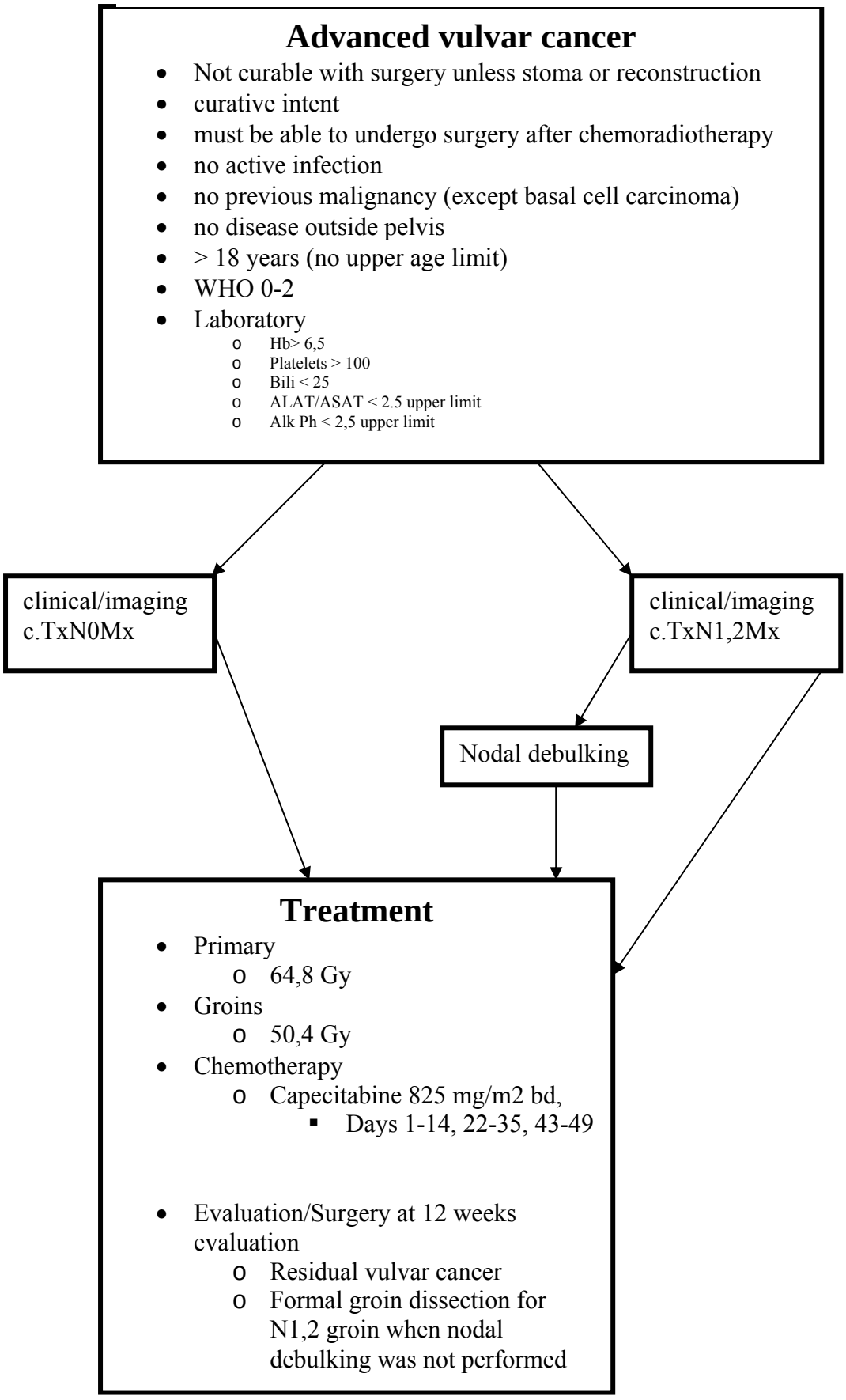


1. Background and introduction

1.1 General introduction

Cancer of the vulva is a relatively rare disease with an annual incidence of 2-3 per 100.000 women. The main histological subtype is squamous cell cancer (75%) followed by basal cell cancer (15%) and other types like adenocarcinoma, melanoma and sarcoma's in 10% of cases [1]. In the Netherlands each year 150-200 new patients are diagnosed with vulvar cancer [2]. A steep rise in age specific incidence rate is seen above 65 years with the majority of patients being 75 years or older. About 70% of patients with squamous cell cancer (SCC) of the vulva present with a local tumor confined to the vulva (cT1/T2). These patients are usually treated with a radical local excision and uni- or bilateral inguinal femoral lymph node dissection [3]. When lymph nodes are negative (70-80% of patients), survival is high with a 5 year disease specific survival of 80-90%. When the groin nodes are positive survival decreases from 30% in case extra capsular tumor is found, till 60% in case the lymph node metastases are intracapsular [4].
In 30% of the patients tumors are classified as T3/T4 tumors with either extension of the tumor to the vagina, the proximal urethra or anus (cT3) or extension to the upper urethra or bladder, upper anal canal or rectum or the tumor is fixed to the pubic bone (cT4). Those cases in which the typical radical surgical excision of the vulva will not remove the cancer with adequate margins are considered to be locally advanced or cT3/T4 vulva carcinoma. The primary tumor causes serious local problems such as pain while sitting, discharge, bleeding from necrotic tumor and a faul odor. Positive lymph nodes are found in 50%-60% of patients with T3/T4 tumors. Frequently these nodes are ulcerating and or fixed to the femoral vessels in the groin. These patients presenting with locally advanced disease (cT3/T4) pose a specific problem regarding the treatment.

1.2 Surgery for locally advanced vulvar cancer

In patients with T3 vulvar cancer, literature data show a 75% local control rate while a survival from 64% to 77% can be achieved after primary surgery (Addendum 1, Table 1). Survival decreases dramatically to 40% in the presence of nodal metastases in the groin [10]. In patients with locally advanced disease local control can only be accomplished by extensive surgical resections. Partial removal of the distal urethra and partial sfincter resections can be performed with preservation of continence, dependant on the extent of the resection [11]. However, when extensive anal and/or urethral involvement is present radical surgery or exenterations will definitely result in stoma formation. Other than the stoma formation also postoperative morbidity and mortality is a significant problem in these patients. Morbidity such as serious wound breakdown, infection, leg edema and lymphocysts is frequently observed after extensive surgery for advanced vulvar cancer [12].

