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Original Research Article

Survival and failure types after radiation therapy of vulvar cancer

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ABSTRACT

Background and purpose: Describe the survival rates and distribution of events on competing failure types in vulvar carcinoma after treatment with chemoradiation (CRT) or radiation (RT) alone.
Material and methods: We included patients with vulvar carcinoma treated with CRT or RT between 2009 and 2014. Survival was estimated using the Kaplan-Meier method. We performed a competing risk analysis and included five competing events: loco-regional failure (LRF), distant metastasis, LRF plus distant metastasis, and death without evidence of disease, with the remaining patients denoted alive without evidence of disease.
Results: 87 patients were treated. Progression free survival (PFS) and overall survival (OS) at 3 years were 40% and 57%, respectively. 41.3% of patients relapsed, most often loco-regionally. We saw significantly worse PFS and OS for patients older than 68 ($p = 0.011$/$p = 0.010$) and for patients treated with definitive RT ($p = 0.004$/$p = 0.005$). Competing risk analysis showed increased risk of LRF, and that death was most often related to vulvar cancer. Death without disease recurrence was less frequent, even in the elderly.
Conclusions: LRF was the most common event. PFS and OS were inferior for elderly patients and patients treated definitively. A better understanding of these differences may be used to define risk adapted treatment strategies.
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Introduction

Vulvar cancer is a rare gynecological malignancy, annually affecting 2–3 per 100,000 women worldwide [1]. In Denmark, the incidence is 80–100 per year, accounting for approximately 0.5% of all cancers in women [2]. The majority of vulvar cancers are squamous cell carcinomas (SCC) (76%) [3]. Vulvar cancer mainly affects elderly women with a median age of 65–70 years. During the past decades, the incidence of vulvar cancer has been increasing, with a trend of younger women under the age of 60 being affected.

Due to the lack of randomized trials and to the low incidence of vulvar cancer, many questions regarding treatment remain unanswered. Surgery is still the main treatment modality for vulvar cancer, but radiation (RT) also has an important role in management. RT is typically delivered either as an adjuvant to surgery or as a definite modality typically in conjunction with chemotherapy. The optimal radiation dose prescription strategy is disputed, and many treatment decisions are guided from clinical trials of cervical- and anal cancer in the absence of sufficient vulvar cancer research [4,5].

The risk of recurrence is correlated to tumor size, lymph node involvement, and vascular invasion [3,6], and, unfortunately, recurrence inside the radiation field is not uncommon. Due to the rarity of this disease, knowledge of the pattern of loco-regional failure after RT is limited.

We describe the fate of vulvar carcinoma patients after treatment with chemoradiation (CRT) or RT in a large single institution series. In particular we investigated the competing risks of death from other causes, local and distant failure.

Materials and methods

At the Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Denmark, we searched the patient registry for referrals with ICD-10 diagnostic codes DC51-529. We excluded patients with cancer of the clitoris and patients with vaginal cancer and retrospectively reviewed the medical records of the remaining patients with vulvar cancer. Patient data including medical history, patient characteristics, tumor type, histopathological information,

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patient scans, treatment, follow-up, response, recurrence status, recurrence location, disease and survival status were obtained from hospital records and registered.

For the primary staging procedure, patients were assessed by both gynecologists and clinical oncologists at diagnosis and later assessed by the multidisciplinary team of gynecologists, radiologists, pathologists and clinical oncologists in order to determine the best treatment option for the individual patient. All patients had CT, FDG PET-CT or MRI scans performed for diagnostic purposes. Patients were staged according to the system of the International Federation of Gynecology and Obstetrics (FIGO). The primary treatment was surgery if possible. Patients who underwent surgery with positive margins or positive lymph nodes were referred to adjuvant RT and thus included in this series, as were patients with medically inoperable tumors referred for definitive RT.

