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Locally advanced adenocarcinoma and adenosquamous carcinomas of the cervix compared to squamous cell carcinomas of the cervix in Gynecologic Oncology Group trials of cisplatin-based chemoradiation

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Abstract

Objective—Conflicting results have been reported for adeno- and adenosquamous carcinomas of the cervix with respect to their response to therapy and prognosis. The current study sought to evaluate impact of adeno- and adenosquamous histology in the randomized trials of primary cisplatin-based chemoradiation for locally advanced cervical cancer.

Methods—Patients with adeno- and adenosquamous cervical carcinomas were retrospectively studied and compared to squamous cell carcinomas in GOG trials of chemoradiation.

Results—Among 1671 enrolled in clinical trials of chemoradiation, 182 adeno- and adenosquamous carcinomas were identified (10.9%). A higher percentage of adeno- and adenosquamous carcinomas were stage IB$_2$ (27.5% versus 20.0%) and fewer had stage IIIB (21.4% versus 28.6%). The mean tumor size was larger for squamous than adeno- and

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Conflict of Interest

The authors wish to disclose that there are no conflicts of interest.

adenosquamous. Adeno- and adenosquamous carcinomas were more often poorly differentiated (46.2% versus 26.8%). When treated with radiation therapy alone, the 70 patients with adeno- and adenosquamous carcinoma of the cervix showed a statistically poorer overall survival (p=0.0499) compared to the 647 patients with squamous cell carcinoma of the cervix. However, when treated with radiation therapy with concurrent cisplatin-based chemotherapy, the 112 patients with adeno- and adenosquamous carcinomas had a similar overall survival (p=0.459) compared the 842 patients with squamous cell carcinoma. Adverse effects to treatment were similar across histologies.

Conclusion—Adeno- and adenosquamous carcinomas of the cervix are associated with worse overall survival when treated with radiation alone but with similar progression-free and overall survival compared to squamous cell carcinomas of the cervix when treated with cisplatin based chemoradiation.

INTRODUCTION

Although adeno- and adenosquamous cancers of the cervix comprise a minority of cervical cancers, their relative and absolute frequency has increased over the last 4 decades despite the wider application of cervical cancer screening [1,2]. A recent large SEER (Surveillance, Epidemiology, and End Results) database study from 1988–2005 found a 1–2 % increase in the incidence of adenocarcinoma and adenosquamous carcinomas with each 6 year increment. Collectively, adenocarcinoma and adenosquamous cancers totaled 21.3%, 22.9% and 24.1%, for the years 1988–1993, 1994–1999 and 2000–2005, respectively [2]. This study also reported that patients with adenocarcinoma have a poorer overall survival than similarly staged squamous cell cancer patients [2]. Patients with advanced stage adenocarcinoma or adenosquamous carcinoma were 21% more likely to die from their disease than advanced stage squamous cell cancer patients. In contrast to the SEER data, a recent large single institution study (N=423) by Katanyoo et al suggests that, when treated according to a standard treatment protocol, adenocarcinoma and adenosquamous carcinomas have a similar outcome to squamous cell carcinoma [3].

In 1999, the NCI released a clinical announcement in strongly urging the use of cisplatin-based chemoradiation for cervical cancer patients requiring radiation for their treatment [4]. However, the role of primary chemoradiation for locally advanced adenocarcinoma and adenosquamous cancers of the cervix has not been established by level 1evidence. Although adeno- and adenosquamous carcinomas were included in randomized trials of cisplatin-based chemoradiation, there were too few patients with adenocarcinoma and adenosquamous histology to allow a subset analysis. Only Peters et al evaluated the role of tumor histology in their randomized trial of post-radical hysterectomy adjuvant chemoradiation for women with positive nodes, parametria or margins [5]. This demonstrated that patients with adenocarcinoma had an apparent poorer 5 year progression-free survival (40% vs 65%) when treated with radiation alone but similar outcome with chemoradiation (80% vs 77%). However, this did not reach statistical significance due to the small number of patients with adenocarcinoma.