1.3 Radio (chemo) therapy for locally advanced vulvar cancer

In anal cancer radiotherapy combined with chemotherapy is very efficacious as sphincter sparing therapy in preventing colostomies [13]. Radiotherapy with or without chemotherapy has also proven it's efficacy in the treatment of vulvar cancer [14]. Collated literature data show a somewhat lower local control rate of 40% after radiochemotherapy compared with surgery (addendum 1, Table 2). But the interpretation of the literature is very difficult because of the heterogeneity of inclusion criteria and differences in end-point or assessment of tumor response. It is clear that radiotherapy in moderate doses combined with chemotherapy, followed by organ sparing surgery has shown its' efficacy in preventing stoma formation [22]. Of 71 patients with locally advanced vulvar cancer (carcinoma of the vulva with unresectable

N2/N3 groin lymph nodes), treated with a combination of 4760 cGy radiotherapy (daily fractions 2 x 170 cGy and given as split course with an interval of 1½ to 2½ weeks) combined with concurrent chemotherapy (cisplatin and 5-FU) resulted in the prevention of either a uro- or colostomy in 49 of 50 patients, although postoperative wound complications were frequent. Others have also shown that the combination of induction radiochemotherapy followed by surgery in the previously irradiated area results in the prevention of stoma formation but can also result in significant wound healing problems and treatment related mortality [23]. Most of the studies as mentioned before used moderate doses of radiotherapy because of poor skin tolerability (inflammation, dry and moist desquamation, fibrosis) of the vulvar area. Some studies suggested a better local control when the gross tumor volume was irradiated with doses above 50 Gy [24]. Therefore, in order to increase local control, either additional surgery or higher radiation doses are warranted.

1.4 Treatment of the inguino femoral lymph nodes

One of the additional problems in patients with locally advanced vulvar cancer is the high incidence of concomitant advanced regional (inguinal) disease. In patients with T3/T4 vulvar cancer the incidence of metastases in the inguino femoral lymph nodes can be as high as 60%. A substantial number of these patients have clinically palpable "bulky" nodes (cN1/2). From various studies it becomes clear that the presence of inguino femoral metastases, especially cN1/2 nodes is the most important significant predictor for survival.
On the basis of the available literature data most authors conclude that radiotherapy is a proper treatment for microscopical (residual) disease in the groin, but not for gross disease [25]. The only study addressing the problem of the efficacy of radiotherapy for the groin in case cN1/2 nodes are present showed that out of 46 patients with vulvar cancer and (inoperable) N2/3 inguinal disease, 37 patients could have surgery after chemoradiation. Finally 15 out of 37 patients operated upon had a pathological complete response [26]. There are no data on definitive treatment with radiochemotherapy for cN1/2 groin nodes.

1.5 Rationale for chemotherapy regimen

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 Mitomycine 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 [27, 28, 29 and 30]. And especially in an older patient population the nephrotoxicity of cisplatin might be of concern. Mitomycin C is not introduced in the newer chemoradiation studies in rectal, cervical or head- and neck cancer, because of its toxicity profile. Especially the extended thrombocytopenia makes repeated administration impossible.
Oral fluoropyramidines, 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 tumour cells [31, 32 and 33]. Capecitabine is rapidly and extensively absorbed as an intact molecule and is metabolized to 5-FU in three steps. Because each step of metabolic conversion occurs successively, and a greater specificity for tumour cells is present, capecitabine potentially reduces systemic exposure to 5-FU while maximizing the dose-intensity of 5-FU within tumour tissue.
Several clinical trials in breast and colorectal cancer have demonstrated a more favourable toxicity profile with capecitabine than the infused fluoropyrimidines although the incidence of the hand-foot syndrome is slightly higher [34, 35 and 36]**.**
The combination of capecitabine with radiotherapy has been studies in several phase I studies. A dosage of 825 – 1000 mg/sqm bid administered without a break during a convential

radiotherapy period of 6 weeks has been shown a feasible and well-tolerated regimen [37, 38, 39 and 40].
Because of the intensive radiotherapy regimen in this relatively older patient population monotherapy with capecitabine with a treatment interruption has been selected for the combined modality approach in this study.

1.6 Rationale of the study

Exenterative surgery for locally advanced vulvar cancer results in a reasonable local control but only at the prize of considerable morbidity including stoma formation. There is very limited experience with radiochemotherapy followed by surgery for locally advanced vulvar cancer. The studies available show a decreased need for stoma formation but still accompanied with considerable morbidity, e.g. especially wound healing problems. More sophisticated radiotherapy targeting and promising chemotherapy schemas have been developed in the past years. However, so far the combination has not been studied substantially in locally advanced vulvar cancer patients. This study will deliver experience with modern radiochemotherapy options and aims at a reasonable local control precluding the need for local salvage surgery.

2. Objectives of the study

2.1 primary objective

The primary objective is to gain experience with primary radiochemotherapy and to determine the locoregional response rate at 12 weeks after radiochemotherapy and after groin dissection for cN1,2 patients.

2.2 secondary objectives

The secondary objective would be to determine short-term morbidity defined as desquamation of the skin, infection, long-term morbidity defined as edema, fibrosis, the incidence of fecal and or urinary continence, and or incidence of reconstructive surgery performed and treatment related mortality. Longterm morbidity and the rate of locoregional recurrences will be evaluated at 24 months after the end of radiochemotherapy.

2.3 endpoints

Primary endpoints

- locoregional control rate defined as clinically or pathologically proven absence of tumor (CR according to RECIST criteria) in the vulvar area, groins and/or pelvis 12 weeks after the end of radiochemotherapy and after groin dissection in cN1,2 patients.