RT was planned and delivered as follows: FDG PET-CT was used for treatment planning unless contraindicated. The FDG PET-CT was merged into the treatment planning system. Target volumes were delineated following department guidelines: Nuclear Medicine Physicians delineated FDG-PET avid volumes (GTV-PET), radiologists with oncologists delineated gross tumor volumes (GTV) and oncologists delineated the clinical target volumes (CTV). Planning target volumes (PTV) were produced by adding a margin of 7 mm to CTV. In patients with no macroscopic disease, only CTV was delineated. The whole vulva was always included in the CTV, if vulva had to be irradiated. If there was metastatic disease in the nodes, the next nodal region was included in the CTV e.g. if patients had metastatic disease in the superficial inguinal lymph nodes, the deep inguinofemoral lymph nodes and lower half of the external iliac lymph nodes were included in the CTV. Furthermore, the nodal CTV included gross tumor of nodes with a 1 cm margin. See Table 1 for average volumes and dose coverage of the delineated regions. Adjuvant or definitive RT was delivered as external-beam RT to the vulva and/or inguinal nodal regions. Patients were treated with either IMRT or Volumetric Modulated Arc Therapy (VMAT). Prescribed dose was 60–64 Gy (2 Gy per fraction) to the GTV for patients with macroscopic disease at the time of treatment, with 50 Gy to regions without macroscopic involvement, delivered as simultaneous integrated boost. For patients without macroscopic disease, the prescribed dose was 46–50.5 Gy (usually 1.8–2 Gy per fraction according to guidelines, but two patients received 1.6 Gy/fraction). For patients deemed fit for chemotherapy, concomitant cisplatin was administered weekly 40 mg/mm^2 with an upper limit to the total cisplatin dose of 70 mg. Neoadjuvant or adjuvant chemotherapy is not a standard of care according to department guidelines.

First follow-up visit after end of RT was at 12 weeks. Subsequent follow-up visits were with 3–4 months interval for 5 years. If a patient at the time of RT planning had macroscopic disease in the nodal area, first follow-up at 12 weeks included an FDG PET-CT scan. If patients relapsed after RT, the multidisciplinary team assessed them once again, in order to determine management of the disease including possible post-radiation surgical resection and/or chemotherapy. Patients with post-radiation treatment failure were offered surgical resection if possible. If the recurrence was unresectable or the patients had disseminated disease, they were offered palliative chemotherapy and/or RT. Patients not eligible for resection and CRT were referred to palliative care units.

The endpoints in our study were progression free survival (PFS), overall survival (OS), time to local recurrence, distant recurrence or simultaneous local and distant recurrence.

PFS was defined as the interval from the date of RT start to the date of recurrence of the disease, death from any cause or last follow-up (LFU) whichever came first. OS was defined as the interval from the date of RT start to the date of death due to any cause. We used a cut off in January 2015 for the OS analysis of the whole series. Survival after a recurrence following RT or CRT was analyzed separately with a cut off in May 2015. Relapse date was defined as the date of documentation of conclusive relapse i.e. relapse determined unequivocally by either pathologist, clinical oncologist or radiologist. For patients with recurrences, OS was defined as the interval from the date of relapse to the date of death due to any cause.

The data were analyzed using IBM SPSS statistics version 22. Survival rates were calculated using the Kaplan-Meier method. Comparisons were made using the log-rank test and a 2-sided p-value of 0.05 was considered significant. Additionally we performed Cox proportional hazards modeling of the impact of age on a continuous scale. Cox regression was used to perform the univariate and multivariate analysis, stratifying for adjuvant versus definitive therapy. Age, tumor stage, use of cisplatin and primary vs. recurrent disease were entered as prioritized covariables. We performed competing risk analysis using the statistical software R version 3.1.2 and the CMPRSK package [7]. We included the following five competing events in our analysis: loco-regional recurrence, distant metastasis, loco-regional recurrence plus distant metastasis, and death without evidence of disease, with the remaining patients denoted alive with no evidence of disease.

The study was approved by The Danish Data Protection Agency (approval No. 30-1322) and The Danish Health and Medicines Authority (approval No. 3-3013-893/1).

Results

Our search produced 160 patients with the previously mentioned ICD-10 codes treated at the Department of Oncology, Rigshospitalet between January 2009 and October 2014. 124 patients had confirmed vulvar cancer. In total, 37 patients were excluded – see

Table 1
Planning target volumes definitions, median target volumes and dose.