Based on their relatively small size, prior retrospective studies of adenocarcinoma and adenosquamous cervical cancers have not established a clear role for cisplatin-based chemoradiation. In the Katanyoo et al study, concurrent platinum-based chemotherapy did not significantly improve overall survival, although only 37.6% of patients received chemoradiation [3]. The impact of concurrent chemotherapy during radiation has been addressed in other retrospective studies with no apparent improvement although the authors have included disclaimers about the regimens employed [6].

Therefore, the current GOG ancillary data study was undertaken to evaluate impact of histology in the prospective randomized trials of primary cisplatin-based chemoradiation for locally advanced cervical cancer.

METHODS

We retrospectively analyzed GOG trials numbered 85, 120, 123, 165 and 191 [7–11]. Patients provided written informed consent consistent with federal, state and local institutional requirements. These trials have been reported previously and included patients with stage IB$_2$: GOG Trials 123, 191 and stages IIA: GOG Trial 191 and stage IIB-IVA: GOG Trials 85,120, 165, and 191. In GOG trials 85 and 120 patients underwent surgical staging to exclude para-aortic nodal metastasis and pelvic nodal dissection was optional. While in GOG trials 123, 165 and 191 surgical staging was optional and performed on 7.5%, 18% and 23.7% respectively. Tumor size measured clinically within 0.5 cm was obtained before treatment. All patients were treated with a combination of external radiation and brachytherapy per protocol guidelines. The duration of external radiation for GOG trials 85, 120 and 123 required external radiation treatment to be given over 10 weeks, while GOG trials 165 and 191 required external radiation treatment to be given over 8 weeks. All patients' tumors underwent central pathologic review for confirmation of histology and tumor grade. Due to the small sample size, we wanted to combine patients with adenocarcinoma and adenosquamous carcinoma based on the fact that in previous studies these two entities had similar patterns of failure, progression-free and overall survival [12]. To justify this combination we performed an analysis comparing adenosquamous carcinoma with adenocarcinoma. With adenosquamous as the referent, adenocarcinoma patients in the PFS model had a HR of 0.93 (95% CI, 0.59–1.48, P=0.769). In the OS model, adenocarcinoma patients had a HR of 0.84 (95% CI, 0.52–1.36, P=0.484). In both models the histology variables were not significant. Therefore, patients with subgroups of adenocarcinoma and adenosquamous carcinoma were combined and compared to patients with squamous cell carcinoma.

Categorical variables were compared between the histology groups by the Pearson chisquare test [13], and continuous variables by the Wilcoxon–Mann–Whitney test [14]. Overall survival was estimated using the Kaplan–Meier method [15]. The Cox proportional hazards model was used to evaluate independent prognostic factors and to estimate their covariateadjusted effects on progression-free and overall survival [16]. Continuous variables exhibiting skewed distribution (i.e. tumor size) were included in the survival model after log transformation, and the nonlinearity of the effect of continuous variables was assessed using restricted cubic splines. All statistical tests were two-tailed with the significance level set at

α=0.0499. Statistical analyses were performed using the R programming language and environment [17].

RESULTS

One thousand six hundred and seventy-one patients treated on the GOG studies were analyzed of which 89.1% (1489) were squamous, and 10.9% (182) had adenocarcinoma or adenosquamous cancers (6% had adenosquamous and 4.8% had adenocarcinoma). The demographics of squamous and adeno- and adenosquamous carcinomas of the cervix are compared in Table 1. Adeno- and adenosquamous carcinomas were more often stage IB$_2$, 27.5% versus 20.0%, and fewer had stage IIIB, 21.4% versus 28.6%, though these differences were not statistically significant (p=0.102). The mean tumor size was larger for squamous (6.5 cm) than adeno- and adenosquamous carcinomas (5.9 cm; t-test for difference in means, p<0.001). Adeno- and adenosquamous carcinomas were more often poorly differentiated, 46.2% versus 26.9%.