Secondary endpoints

- morbidity and treatment related toxicity
- incidence of fecal and/or urinary continence and/or reconstructive surgery performed
- locoregional recurrence rate at 24 months after the end of radiochemotherapy

3. Patient selection criteria

3.1 Eligibility criteria:

- squamous cell cancer of the vulva with locally advanced disease not curable with surgery unless extensive reconstructive surgery or a colostomy or urostomy is performed
- Amenable to curative treatment
- No disease present outside the pelvis
- Performance status WHO 0-2
- Patients must be fit enough to undergo salvage surgery after chemo radiotherapy
- Measurable disease at least locally (vulvar area)
- Pretreatment laboratory values
  - Hb> 6.5 mmol/l
  - Neutrophil count> 1.5 x 10^9/l
  - Platelets ≥ 100 x 10^9/l
  - Bilirubin < 25µmol/l
  - Adequate liver function: ALAT and ASAT < 2.5 upper normal limit
  - Alkaline phosphatase < 2.5 upper normal limit
- No upper age limit specified. Patients should mentally, physically and geographically be able to undergo treatment and follow-up
- Patients must be > 18 years old
- Written informed consent
- No psychosis, CNS disease or other expected difficulty for follow-up
- No active uncontrolled infection
- No concomitant or previous malignancy other than basal cell carcinoma of the skin or CIN of the cervix

4. Trial design

The trial is a non-randomized multi-centre phase II study. The primary endpoint is the locoregional control rate defined as clinically or pathologically proven absence of tumor in the vulvar and groin area 12 weeks after the last dosis of radiochemotherapy and after groin dissection in cN1,2 patients. The optimal two-stage design [59] is proposed in order to minimize the sample size if the treatment has low activity defined as poor locoregional control.

5. Treatment schedule, expected toxicities, dose modifications

The general treatment principle is that definitive radiochemotherapy is the main treatment for the locally advanced vulvar disease. Surgery for the primary vulvar tumor will only be performed in case of:

1. progressive disease
2. the presence of histologically proven residual disease 12 weeks after the last course of radiochemotherapy treatment.

Patients will only undergo a groin lymph node dissection when the nodes are pathologically positive, bulky on clinical examination or bulky on imaging studies.

5.1 Radiotherapy

External beam radiotherapy (EBRT) target definition (GTV, CTV, PTV) and organ at risk definition according to ICRU-62.

Gross tumor volume (GTV)

The GTV includes:
- GTV_{PT} = primary tumor (based on clinical examination and/or CT/MR).
- GTV_{LN} = cytologically / histologically confirmed pathologic lymph nodes.

Clinical target volume (CTV)

The clinical target volume (CTV) should include:
- $CTV_{PT} = GTV_{PT}$ with a minimal safety margin of 1 cm
- $CTV_{LN} = GTV_{LN}$ with a minimal safety margin of 1 cm
- CTV_{LD} = the lymphatic drainage including the (1) mons veneris, (2) inguinal nodes, (3) femoral nodes and (4) the external and internal iliac nodes (5) fossa obturatoria.

The CTV_{LD} will be defined on a planning CTscan as
- The corresponding vascular structures (femoral-, inguinal- and iliac vessels) with a margin of 0.5 cm.
- any visible lymph node in this area with a margin of 0.5 cm

Of notice: the inguinal area should extend from the syphilis pubis (medial) to the crista iliaca anterior superior (lateral).

Planning target volume (PTV)

$PTV_{PT} = CTV_{PT}$ with a minimal safety margin of 1 cm
$PTV_{LD} = CTV_{LN} + CTV_{LD}$ with a minimal safety margin of 1 cm

Organs at risk (OAR)

The OAR are the bladder, the rectum, femoral head, vulvar skin. The outer contour of the OAR will be delineated on a planning CT scan for DVH calculations.

EBRT treatment planning

A planning CT scan is acquired in supine treatment position with full bladder instruction. Adjacent 5 mm-thick transverse images are collected and transferred to a 3D treatment-planning system.

Following delineation of the GTV, CTV, PTV and OAR, a 3D treatment plan will be 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 are to be treated with megavoltage radiation using photons with or without electrons according to local guidelines.

Any treatment technique satisfying dosimetric requirements for the PTV and the OAR is allowed. The use of bolus is usually needed for superficial parts of the PTV (primary tumor and pathologic groin lymph nodes).

A dose volume histogram should be calculated for the OAR. Volumetric and dosimetric parameters to be correlated with clinical toxicity (CTCAE v.3.0) are:
Target dose:

- The dose delivered to 100%, 95% and 90% of the PTV_{PT} + PTV_{LD} (D100, D95, D90)
- The volume of the PTV_{PT} + PTV_{LD} receiving ≥100%, ≥95% and ≥90% of the prescribed dose (V100, V95, V90).

OAR:

- The mean dose to the bladder and rectum.
- The dose to 0.1cc, 1cc, 2cc and 5cc of the bladder and rectal wall.
- The maximum dose to the vulvar skin.
- The mean, minimum and maximum dose to the femoral head.

Dose and fractionation EBRT

General treatment guidelines:

- EBRT will be delivered in a planned overall treatment time of 7 weeks **without a planned treatment break.**
- All PTV's will be treated with fraction doses of 1.8 Gy.
- Treatment will start on Monday with radiation of the PTV_{PT} only.
- Treatment of the $PTV_{LN\ \&\ LD}$ will start on Wednesday during the second week of treatment.

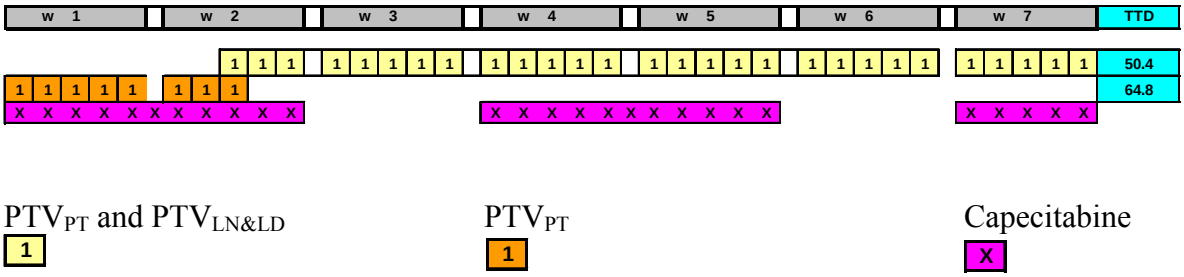
This treatment setup is chosen in order the finish treatment on the same day as PTV_{PT} to facilitate a good evaluation of the result after 12 weeks in order to avoid variable evaluation time points and subsequent planning for surgery. This is particularly so for patients with cN1/2 groins. In addition, this schedule is also chosen for cN0 groins in order to have similar treatment schedules for the macroscopic tumor with respect to the chemoradiation schedule.