Volumes	Definition	Dose	Adjuvant RT (median target volume, cm^3 (range))[1]	Definitive RT (median target volume, cm^3 (range))[1]
GTV-PET	FDG-PET avid volumes	64 Gy	3 (1–30)	17.5 (3–232)
GTV_{64}[2]	All GTV volumes prescribed 64 Gy	64 Gy	2 (1–342)[3]	105.5 (5–320)
PTV_{64}	All PTV volumes prescribed 64 Gy	64 Gy	62 (10–663)	488.5 (54–1036)
CTV_{50}	All CTV volumes prescribed 50 Gy	50 Gy	821 (71–3704)	1157 (242–2685)
Volumes	Definition	Dose	Adjuvant RT (median dose, Gy (range))[1]	Definitive RT (median dose, Gy (range))[1]
$D_{98\%}$ GTV_{64}[4]	Given dose to 98% of GTV_{64}	64 Gy	64.1 Gy (61.3–66.8)	62.9 Gy (62.3–65.4)
$D_{98\%}$ CTV_{50}	Given dose to 98% of CTV_{50}	50 Gy	48.8 Gy (43.1–53.4)	49.2 Gy (48.1–50.9)

One patient was excluded from the entire analysis. The patient was treated with electron fields that could not be reconstructed.
[1] Patients without the target volume/dose in question were excluded in the analyses for median target volumes/dose.
[2] One patient was excluded from the GTV_{64} volume analysis since the boost dose was only 60 Gy.
[3] GTV in the adjuvant setting may include the entire remaining vulva in case of positive surgical margins.
[4] For patients without GTVs, only CTVs are reported.

Fig. 1. We included a total of 87 patients with vulvar cancer treated with RT +/− chemotherapy with intent to cure. All 87 patients had SCC of the vulva. Concomitant cisplatin was administered to 61 patients. Patient, tumor, treatment and recurrence characteristics are shown in Table 2.

Lymph node status of the patients is presented in detail in Table 2. Lymph nodes were left unresected either because the nodes were unresectable, the primary tumor was unresectable and therefore patients did not undergo any surgery, or patients were not healthy enough to undergo major surgery. A few patients had new FDG-avid nodes on the planning PET-CT scan, which were then treated with RT. For the patients who underwent surgery ($n = 68$), vascular invasion was seen in only four cases.

The median follow-up time was 29 months (range 4–69 months) calculated as median time to censoring in patients without events. Median time to recurrence or death in the 42 patients experiencing these events was 7.4 months (range 2–31 months). Response was assessed at the first follow-up visit after the end of treatment. A total of 64 patients had a complete response based on clinical examination possibly supplemented by FDG PET-CT ($n = 22$). Fifteen patients had progressive disease; of these, one had distant metastases, seven failed loco-regionally, and seven had both distant metastases and loco-regional recurrences. Five patients had suspected residual disease at the time of first follow-up, which was later confirmed. Four of those patients failed loco-regionally, and one had both distant metastases and loco-regional disease. Two patients were lost to follow-up, and one patient died before her first appointment, though all 87 patients are included in the survival analysis as OS data is extracted from the Danish Civil Registration System.

For the entire series, PFS and OS rates at 1 year were 64% (95% CI: 54 to 74) and 81% (95% CI: 73 to 89) and at 3 years 40% (95% CI: 27 to 53) and 57% (95% CI: 44 to 70), respectively. We found no significant difference in PFS and OS between patients with a primary tumor at the time of diagnosis and patients with recurrent disease referred for curative CRT; Patients with a primary tumor had 3 years PFS of 42% (95% CI: 27 to 57) compared to 32% (95% CI: 6 to 58%) for patients with recurrent disease ($p = 0.533$). Similarly we saw no difference in OS between the two groups ($p = 0.752$).

The median age of the included patients was 68 years. For patients $\leq$68 years compared to patients >68 years, PFS rates at 1 year were 71% (95% CI: 57 to 85) vs. 56% (95% CI: 41 to 71) and at 3 years 58% (95% CI: 40 to 76) vs. 22% (95% CI: 6 to 38) ($p = 0.011$). OS rates at 1 year were 86% (95% CI: 76 to 96) vs. 76% (95% CI: 63 to 89) and at 3 years 72% (95% CI: 56 to 88) vs. 40% (95% CI: 22 to 58) ($p = 0.010$) – see Fig. 2. We see the same dependence of age when treated as a continuous variable in the Cox proportional hazards model, HR = 1.44 (95% CI: 1.1 to 1.88)