The treatment regimens by tumor histology are represented in Table 2. Cisplatin-based chemoradiation was utilized in 56.5% of squamous cell carcinoma patients compared to 61.5% of adenocarcinoma and adenosquamous cervical carcinoma patients. Adjusted rates of morbidity for adeno- and adenosquamous - vs. squamous histology are presented in table 3. Although most toxicities were equivalent between the 2 histologies, neurologic, auditory and visual toxicities were more common in squamous cell carcinoma patients, while pulmonary toxicities were more common among adenocarcinoma and adenosquamous carcinoma patients.

Multivariate Cox modeling was used to analyze prognostic factors for progression-free and overall survival for all patients (Table 4), controlling for treatment by stratification; and for patients treated without concurrent cisplatin (i.e. radiation alone, radiation with 5-fluorouracil, and radiation with hydroxyurea) and for patients treated with concurrent cisplatin (i.e. cisplatin alone; cisplatin with 5- fluorouracil; cisplatin, 5- fluorouracil and hydroxyurea; and cisplatin with recombinant human erythropoietin) respectively. Overall survival was poorer for adeno- and adenosquamous carcinomas compared to squamous carcinomas when analyzed together. African-American race is associated with a significantly poorer overall survival (p=0.010) and Asian race is associated with a significantly improved overall survival (p=0.013). However, African-Americans did equally as poorly with squamous and non-squamous histologies. However, the effect of race was only present for patients receiving radiation without cisplatin and was not present among cisplatin-treated patients. Performance status 0 versus 1 and 0 versus 2 significantly affected overall survival p=0.019 and 0.014, respectively. For both squamous and adeno- and adenosquamous carcinomas there were statistically poorer overall survival rates for patients with stage IIB and greater stages as compared with stage IB$_2$. Similarly, when analyzed by tumor size, poorer overall survival was noted for each increment in tumor size for both squamous and adeno- and adenosquamous carcinomas. Based on the Cox model, each 10% increase in tumor size was associated with a 3% increase in risk of disease progression and a 2% decrease in overall survival.

When treated with radiation therapy without concurrent cisplatin, the 70 patients with adeno- and adenosquamous carcinomas of the cervix showed a statistically slightly poorer overall survival (p=0.0499) compared to the 647 patients with squamous cell carcinoma of the cervix. (Figure 1) However, when treated with concurrent cisplatin-based chemotherapy during radiation therapy the 112 patients with adeno- and adenosquamous carcinomas had a similar progression-free (p=0.315) and overall survival (p=0.459) compared the 842 patients with squamous cell carcinoma (Figure 2). Adverse effects to treatment were similar among squamous and non-squamous patients with the exception of pulmonary toxicity seen in 1.1% of squamous cell patients and 3.3% of adeno- and adenosquamous carcinoma patients (and neurologic, auditory and visual symptoms which are slightly more common in the squamous cell carcinoma patients 5.4% versus 1.6%.

DISCUSSION

This is the first GOG study to retrospectively evaluate locally advanced stage adeno- and adenosquamous carcinomas of the cervix treated with radiation with or without concurrent chemotherapy. Compared to squamous carcinomas, adenocarcinoma and adenosquamous carcinomas were more commonly stage IB_2 27% versus 20%. This is not completely unexpected, since in contrast to squamous cell cervical carcinoma, adenocarcinoma and adenosquamous carcinomas arise within the endocervical canal. As they grow, they distend the cervical stroma creating a barrel shaped cervix, which does to have definitive parametrial invasion and precludes classification as stage IIB. There was statistically poorer overall survival for patients with stage IIB and greater compared with stage IB_2. The confidence intervals of stage IIB to IVA overlapped. Since large tumor size can often be reached with expansile endocervical tumors, we chose to analyze the effect of clinical tumor size on overall survival, which was poorer with increasing tumor size. However, the adverse effect of increasing tumor size was equal among squamous and non-squamous histologies.