- At day 8 of treatment patients will receive 2 fractions on 1 day (i.e. PTV_{PT} only and PTV_{PT} together with $PTV_{LN\ \&\ LD}$), separated by at least 6 hrs, preferably 8 hrs.
- Capecitabine will be given concomitantly during week 1& 2, week 4 & 5 of treatment and week 7 of treatment.

Dose guidelines

- The PTV_{PT} will receive a TTD 64.8 Gy.
- The $PTV_{LN\ \&\ LD}$ will receive a TTD 50.4 Gy.

Treatment Schedule



Normal tissue sparing
Customized blocks can be designed to spare the small bowel, the rectum and the caput femoris.

Verification of external beam radiation treatment
The positioning of the IRP should be verified and adjusted if necessary according to local verification protocols, using local imaging techniques (i.e. megavoltage films or electronic portal imaging) according to the following rules:

1. at at least 3 consecutive days during the first week of treatment.
2. at least weekly thereafter.

5.2 Chemotherapy
Capecitabine will be given orally twice daily at 825 mg/sqm day 1- 14, 22- 35 and 43-49. of radiotherapy (equivalent to a total dose of 1650 mg/sqm/day). Capecitabine should be taken at approximately 12-hours intervals with water within 30 minutes of a meal.

5.2.1 Dose modifications
If a patient experience a grade 2 or 3 toxicity that is considered possibly related to capecitabine treatment or clearly not related solely to radiation, capecitabine treatment will be interrupted. When the toxicity has resolved to grade 0 to 1, treatment will be restarted without dose adjustment. However, in the case of grade 3 nausea/vomiting or diarrhea not resolving to grade 0 to 1 within 2 days of interruption despite symptomatic treatment, capecitabine treatment will be restarted with a 25 % dose reduction. On the recurrence of toxicity at grade 2 or more severe intensity, treatment will be again interrupted until the toxicity has resolved to grade 0 to 1. Treatment will then be restarted with a dose reduction of 25%.
All dose modifications and symptomatic treatments should be documented.

5.3 Surgery

5.3.1. treatment for the primary
Whenever 12 weeks after radiotherapy clinical tumor residue is present on the vulva, a local resection of that area with a clinical tumorfree resection margin of at least 1 cm must be performed. It is to be preferred, depending on the size of the defect to close this with a well vascularized flap.

5.3.2 treatment for the regional lymph nodes
Patients with cN0 groin lymph nodes and no enlarged/suspicious lymph nodes on imaging (ultrasound/CT/MRI) will be treated with radiochemotherapy only. Patients with cN1/2 groin lymph nodes are treated with either a nodal debulking upfront or a bilateral inguino-femoral lymph node dissection 8-12 weeks after the radiotherapy. It is recommended, in case of residual vulvar disease, to combine local and regional surgical treatment.

5.4 Toxicity

5.4.1 Radiotherapy:

Short term side effects are skin desquamation in the majority of patients and ddiarrhoea, nausea and spasmic abdominal pain. Late effects are a mild form of lymph edema, skin fibrosis and a higher risk on femoral neck fractures.

5.4.2 Chemotherapy:

Most side effects are on the short term and constitute of vomiting, bone marrow depression, diarrhea, mild alopecia, and hand-foot syndrome.

5.5 Treatment duration

Treatment duration is until all radiotherapy has been administered. In case for some reason (eg progression under radiotherapy) it is decided to discontinue protocol treatment, this should be clearly explained and specified on the treatment forms stating the reason and the treatment applied. Patients will be evaluated according to the intention to treat analysis.
Patients may also discontinue protocol therapy in the following instances:
1. Intercurrent illness which would, in the judgment of the investigator, affect patient safety, the ability to deliver treatment or the primary study endpoints
2. Request by patient.
3. Unacceptable toxicity.
4. At time of progression of disease outside the loco regional area.
5. Patients will have follow-up at least up to two years after study entry, and every six months thereafter, preferably until death. (see 6.5)

5.6 Concomitant therapy

Other anti-cancer treatment or investigational therapy while patient is enrolled in the protocol treatment is prohibited. A different radiotherapeutic regimen other than specified by the protocol is prohibited. Medication for other disease is allowed, but generic name and dose have to be stated on the on-study form, or on the treatment forms.
Medication for pain-relief, anti-emetic medication or other supportive medication is permitted.

6 Clinical evaluation, laboratory tests, follow-up

Patients can be registered for this study if they have pathologically proven squamous cell cancer of the vulva amenable for curative treatment but not curable with surgery unless extensive reconstructive surgery or a colostomy or urostomy is performed. Protocol treatment should start within 4 weeks of registration.

6.1 Before treatment start

The following examinations should be performed within 4 weeks prior to treatment:

- Medical history
- Physical and gynecological examination
- WHO performance status
- TNM stage

- A photograph of the tumor with an adjacent ruler must be taken.
- Pathology of the primary tumor.
- The primary tumor must be localized exactly, measured in two dimensions and the margins towards the vagina, urethra, anus and clitoris must be stated in mm.
- The clinical description of the groin nodes must include: number of palpable nodes, side of nodes, size, mobility and whether or not a lymphangitis is present.
- CT, MRI or US scan of the groin region (If CT/MRI/US scan shows a suspicious lymph node or in case of clinical suspicion, FNA should be performed).
- Chest X-ray
- Routine blood tests (leukocytes, platelets, Hb, HT)
- Serum creatinine, ASAT, ALAT, bilirubin and alkaline phosphatase
- Socio-demographic data

6.2 During radiochemotherapy

- Laboratory examination weekly: haematology: Hb, Ht, platelets, leucocytes; cchemistry: Na, K, Ca, Alb, Creatinine, Bilirubin, gGT, AF, ASAT, ALAT, LDH. Creatinin clearance if plasma creatinine > 100 umol/l.
- Morbidity according to CTCAE criteria version 3 (addendum 2, page 23)
    - signs of early toxicity (eg skin)
    - monitoring of other radiotherapy-related toxicity (bowel, GU)

During radiotherapy patients will be seen weekly by the radiation oncologist and medical oncologist to monitor morbidity and treatment related toxicity

6.3 During first follow-up after radiotherapy at 4 and 8 weeks and response assessment at 12 weeks.

The patient will be seen 4 and 8 weeks after the end of the radiochemotherapy by the radiation oncologist and gynaecologist and physical and gynaecological examination will be performed. At that time short term morbidity must be assessed and progression of disease must be ruled out. At 12 weeks after the end of the radiochemotherapy response assessment will be done by the radiation oncologist and gynaecologist. Special attention is to be given to the vulva and groin area by visual examination and palpation in search of residual disease. Lesions suspicious for recurrence are to be biopsied. Response will be reported according to RECIST criteria (addendum 2, page 23).