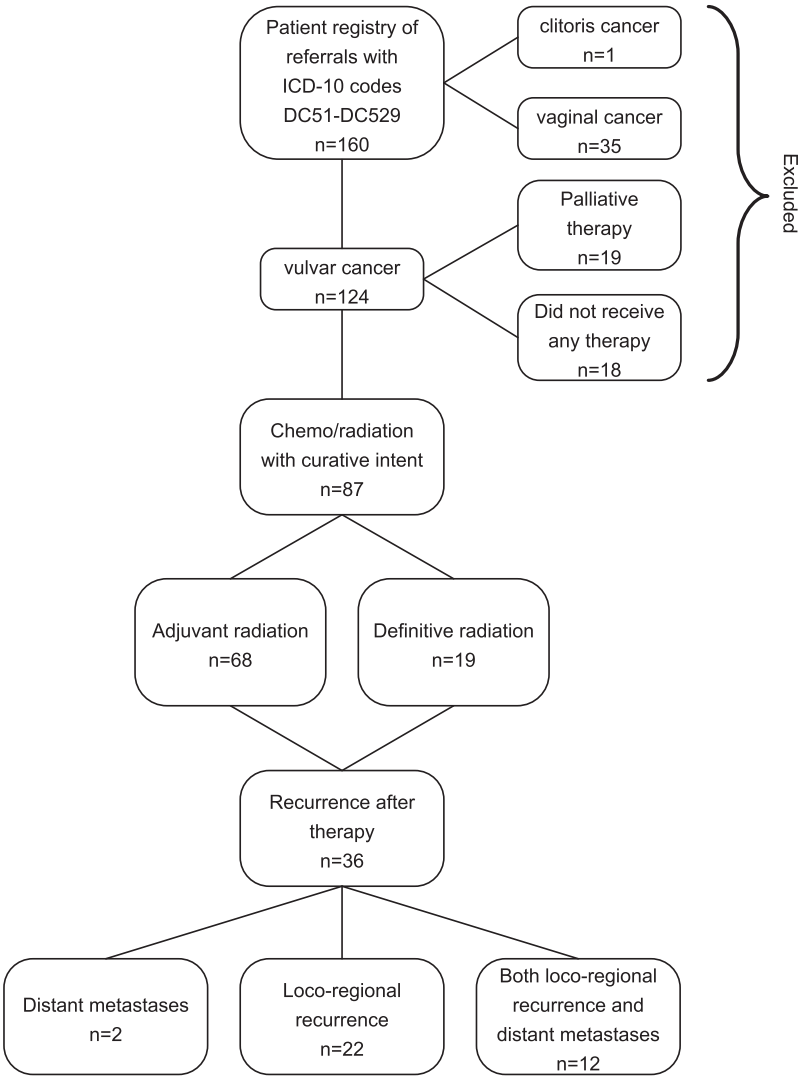

Fig. 1. Flowchart of the identification of patients.

Table 2
Patient, tumor, treatment and recurrence characteristics.

Variables	Adjuvant RT	Definitive RT	All recurrence locations	Loco-regional recurrences	Distant metastases	Loco-regional + distant metastases
Total no. of patients	n = 68	n = 19	n = 36	n = 22	n = 2	n = 12
Age (years)						
median	66.5	70	70	72	64.5	68.5
range	34–88	44–88	39–88	53–88	52–77	39–77
Tumor type						
primary	57	12	26	16	2	8
recurrence	11	7	10	6	0	4
Tumor stage (FIGO)						
II	12	2	3	3	0	0
IIIA	26	2	8	5	1	2
IIIB	5	0	3	3	0	0
IIIC	14	2	9	3	1	5
IVA	0	6	3	2	0	1
recurrence	11	7	10	6	0	4
Treatment given (RT+/− cisplatin)						
adjuvant	-	-	24	15	2	7
definitive			12	7	0	5
Positive margins						
yes	50	-	18	11	1	6
no	17	-	6	4	1	1
n/a (no surgery/only groin surgery)	1	19	12	7	0	5
Vascular invasion						
yes	4	-	1	0	1	0
no	63	-	23	15	1	7
n/a[*]	1	19	12	7	0	5
Node resection						
resected	62	3	23	14	2	7
not resected	3	13	10	5	0	5
no positive nodes[**]	3	3	3	3	0	0
Pathologically positive nodes						
yes[***]	49	8	26	13	2	11
no	13	0	2	2	0	0
n/a	6	11	8	7	0	1
Extracapsular spread						
yes	15	1	8	3	1	4
no	47	2	15	11	1	3
n/a	6	16	13	8	0	5
Chemotherapy						
cisplatin (5–6 cycles)	34	8	13	8	1	4
cisplatin (1–4 cycles)	17	2	10	4	0	6
none	17	9	13	10	1	2
Radiation dose						
40 Gy[****]	1	0	0	0	0	0
46–50.5 Gy	43	0	11	6	2	3
≥60 Gy	24	19	25	16	0	9