Despite smaller tumor size, which should confer a better prognosis, patients with adenocarcinoma and adenosquamous carcinoma had a poorer overall survival when treated with radiation alone. There are inherent limitations to tumor measurement clinically, however, a previous GOG study demonstrated clinical tumor measurement was closely associated with progression-free and overall survival [18]. Clinical tumor measurement may be more significant in adeno- and adenosquamous carcinomas which occur higher in the genital tract. MRI was not available in the earlier years of these studies and is an option although not currently mandated in our most recent cervical cancer trials of chemoradiation.

The most important finding of our study is the poorer outcome noted for locally advanced stage adenocarcinoma and adenosquamous cancers treated with radiation without cisplatin when compared to squamous cancers and nullification of this difference with the use of concurrent cisplatin-based chemoradiation. This provides the strongest support to date for the use of concurrent cisplatin-based chemoradiation for locally advanced non-squamous cervical cancer. Recently, Wright et al characterized the molecular profile of 40 adenocarcinomas and 40 squamous of the cervix [19]. They found significant differences in KRAS mutations 17.5% vs 0% and non-significant differences in EGFR mutations 0% vs 7.5%, PIK3CA mutations 25% vs 37.5%, for adenocarcinoma and squamous carcinoma,

respectively. Adjusted analysis demonstrated tumors with PIK3CA mutations were associated with a shorter overall survival, HR=9.1. They proposed this may account for the differences in outcome and targeting distinct subsets of cervical cancer patients may improve outcome. However, since PIK3CA mutations were more common in squamous cancers, they should have the poorer overall survival. The current study finds a poorer outcome for adenocarcinoma and adenosquamous cancers compared to squamous carcinomas treated with radiation alone but not when treated by cisplatin-based chemoradiation. Toxicity of chemoradiation was very similar between the two histologies. Other strategies to incorporate chemotherapy into the primary radiation treatment of cervical cancer include adjuvant and neoadjuvant. Phase II and III studies that have used concurrent and post-radiation chemotherapy have demonstrated improvement in overall survival [5,12,20]. In these studies, it is difficult to know the relative benefit of concurrent vs adjuvant chemotherapy. The impact of post-radiation adjuvant chemotherapy following concurrent chemotherapy for locally advanced cervical cancer is unknown but is currently being studied in the Outback trial in which patients are randomized to adjuvant chemotherapy with carboplatin and paclitaxel for 4 cycles or observation following weekly cisplatin during radiation.[21] The impact of concurrent and adjuvant cisplatin-based chemoradiation on adenocarcinoma and adenosquamous cervical carcinomas was noted in the study of post-radical hysterectomy by Peters et al [5]. This trial administered two doses of cisplatin and 5-fluorouracil chemotherapy during radiation therapy and two courses following radiation. An improvement was noted for patients who received the post-radiation chemotherapy but a subset analysis by histology was not performed.

The use of both neoadjuvant and adjuvant chemotherapy with concurrent chemoradiation in adenocarcinomas was recently reported by Tang et al [22]. In their trial, 880 patients with adenocarcinoma of the cervix were randomized to concurrent chemoradiation or concurrent chemoradiation preceded by one cycle of neoadjuvant and two cycles of adjuvant chemotherapy with cisplatin and paclitaxel. Patients who received chemoradiation with adjuvant chemotherapy showed a significantly longer disease-free (P<.05), cumulative overall survival (P<.05) and long-term local tumor control (P<.05). They also had decreased rates of both local and distant failure (P<.05).

In summary, this analysis demonstrates that both adenocarcinoma/adenosquamous and squamous cell cancer appear to respond well to chemoradiation with no differences detected in this large retrospective analysis of prospectively collected data. The role of other strategies of chemoradiation awaits ongoing and future trials.

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Research Highlights

- We retrospectively analyzed histology in locally advanced cancers of the cervix treated in GOG randomized trials of chemoradiation.

- Adenocarcinoma or adenosquamous (non-squamous) carcinoma had a poorer survival compared to squamous carcinoma.