6.4 After surgery

After the surgical procedure the following parameters will be recorded:

- Surgery associated morbidity
- Formation of urostomy/colostomy or reconstructive surgery
- Need for antibiotics
- Lymphedema of the legs or other morbidity involving the legs (eg infection)
- Duration of surgery
- Long-term morbidity: this is defined as morbidity as from the day the patient left the hospital. This will be monitored from the first-follow-up visit
- Length of hospitalization

6.5 During follow-up

In the first two years after treatment patients will be closely monitored. Follow-up visits will take place every three months (by the radiation oncologist and/or gynaecologist) as is normal standard of care and the following examinations will take place:

- Physical and gynaecological examination. Special attention is to be given to the vulva and groin area by visual examination and palpation in search of recurrent disease. Lesions suspicious for recurrence are to be biopsied.
- Long-term morbidity: this is defined as morbidity as from the day the patient left the hospital. This will be monitored from the first-follow-up visit

From two to five years after registration patients will be seen every 6 months and apart from the medical history (with explicit inquiries about experienced morbidity) the above mentioned examinations are required. No routine laboratory investigations are performed.

6.6 Summary Table

Required investigations	**Prestudy**	**After initial surgery***	**During radiochemotherapy**	**After radiochemotherapy**	**After secondary surgery****	**During follow up** **yr. 1-2: 3-monthly** **yr 2-5: 6-monthly**
Day	**-28 tot 0**	**-28 tot 0**	**Start day 0** **weekly**	**4, 8 and 12 weeks after last radiochemotherapy**	**> 12 weeks after last radiochemotherapy**	
History	**X 1**					
Phys/gyn exam	**X 1/ 2**			**X 1/2**		**X 1/2**
WHO	**X 1**		**X 2/ 3**	**X 2**		
TNM	**X 1**					
Photo	**X 1**			**X 2**		
Chest X-ray	**X 1**					
CT/MRI/US	**X 1**			**X 1/2 *** **		
Haematology	**X 1**		**X 2/ 3**	**X 1**		
Biochemistry	**X 1**		**X 2/ 3**	**X 1**		
Path lymph nodes		**X 1**			**X 1**	
Path primary tumor	**X 1**				**X 1**	
Short-term morb		**X 1**	**X 2/ 3**	**X 2**	**X 1**	
Long term morb						**X 1/2**

* Only when upfront surgery is performed for clinically (and pathologically confirmed) positive groin lymph node metastases
** Only when salvage surgery for the primary or groin dissection is performed
*** Optional

1) gynecologic oncologist
2) radiation oncologist
3) medical oncologist

[1] Haematology: Hb, Ht, platelets, leucocytes
Chemistry: Na, K, Creatinin, ureum, Bilirubin, gGT, AF, ASAT, ALAT, LDH.
Creatinin clearance if plasma creatinin > 100 umol/l.

7 Criteria of evaluation

Evaluable for response: all eligible patients will be included in the response rate calculation.

7.1 Assessment of locoregional tumor response

Twelve weeks after the full course of radiochemotherapy the patient will be assessed by the radiation oncologist and gynecologic oncologist. A photograph of the tumor with an adjacent ruler must be taken. The residual primary tumor will be measured in two directions and the longest diameter is assessed according to the RECIST criteria (see addendum 2). In case a clinical complete response is confirmed the groins will be treated as described in section 5.3 whenever no upfront debulking was performed. A complete response of the groin lymph nodes is defined as no residual disease in the groins after radiochemotherapy and surgery. No further surgery for the vulvar area is considered. Only when there is doubt about the clinical complete response or no agreement between gynecologist and radiation oncologist can be achieved, a mapping procedure must be performed to confirm the complete response also pathologically. In all other cases salvage surgery must be considered and if necessary reconstructive surgery or exenterative surgery with stoma formation must be considered.

7.2 Short-term morbidity

This is defined as any treatment related morbidity until the end of radiotherapy or discharge from the hospital. Any toxicity/morbidity should be reported according to the CTC guidelines version 3 (addendum 2). Most common complications are: skin toxicity, infections, gastrointestinal toxicity, and urinary toxicity. Surgical morbidity can consist of excessive blood loss during surgery (>500ml), damage/laceration to femoral vein, artery or nerve or wound breakdown after surgery and/or severe infections (sepsis).

7.3 Long-term morbidity

Long-term morbidity is defined as all morbidity which has developed after the end of the radiochemotherapy or discharge from hospital. The most common long-term morbidity in this disease after treatment is lymphedema of the legs, pain, infection (cellulitis, erysipelas), need for antibiotics for leg/groin infection, radiation enteritis. All long-term morbidity should be reported according to the RTOG/EORTC guidelines (addendum 3).

7.4 Assessment of locoregional recurrence 24 months after registration

Two years after the full course of radiochemotherapy the patient will be assessed by the radiation oncologist and gynecologic oncologist. A photograph of the local situation at the vulva area with an adjacent ruler must be taken. Measurements should be done according to RECIST criteria (Addendum 2). Whether or not reconstructive surgery or exenterative surgery with stoma formation has been performed should be mentioned. Morbidity should be described such as lymphedema, fibrosis, and continence (both urinary and fecal).

7.5 Overall survival

Overall survival is the time from registration of the patient in the trial until date of death due to any cause. Patients still alive at time of analysis will be censored at the date she was last known to be alive. Date of death should be reported on the follow-up forms.
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8. Statistical considerations

Statistical and Analytical Plan
This is a phase II study to investigate the efficacy of definitive radiochemotherapy in patients with locally advanced vulva carcinoma. In order to minimize the expected number of patients treated in the event that the regimen proves to be very disappointing, a two-stage design will be used for patient accrual [41].
Primary endpoint of this study is percentage of patients obtaining an objective complete (locoregional) remission according to RECIST criteria [42] at 12 weeks after the end of the radiochemotherapy.