Notes: RT = radiation therapy.
[*] No surgery/biopsy only. Biopsies only without vascular invasion.
[**] No positive nodes on imaging or histologically.
[***] Some patients had lymph node biopsy only with a positive result, but the nodes were left unresected.
[****] Patient did not complete planned course of 50 Gy (refusal). The patient is alive without evidence of disease.

per 10 years increase in age for PFS and HR = 1.50 (95% CI: 1.09 to 2.06) per 10 years increase in age for OS.

A total of 36 patients relapsed after treatment. Twenty-two patients had loco-regional recurrences, two patients had distant metastases as first sign of recurrence, and 12 patients had simultaneously detected loco-regional and distant relapse. The risk of progression was substantial for elderly patients and for patients treated definitively, and the risk decreased with the use of concomitant chemotherapy – see Fig. 2. Also, patients who had nodes left unresected, and patients who had nodes with extra capsular spread were at a higher risk of progression – see Table 2.

Cumulative incidence plots in the competing risk model are shown in Fig. 3. Patients above 68 years and patients treated with definitive RT were at risk of especially loco-regional recurrences (Gray's test for difference in local control: $p = 0.053$ (age) and $p = 0.146$ (adjuvant vs. definitive RT)). Survival after a recurrence following CRT was poor as shown in Fig. 4. Cox regression results are given in Table 3 including age, use of cisplatin, tumor stage and primary vs. recurrent disease. As a note of caution, in this retrospective analysis the HR for use of cisplatin includes patient selection due to general health condition.

Discussion

A substantial amount of patients treated for vulvar carcinoma experience a recurrence after treatment. Our study showed a recurrence rate of 41.3%. This is in accordance with Maggino et al. [6] (37.3%) and Mak et al. [8] (45.4%). Absolute rates of recurrence in an individual institution will clearly depend on the selection of patients for CRT or RT.

The use of CRT to treat patients with vulvar carcinoma has been adopted from trials on anal- and cervical cancer [4,5]. Some smaller studies and a few phase II trials have indicated CRT to be