- Non-squamous patients had poorer survivals when treated with radiation without concurrent cisplatin but similar survival when treated with concurrent cisplatin.

Figure 1.
Overall survival for patients with squamous and adeno- and adenosquamous carcinomas treated with radiation alone

P = 0.46

HR: 1.00

HR: 1.12

Probability

1.0   0.8   0.6   0.4   0.2   0.0

squamous-cell carcinoma
adeno- & adenosq. carcinoma

0   30   60   90   120

Time (months)

| 842 | 586 | 455 | 330 | 203 | squamous |
| 112 | 75 | 56 | 47 | 28 | adeno. |

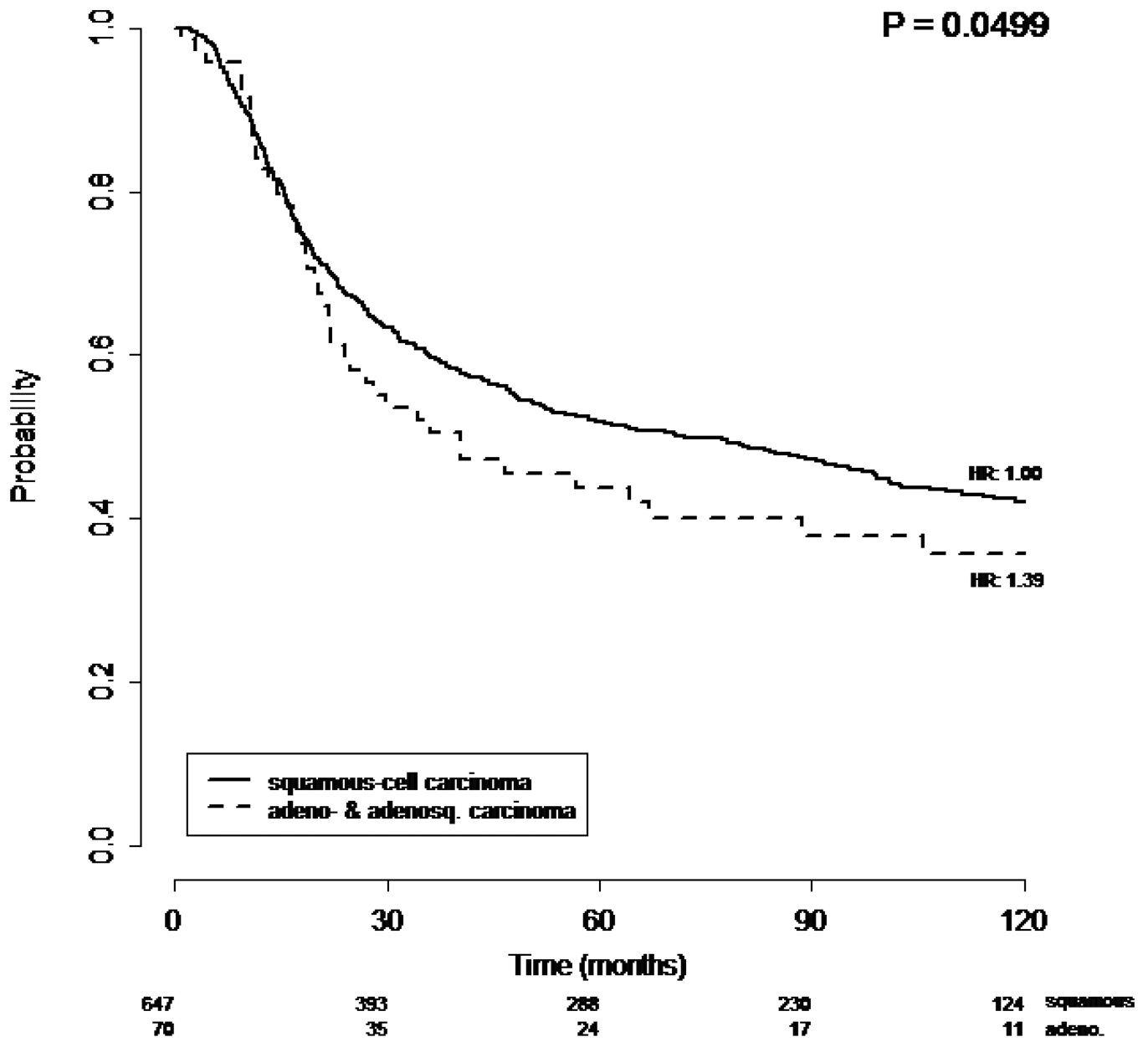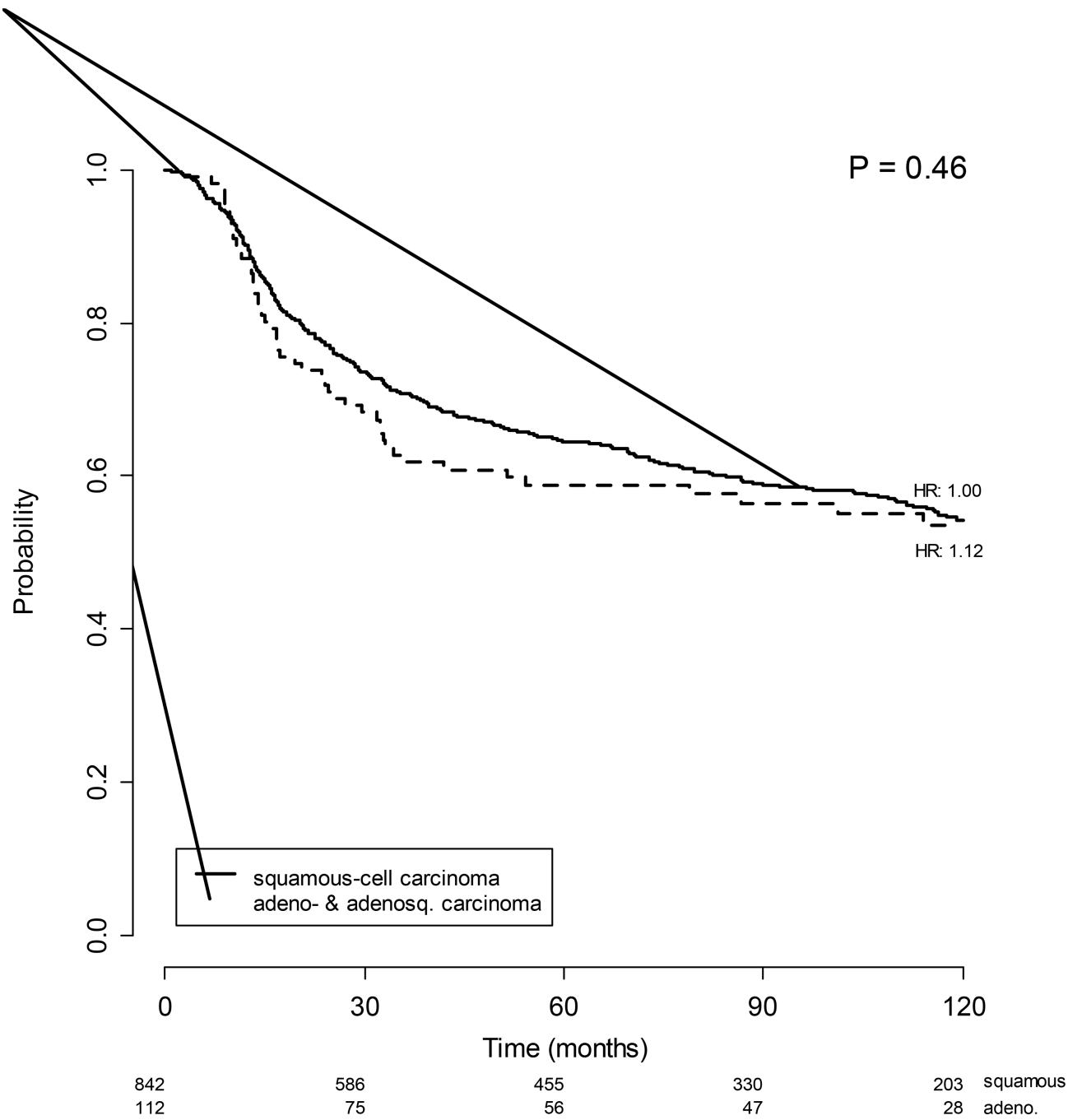**Figure 2.**