Although the radiochemotherapy combination will result in fewer stoma formations it will not be of much interest if the complete response rate is less than 35%. In that case 65% or more patients need salvage surgery with an unacceptable increase in morbidity. However, a response rate of 50% or more will be considered interesting enough to warrant further research because it approaches the local control rate of extensive surgery except for the price of 100% stoma formation. With α set at 0.05 and β at 0.2 the minimax design suggests 42 patients for the first stage. If less than 14 responses are observed among the first 42 patients then the trial will be terminated. Otherwise the trial will continue to accrue up to 68 patients. A total of at least 30 responses would then be required in order to claim activity under these predefined constraints.

It is expected that the participating institutes will be able to accrue approximately 20-30 patients per year. Therefore, the estimated total accrual time will be about three years.

Statistical analysis
All patients that started the primary radiochemotherapy will be considered in the analysis of locoregional response and toxicity. Subjects will be designated as responders and non-responders at week 12 after the end of radiochemotherapy.

Safety Monitoring
Adverse events will be monitored on an ongoing basis and their frequencies reported semi-annually. Toxic effects will be categorized using the NCI Common Terminology Criteria for Adverse Events, Version 3.0. The worst event for each patient will be described. Both events related and unrelated to treatment will be captured.
Clinical and laboratory data will be tabulated and compared to normal ranges for the institution.

9 Investigator authorization procedures

Investigators will be authorized to register patients in this trial only when they have returned to their Data Centre (study-coordinator):

- The updated signed and dated Curriculum Vitae of the Principle Investigator
- The (updated) list of the normal ranges, in their own institution, of all laboratory data required by the protocol.
- A commitment statement / study acknowledgment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial,
- A signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared on the commitment form.
- A copy of the favourable opinion of their local ethics committee mentioning the documents that have been reviewed (incl. version number and date of documents) and indicating the list of the ethics committee members.
- A copy of the adapted (according to all national requirements), Patient Information / Informed Consent sheet, clearly mentioning the version number and the date.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level or delegations.

10 Patient registration procedures

Patient's registration will only be accepted from authorized investigators (see chapter 9). Before registration a registration checklist should be filled in and eligibility needs to be checked.

Questions on the registration checklist:

Standard questions: Name (number) of institution, patients' initials (max 3), patients' sequential study number

Protocol specific questions: all eligibility criteria, confirmation of informed consent, date of informed consent.

A patient can be registered after verification of eligibility (form 3 eligibility form) by fax: 31-20-3462525 or telephone +31-20-3462544, before the start of treatment.

At the end of the registration procedure, a number will be allocated to the patient (patient sequential study number) send by the study secretariat by fax or email. This number has to be recorded on form 3 (eligibility form), along with the date of the registration. The study identification number attributed to the patient at the end of the registration procedure identifies the patient and must be reported on all case forms.

11 Forms and procedures for collecting data

11.1 Data collection

The data for this project will be collected on separate case report forms (CRF's) which will be developed in collaboration between IKA Data Centre and study coordinators for this study. Before treatment starts the following case report forms need to be received by the study-coordinator:

- registration checklist

11.2 Case report forms and schedule for completion

Patient data will be collected in standard case report forms with NCR (non carbon required) paper. Identification will be by patient sequential study number and patients' initials. Patient data are only available to the principal investigators at each participating institution. CRFs must be completed and signed by the investigator as soon as the requested information is available, according to the schedule (see below). It is the responsibility of the investigator to check that all original CRFs have been sent to the Study secretariat and that they are completely and correctly filled out. The original CRF papers must be send to the study secretary, the copies of the NCR papers remain in the study centre.
Data, as collected in the CRF will be sent to the study-secretary:

Trialbureau IKA
Integraal Kankercentrum Amsterdam (IKA)
Plesmanlaan 125
1066 CX Amsterdam, the Netherlands.
Fax: 00-31-20-3462525
Tel: 00-31-20-3462555

CRFs must be completed according to the "instruction form" included in the CRF

11.3 Data flow

The case report forms must be completed, dated and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available. In all cases, it remains the responsibility of the investigator to check that original case report forms are sent to the adequate Data Centre and that they are completely and correctly filled out.
The original copy must be immediately returned to the investigator's group Data Centre and the investigator must keep a copy.
Queries will be sent for missing forms or inconsistent data.
If an investigator wants to change data on a CRF, he/she will send a corrected CRF with signature and an accompanying letter (also signed).

12 Reporting adverse events

12.1 Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following treatment regardless of the dose or causal relationship. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment. *(ICH-GCP).*
A **Serious Adverse Event (SAE)** is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. Adverse events and adverse drug reactions which are considered as **serious** are those which result in:
♦ Death

♦ A life threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
♦ Hospitalization or prolongation of hospitalization
♦ Persistent or significant disability/incapacity
♦ A congenital anomaly/birth defect
♦ Any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above)
(ICH-GCP).

12.2 Reporting procedure

♦ All Serious Adverse Events (SAE) occurring during the treatment period and within 30 days after the end of the last protocol treatment must be reported.
♦ All Serious Adverse Events related to the protocol treatment, and occurring after this 30-day period must also be reported.
♦ All Serious Adverse Events must be reported by fax on a Serious Adverse Event Form **within 24 hours** of the initial observation (fax: 00-31-20-3462525)
♦ A completed SAE-form must be sent back within 10 calendar days of the initial observation of the Serious Adverse Event.
ALL Forms must be dated and signed by the responsible investigator or one of his/her authorized staff members

13 Quality assurances

13.1 Audits (for multi-centre studies only when data are sent to Data Centre or similar)

To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the study coordinators may conduct site visits to institutions participating to protocols.
The local investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by the study coordinators as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorized individuals.

14 Ethical considerations

14.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice
(Ref: http://www.ifpma.org/pdfifpma/e6.pdf). The protocol will be approved by the Local, Regional or National Ethics Committees.

14.2 Subject identification

All CRF's will be identified by the identification number of the patient, the birthdate of the patient and the institution number of the patient. Any written information with the name of the patient should be removed and all forms should be economized.