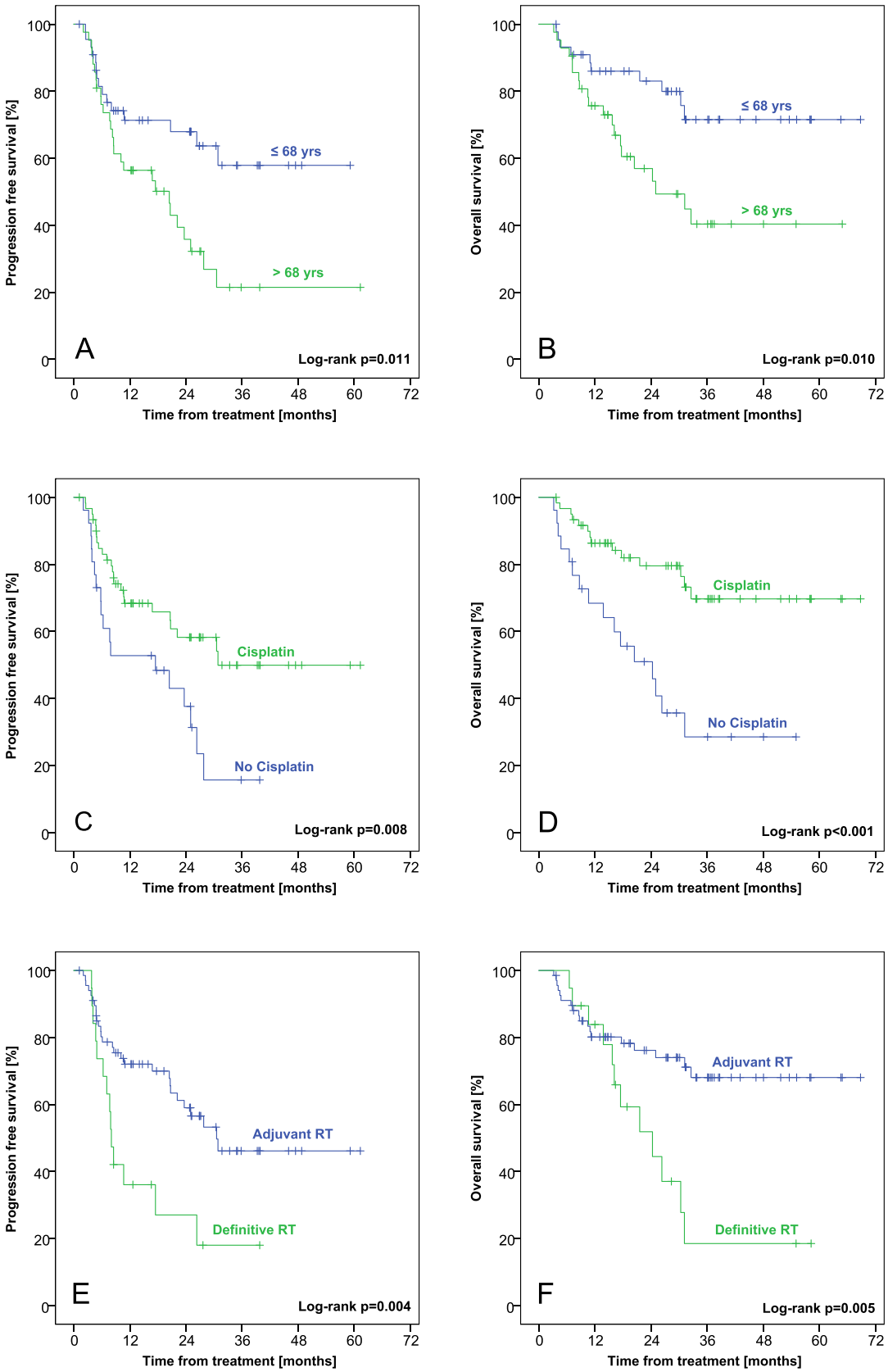

Fig. 2. Progression free survival (left) and overall survival (right) depending on age (A + B), administration of concomitant chemotherapy (C + D) and type of radiotherapy (E + F).