Overall survival for patients with squamous and adeno- and adenosquamous carcinomas treated with radiation and concurrent cisplatin chemotherapy

Table 1

Patient Characteristics by Tumor Histology

	N	squamous-cell carcinoma $N = 1489$	adeno- & adenosq. carcinoma $N = 182$	Test Statistic
Age (years)	1671	46.5 (38.8–55.9)	46.0 (54.6–39.4)	$P = 0.56^1$
Race/Ethnicity	1671			$P = 0.077^2$
White		59.9% (892)	64.8% (118)	
Black		24.3% (362)	15.9% (29)	
Hispanic, other		12.2% (182)	15.4% (28)	
Asian		3.6% (53)	3.8% (7)	
Performance status	1671			$P = 0.459^2$
normal, asymptomatic		70.9% (1055)	75.3% (137)	
symptomatic, ambulatory		25.4% (378)	21.4% (39)	
symptomatic, in bed		3.8% (56)	3.3% (6)	
Tumor size (cm)	1659	6.0 (5.0–8.0)	6.0 (5.0–7.0)	$P < 0.001^1$
Tumor size (cm)	1659			$P = 0.005^2$
< 5.0		15.8% (234)	22.5% (41)	
5.0–6.0		18.8% (278)	24.7% (45)	
6.0–7.5		38.9% (575)	35.2% (64)	
7.5		26.4% (390)	17.6% (32)	
FIGO stage	1671			$P = 0.102^2$
IB_2		20.0% (298)	27.5% (50)	
IIB		47.1% (702)	47.3% (86)	
IIIA		1.3% (20)	1.6% (3)	
IIIB		28.6% (426)	21.4% (39)	
IVA		2.9% (43)	2.2% (4)	
Tumor grade (differentiation)	1671			$P < 0.001^2$
well		5.5% (82)	14.3% (26)	
moderate		65.3% (972)	37.9% (69)	
poor		26.9% (400)	46.2% (84)	
not graded		2.4% (35)	1.6% (3)	
Hydronephrosis	1671			$P = 0.6^2$
none		88.9% (1324)	91.2% (166)	
unilateral		8.8% (131)	6.6% (12)	
bilateral		2.3% (34)	2.2% (4)	
Parametrial involvement	1671			$P = 0.108^2$
none		21.7% (323)	28.6% (52)	
unilateral		46.3% (689)	42.9% (78)	
bilateral		32.0% (477)	28.6% (52)	
Pelvic nodes	1671			$P = 0.033^2$
positive		10.3% (154)	15.9% (29)	

	N	squamous-cell carcinoma N = 1489	adeno- & adenosq. carcinoma N = 182	Test Statistic
negative		62.8% (935)	63.2% (115)	
unknown		26.9% (400)	20.9% (38)	

b (a–c) represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables.

N is the number of non–missing values.

Numbers after percents are frequencies.

Tests used:

[1] Wilcoxon test;

[2] Pearson test

Table 2

Treatment Regimen by Tumor Histology

	N	squamous-cell carcinoma N = 1489	Adeno/adenosquamous carcinoma N = 182
Treatment	1671		
RT		11.6% (173)	14.3% (26)
RT+5FU		8.9% (133)	12.1% (22)
RT+HU		22.9% (341)	12.1% (22)
RT+CDDP		32.6% (485)	37.4% (68)
RT+CDDP+5FU		10.4% (155)	11.5% (21)
RT+CDDP+5FU+HU		10.2% (152)	10.4% (19)
RT+CDDP+rHuEPO		3.4% (50)	2.2% (4)

RT = Radiation therapy

5FU = 5-fluorouracil

HU = hydroxyurea

CDDP = cis-diamminedichloroplatinum

rHuEPO = recombinant human erythropoietin

N is the number of non–missing values.