14.3 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.
The competent ethics committee for each institution must validate local informed consent documents before the centre can join the study. It is the responsibility of the Local Ethical Committee to guarantee that the informed consent is conforming to the ICH-GCP guidelines. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care.
Documented informed consent must be obtained for all patients included in the study before they are registered or randomized in the study. This must be done in accordance with the national and local regulatory requirements.
The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

15 Administrative responsibilities

The Study Coordinators will be responsible for writing the protocol, reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. They will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

16 Trial sponsorship and financing

- Data management and statistical analysis will hopefully be supported by the financial support of the CKTO
- All components of the study (radiotherapy, capecitabine) are standard of care. The aim of this study is to gain experience with the combination and to analyse the results of this national study at a central level.

17 Trial insurance

Insurance:

Als gevolg van art. 7 van de Wet medisch wetenschappelijk onderzoek met mensen (Stbl. 1998, 161) dient voor de deelnemende proefpersonen een verzekering afgesloten te worden die de door het onderzoek veroorzaakte schade door dood of letsel van de deelnemende proefpersonen dekt. Deze verzekering moet voldoen aan de bepalingen van het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen (Stbl. 2003, 266). Aan het onderzoek deelnemende proefpersonen zullen schriftelijk worden ingelicht over deze verzekering.Elke aan het onderzoek participerende instelling draagt zorg voor de verzekering van de in de eigen instelling te includeren proefpersonen.

18 Publication policy

First author of the manuscript reporting the trial results should be a study-coordinator. Other authors of the manuscript will include the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), and other persons who made a major contribution to the trial (as to be decided by the study-coordinators) such as the data manager and statistician.

Addendum 1

Table 1. Surgical treatment for stage T3 squamous cell cancer of the vulva

Author	n	Local recurrence	5 yr survival	Follow-up
[5]	66	?	70%	2 years
[6]	71	24%	68%	3-23 years
[7]	62	< 25%	65%	5 years
[8]	41	27%	77%	5 years
[9]	60	< 23%	64%	5 years
Total	**300**	**23- 27**	**64-77**	**>2-23 years**

Table 2. Efficacy of radiochemotherapy for squamous cell cancer of the vulva

Author	TNM	Dose	Chemo	CR	Locrec	Surv	Fup(months)
[15]	T2-3 N2	40	5FU/P	66%	50%	33%	6-28
[16]	T1-3 N0-3	45-85		63%	25%	26%	> 60
[17]	Med 4 cm	45-60	5FUMMC	67%	50%	67%	5-43
[18]	T3-4 N0-1	45-51	5FUMMC	52%	10%	89%	11-56
[19]	T2-4 N0-2	34-72	5FU/P	89%	16%	83%	2-52
[20]	T3-4	50-65	5FU/P	64%	11%	?	7-81
[21]	T3-4 N2-3	45	5FUMMC	44%	30%	33%	6- 36
Total	**T1-T4**	**34-85**		**44-89**	**11-50**	**26-89**	**2-81**

Addendum 2: Criteria of evaluation

- **CTCAE version 3**

http://ctep.cancer.gov/reporting/ctc.html

- **Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:**

* Complete Response (CR):	Disappearance of all target lesions
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

http://ctep.cancer.gov/forms/quickrcst.doc

Addendum 3

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for toxicity occurring greater than 90 days after radiation therapy.

Grade Toxicity	0	1	2	3	4
Bladder- Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency/ generalized telangiectasia/ intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Necrosis/contracted bladder (capacity < 100 cc)/severe hemorrhagic cystitis
Bone- Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/ spontaneous fracture
Brain- Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus- Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/ perforation; fistula
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia > 110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade/severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation
Kidney- Late RT Morbidity Scoring	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25 - 35 mg%; creatinine 1.5 - 2.0 mg%; creatinine clearance > 75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea > 36 - 60 mg%; creatinine clearance > 50 - 74%	Severe albuminuria; severe hypertension; persistent anemia (< 10 g%); severe renal failure; urea > 60 mg%; creatinine > 4 mg%; creatinine clearance < 50%	Malignant hypertension; uremic coma/urea > 100%
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Use for toxicity occurring greater than 90 days after radiation therapy.

Grade **Toxicity**	**0**	**1**	**2**	**3**	**4**
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis/hepatic coma or encephalopathy
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency/ continuous O_2/assisted ventilation
Mucous membrane- Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/ perforation fistula
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Eye- Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthalmitis; blindness
Radiation-Other (Specify, _____)	None	Mild	Moderate	Severe	Life-threatening or disabling

REFERENCES

1. Van der Velden J, Van Lindert AC, Gimbrere CH, Oosting H, Heintz AP. Epidemiologic data on vulvar cancer: comparison of hospital with population-based data. Gynecol Oncol, 1996; 62: 379-383.

2. Dutch Cancer registration, Gynaecological tumours in the Netherlands 1989-1993, IKC publication.

3. Hacker NF, Van der Velden J. Conservative management of early vulvar cancer. Cancer, 1993; 71:1673-1677.

4. Van der Velden J, Van Lindert ACM, Lammes FBI, Ten Kade FJ, Silo MTS, Oosting H, Heintz APM. Extracapsular growth of lymph node metastases in squamous cell cancer of the vulva, the impact on recurrence and survival. Cancer, 1995; 75: 2885-2890.

5. Rutledge F, Smith PJ, Franklin EW. Carcinoma of the vulva. Am J Obstet Gynecol, 1970; 106: 1117-1130.

6. Podratz KC, Symmonds RE, Taylor WF. Carcinoma of the vulva; analysis of treatment failures. Am. J Obstet Gynecol 1982; 143:340-347.

7. Andreasson B, Bock JE, Weberg E. Invasive cancer in the vulva region. Acta Obstet Gynecol Scand, 1982; 61:113-119.

8. Malfetano J, Piver MS, Tsukada Y. Stage III and IV squamous cell carcinoma of the vulva. Gynecol Oncol, 1986; 23:192-198.

9. Ansink AC, Van Tinteren H, Aartsen EJ, Heintz APM. Outcome, complications and follow-up in surgically treated squamous cell carcinoma of the vulva 1956-1982. Eur J Obstet Gynecol Reprod Biol, 1991; 42: 137-143.

10. Morley GW. Infiltrative carcinoma of the vulva: results of surgical treatment. Am J Obstet Gynecol.1976;124:874-888

11. Reid GC, Delancy JO, Hopkins MP, Roberts JA, Morley GW. Urinary incontinence following radical vulvectomy. Obstet Gynecol, 1990; 75, 852-858.