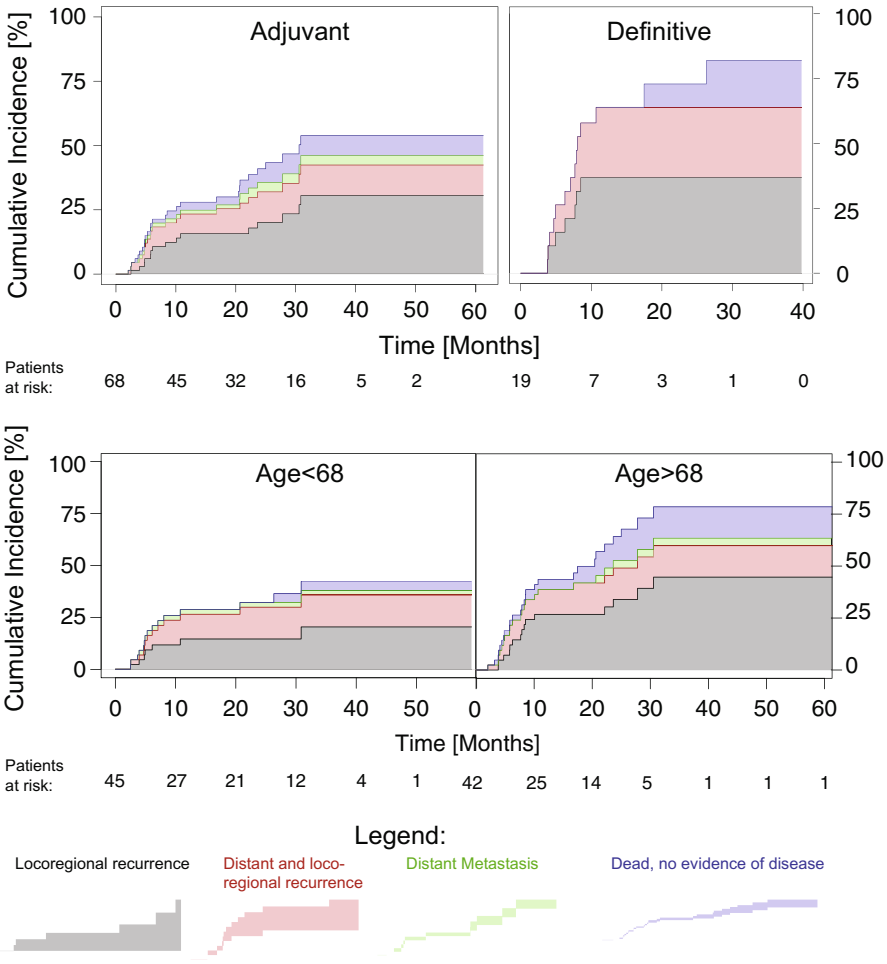

Fig. 3. Cumulative incidence plots in the competing risk model. Mutually exclusive endpoints add up to 100%. Probability of being alive without evidence of disease is the white area at the top. Note that loco-regional recurrence and loco-regional recurrence plus distant metastases are the main reasons for the deteriorated outcome in elderly patients. Gray's test for difference in local control in elderly vs. younger patients: $p = 0.053$. Gray's test for difference in local control between patients treated with adjuvant and definitive radiotherapy: $p = 0.146$.

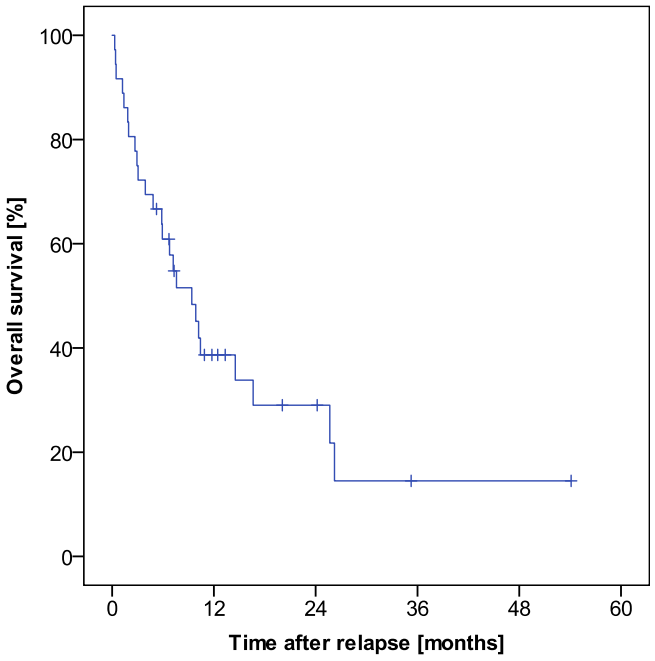

Fig. 4. Overall survival after a recurrence.

Table 3
Cox regression stratified for adjuvant versus definitive therapy.

Variables	Univariate	Multivariate
Progression free survival		
Adjuvant vs. definitive therapy	*Stratified*	*Stratified*
Age*	HR = 1.40 [1.07–1.82] $p = 0.014$	HR = 1.29 [0.95–1.8] $p = 0.11$
Cisplatin (yes vs. no)	HR = 0.5 [0.3–1.0] $p = 0.055$	HR = 0.8 [0.4–1.7] $p = 0.51$
FIGO tumor stage**	HR = 1.2 [0.9–1.3] $p = 0.50$	HR = 1.2 [0.9–1.6] $p = 0.22$
Primary vs. recurrent disease	HR = 0.8 [0.4–1.6] $p = 0.50$	HR = 0.5 [0.2–1.6] $p = 0.25$
Overall survival		
Adjuvant vs. definitive therapy	*Stratified*	*Stratified*
Age*	HR = 1.48 [1.07–2.02] $p = 0.016$	HR = 1.20 [0.83–1.74] $p = 0.35$
Cisplatin (yes vs. no)	HR = 0.3 [0.2–0.7] $p = 0.004$	HR = 0.4 [0.2–1.0] $p = 0.061$
FIGO tumor stage**	HR = 1.1 [0.9–1.4] $p = 0.37$	HR = 1.3 [0.9–1.8] $p = 0.13$
Primary vs. recurrent disease	HR = 1.0 [0.4–2.2] $p = 0.92$	HR = 0.4 [0.1–1.4] $p = 0.16$

In progression free survival analysis, death of any cause or progression is treated as events.

* Age as continuos covariable. HR given per 10 year increase.