Numbers after percents are frequencies.

Table 3

Adjusted Rates of Morbidity for Adeno- vs. Squamous Histology

Variable	Odds ratio[*]	95% CI
Toxicity		
WBC	0.85	0.60–1.18
peripheral neuropathy	0.87	0.13–3.35
neurologic, auditory, visual	0.32	0.08–0.89
other hematologic	0.74	0.52–1.06
skin	1.00	0.56–1.68
genitourinary	0.98	0.57–1.61
lymphatic	2.15	0.29–10.24
gastrointestinal, hepatic	0.91	0.65–1.26
constitutional, fever	0.82	0.43–1.44
pulmonary	3.05	1.04–7.91
allergy, immunological	0.99	0.05–5.78
cardiovascular	1.52	0.56–3.54
other	0.84	0.47–1.43

[*] Adjusted for age, race, performance status, tumor size, stage, grade, and treatment.

Table 4

Progression-free and Overall survival Analysis of Patients with Squamous or Adeno- and Adenosquamous Carcinoma

	N	N_event	Adj. HR (PFS)	P†	N_event	Adj. HR (OS)	P†
Histology							
squamous-cell carcinoma	1489	777	referent	—	718	referent	—
adeno- & adenosq. carcinoma	182	97	1.21 (0.98–1.51)	0.083	92	1.25 (1.00–1.56)	0.0499
Age (years)	1671	874	1.00 (0.99–1.01)	0.883	810	1.00 (1.00–1.01)	0.299
Race/Ethnicity							
White	1010	530	referent	—	495	referent	—
Black	391	227	1.21 (1.03–1.42)	0.018	215	1.24 (1.05–1.46)	0.010
Hispanic, other	210	92	0.91 (0.73–1.14)	0.419	82	0.87 (0.69–1.11)	0.265
Asian	60	25	0.76 (0.50–1.15)	0.196	18	0.54 (0.33–0.88)	0.013
Performance status							
normal, asymptomatic	1192	580	referent	—	526	referent	—
symptomatic, ambulatory	417	251	1.16 (0.99–1.36)	0.061	242	1.22 (1.03–1.43)	0.019
symptomatic, in bed	62	43	1.39 (1.01–1.93)	0.046	42	1.51 (1.09–2.11)	0.014
log Tumor size (cm)	1659	874	1.32 (1.07–1.62)	0.009	810	1.28 (1.04–1.58)	0.021
FIGO stage							
IB	348	133	referent	—	113	referent	—
IIB	788	385	1.39 (1.06–1.84)	0.018	357	1.51 (1.12–2.03)	0.006
IIIA	23	17	3.47 (1.96–6.14)	< 0.001	17	4.61 (2.58–8.24)	< 0.001
IIIB	465	302	2.13 (1.59–2.85)	< 0.001	289	2.37 (1.74–3.24)	< 0.001
IVA	47	37	3.46 (2.25–5.31)	< 0.001	34	3.27 (2.08–5.15)	< 0.001
Tumor grade (differentiation)							
good	108	51	referent	—	50	referent	—
moderate	1079	552	1.11 (0.83–1.49)	0.481	507	1.04 (0.78–1.40)	0.773
poor	484	271	1.44 (1.06–1.95)	0.018	253	1.35 (0.99–1.84)	0.055

b (a–c) represent the lower 95% confidence limit a, the value b, and the upper 95% confidence limit c.

Progression-free survival (PFS) and overall survival (OS) are given in months; hazard ratios (HR) are unitless.

Tests used:

†Wald test