12. Hoffman MS. Squamous-cell carcinoma of the vulva: locally advanced disease. Best Practice & Research Clinical Obstetrics & Gynaecology Vol. 17, No. 4, pp. 635–647, 2003

13. Flam M, Madhu J, Pajak TF, Pterelli N, Myerson R, Doggett S, Quivey J, Rotman M, Kerman H, Coia L, Murray K. Role of radiotherapy in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol, 1996; 14, 2527-2539.

14. Blake P. Radiotherapy and radiochemotherapy for carcinoma of the vulva. Best Practice & Research Clinical Obstetrics & Gynaecology Vol. 17, No. 4, pp. 649–661, 2003.

15. Eifel PJ, Morris M, Burke TW, Levenback C, Gershenson DM. Prolonged continuous infusion cisplatin and 5-fluorouracil with radiation for locally advanced carcinoma of the vulva. Gynecol Oncol. 1995; 59:51-56.

16. Pirtoli L, Rottoli ML. Results of radiation therapy for vulvar carcinoma. Acta Radiol Oncol. 1982; 21:45-48.

17. Thomas G, Dembo A, DePetrillo J, Ackerman I, Bryson P, Balogh J Concurrent radiation and chemotherapy in vulvar carcinoma. Gynecol Oncol, 1989; 34:263-267.

18. Wahlen SA, Slater JD, Wagner RJ, Wang WA, Keeny ED, Hocko JM, King A, Slater JM. Concurrent radiation therapy and chemotherapy in the treatment of primary squamous cell carcinoma of the vulva. Cancer, 1995; 75:2289-2294.

19. Russell AH, Mesic JB, Scudder SA, Rosenberg PJ, Smith LH, Kinney WK, Townsend DE, Trelford JD, Taylor MH, Zukowski CL. Synchronous radiation and cytotoxic chemotherapy for locally advanced or recurrent squamous cancer of the vulva. Gynecol Oncol. 1992; 47:14-20.

20. Cunningham MJ, Goyer RP, Gibbons SK, Kredentser DC, Malfetano JH, Keys H. Primary radiation, cisplatin, and 5-fluorouracil for advanced squamous carcinoma of the vulva. Gynecol Oncol. 1997; 66:258-61.

21. Sebag-Montefiore DJ, McLean C, Arnott SJ, Blake P, Van Dam P, Hudson CN, Shepherd JH. Treatment of advanced carcinoma of the vulva with radiochemotherapy - can exenterative surgery be avoided? Int J Gynecol Cancer. 1994; 4:150-155.

22. Moore DH, Thomas GM, Montana GS, Saxer A, Gallup DG, Olt G. Preoperative chemoradiation for advanced vulvar cancer: a phase II study of the Gynecologic Oncology Group. Int J Radiat Oncol Biol Phys, 1998; 42:79-85.

23. Lupi G, Raspagliesi F, Zucali R, Fontanelli R, Paladini D, Kenda R, di Re F.Combined preoperative radiochemotherapy followed by radical surgery in locally advanced vulvar carcinoma. A pilot study. Cancer. 1996; 15; 77(8):1472-8.

24. Koh WJ, Wallace HJ, Greer BE, Cain J, Stelzer KJ, Russell KJ, Tamimi HK, Figge DC, Russell AH, Griffin TW. Combined radiotherapy and chemotherapy in the management of local-regionally advanced vulvar cancer. Int J Radiot Oncol Biol Phys, 1993; 26:809-16.

25. Van der Velden J, Ansink A. Primary groin irradiation vs primary groin surgery for early vulvar cancer. Cochrane Database Syst Rev. 2000 ;(3):CD002224.

26. Montana GS, Thomas GM, Moor DH, Saxer A, Mangan CE, Lentz SS, Averette HE. Preoperative chemo-radiation for carcinoma of the vulva with N2/N3 nodes: A Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys 2000; 48:1007-1013.

27. Han SC, Kim DH, Higging SA et al. Chemoradiation as primary or adjuvant treatment for locally advanced carcinoma of the vulva. Int J Radiat Oncol Biol Phys 2000, 47(50: 1235-44

28. Landoni F, Maneo A Zanetta G et al. Concurrent preoperative chemotherapy with 5-fluorouracil and mitomycin C and radiotherapy (FUMIR) followed by limited surgery in locally advanced and recurrent vulvar cancer. Gyn Oncol 1996, 61: 321-327

29. Lupi G, Raspagliesi F, Zucali R et al. Combined preoperative chemoradiotherapy followed y radical surgery in locally advanced vulvar carcinoma. Cancer 1996, 77: 142-8

30. Ryan DP, Compton CC and Mayer RJ. Carcinoma of the anal canal. N Engl J Med 200 342: 792-800

31. Ishikawa T, Utoh M, Sawada N et al. Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts. Biochem Pharmacol 1998, 55:1091-1097

32. Miwa M, Nishida UM, Ishikawa ST et al. 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 1998, 34:1274-1281

33. Bajetta E, Carnaghi C, Somma L et al. A pilot safety study of capecitabine, a new oral fluoropyrimidine, in patients with advanced neoplastic disease. Tumori 1996, 82:450-452

34. Blum JL, Dieras V, Lo Russo PM, et al. Multicenter, phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. Cancer 2001, 92: 1759-1768

35. Cutsem van E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous 5-fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001, 19: 4097-4106

36. Hoff PM, Ansari R, Batist G et al. Comparison of oral capecitabine versus intravenous fluorouracil as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 2001; 19:2282-2292

37. Dunst J, Reese Th, Sutter Th et al. Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer. J Clin Oncol 2002, 20: 3983-3991

38. Patel B, Forman J, Fontana J, et al. A single institution experience with concurrent capecitabine and radiation therapy in weak and/or eldery patients with urothelial cancer. Int J Radiat Oncol Biol Phys 2005; 62: 1332-1335

39. Kim JC, Kim TW, Kim JH et al. Preoperative concurrent radiotherapy with capecitabine before total mesorectal excision in locally advanced rectal cancer. Radiat Oncol Biol Phys 2005; 63: 346-349

40. Ngan SY, Michael M, McKendrick J et al. A phase I trial of preoperative radiotherapy and capecitabine for locally advanced, potentially resectable rectal cancer. Br J Cancer 2004, 91: 1019-1024

41. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials 1989; 10: 1-10.

42. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000 Feb 2;92(3):205-16.