** FIGO stage I-IV as continuos covariable.

effective in the treatment of vulvar cancer patients [8–13], but the optimal treatment regime still remains to be found in order to secure loco-regional control while keeping toxicity low. Our results demonstrated improved outcome on PFS and OS in patients treated with concomitant chemotherapy. However, this effect must be expected to be biased in this retrospective analysis due to the selection of patients deemed fit for treatment with chemotherapy. The prescription of cisplatin is correlated to the age of the patient. In the univariate analyses the two factors are separately analyzed and both carry the entire signal and are significant or close to significant on PFS and OS. In the multivariate analysis, they share part of the overall effect (due to poor prognostic of age and omission of cisplatin coincide in many of the patients) and both point estimates go towards 1 compared to the univariate analyses. They loose individual significance in the multivariate analyses, probably also due to the limited sample size. It should be noted that the age variable is the most robust of the two univariate predictors emphasizing that assessment of the true value of cisplatin prescription requires randomization.

Inferior outcome in elderly patients is documented with significantly worse PFS and OS for elderly patients (Fig. 2) whether assessed as older/younger than median or as a continuous variable in univariate Cox regression. The competing risk analysis allows subdivision of the events in PFS analysis in the competing failure modes [14]. This analysis showed that elderly patients have increased risk of all disease specific endpoints, especially loco-regional failure. In other words, the inferior outcome of the elderly patients is primarily disease related and not due to the patients dying from non-cancerous courses. Treatment of elderly patients with CRT can be challenging due to possible comorbidities and the risk of treatment complications. Our results indicate that while clinical decisions regarding the de-intensification of therapy for frail patients are, of course, necessary, loco-regional recurrence should still be expected to be the dominant cause of mortality in these patients. Decreasing treatment intensity solely on the basis of patient age is probably not a wise choice.

Part of the explanation for the difference in prognosis between old and young could be related to a potential different biology of the disease. Different risk factors for development of vulvar carcinoma have been shown [15], and besides chronic skin diseases such as lichen sclerosis, human papillomavirus (HPV) infection also plays a role in the development of SCC of the vulva. The literature suggests two different pathways leading to SCC of the vulva; an HPV-dependent and an HPV-independent pathway [16,17]. The prognostic role of HPV infection still remains unclear, as some studies have found no significant difference in prognosis between HPV-positive and HPV-negative patients [18,19], whereas others suggest improved survival in HPV-positive patients [20,21]. The reason for the observed difference in prognosis between young and elderly in our series is, however, speculation at present.

Vulvar cancer is a rare disease, but the centralization of treatment in the Danish healthcare system has allowed the extraction of data on 87 patients in the current single institution series. In comparison, the included studies in a recently published systematic review [22] had a mean inclusion of seven patients. Stuckey et al. [22] found a non-significant trend towards elderly patients being more likely to die from intercurrent disease and from treatment complications compared to non-elderly patient, but available data did not allow proper survival data analysis. Survival obviously decreases with age at diagnosis as death from intercurrent disease increases with age. However, with proper survival analyses our results still suggest that the inferior prognosis for the elderly patients is vulvar cancer related. To overcome the rarity of the disease and to gain more statistical power, the optimal solution would of course be to conduct multi-institutional studies, and these should put emphasis on improving loco-regional therapy to the elderly and to patients treated definitively.

The retrospective nature of our study and wide inclusion criteria required to obtain a meaningful sample size for analysis inevitably lead to some heterogeneity in the patients studied, see Table 2, and should be acknowledged as a limitation. However, the hypotheses presented and proper (albeit descriptive) survival statistics are important in this narrow field. Furthermore, treatment was quite homogenous within the adjuvant and definitive groups; Department protocol was in place, and patients were treated in a consistent fashion. Subdividing patients further into smaller groups to investigate different prognostic factors is unfortunately not statistically feasible, and a more detailed analysis of the pattern of failure is beyond the scope of this article. However, our study does illustrate a clear pattern, with loco-regional recurrences being the most frequent type of failure. Especially elderly patients and patients treated definitively are at a substantial risk of loco-regional recurrence or synchronous loco-regional recurrence and distant metastasis. The fact that the patients most often relapse locally within the radiation field suggests room for improvement of the local therapy, either in the form of development of improved surgical procedures or more aggressive RT. Further systematic analyses of recurrences after RT could hold a potential to investigate the use of more targeted radiation dose prescription in the future, for example using radiation dose painting [23,24].

Conflict of interest statement

The authors declare that actual or potential conflicts of interest with relationship to this work do not exist.

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