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Impact of tumour histology on survival in advanced cervical carcinoma: an NRG Oncology/Gynaecologic Oncology Group Study

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Background: Based primarily on studies concerning early-stage tumours (treated surgically), and locally advanced disease (treated with chemoradiation), the prognosis for women with adenocarcinoma (AC) or adenosquamous (AS) carcinoma has been reported to be poorer than those with squamous cell carcinoma (SCCA) of the cervix. It is unclear whether differences in prognosis also persist in the setting of recurrent or metastatic disease treated using chemotherapy doublets with or without bevacizumab.

Methods: Cases were pooled from three Gynaecologic Oncology Group randomised phase III trials of chemotherapy doublets. Pearson's test was used to evaluate response rate (RR) of AC/AS *vs* SCCA, Kaplan–Meier method to estimate progression-free survival (PFS) and overall survival (OS), and Cox proportional hazards model to estimate the impact of histology on PFS and OS.

Results: Of 781 evaluable patients, 77% ($N=599$) had SCCA and 23% ($N=182$) AC/AS. There were no significant differences in RRs between histologic subgroups. The adjusted hazard ratio (HR) for death for SCCA *vs* AC/AS was 1.13 (95% CI 0.93, 1.38 $P=0.23$). When comparing SC/AS ($N=661$, 85%) to AC alone ($N=120$, 15%), the adjusted HR for death was 1.23 (95% CI 0.97, 1.57, $P=0.09$).

Conclusions: AC/AS and SCCA have similar survival in recurrent or metastatic cervical carcinoma when treated with chemotherapy doublets.

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Cervical cancer remains a disease of epidemic proportions globally with 500 000 new diagnoses each year worldwide and ~250 000 deaths (Jemal *et al*, 2011). Screening through cytology with and without high-risk human papillomavirus (HPV) DNA testing has significantly reduced the burden of disease in developed countries. The annual incidence and mortality rates in England are 2900 and 1000, respectively, while in the United States, the American Cancer Society estimates that there will be 12 820 new cases and 4210 deaths in 2017 (Siegel *et al*, 2017). In Europe, cervical cancer is the sixth most common cancer among females, with nearly 55 000 new cases diagnosed annually (Jemal *et al*, 2011). As a consequence of lack of universal screening, the poorest regions of the world (i.e., in Africa, Asia, and South America) are most deeply affected (Jemal *et al*, 2011).

Interestingly, the stratified squamous epithelium of the ectocervix and transformation zone lend themselves to cytologic sampling (i.e., Pap smear), allowing for the precursor of squamous cell carcinoma (SCCA), cervical intraepithelial neoplasia 3 (CIN3), to be readily identified and treated. This has resulted in a significant decrease in SCCA over the preceding three decades. However, glandular lesions (adenocarcinoma (AC) and adenosquamous (AS) carcinoma) harboured deeper within the canal are less easily detected and comprise 25% of newly diagnosed cases today (Smith *et al*, 2000; Young and Clement, 2002; Wang *et al*, 2004; Gien *et al*, 2010; Galic *et al*, 2012).

Despite distinct HPV aetiologic subtypes, genetic aberrations, and histologic features of SCCA and AC/AS, divergence of therapy is not predicated on histology. While early-stage, lymph node-negative carcinomas of either histologic class (FIGO stage I-IB_1) can be cleared by radical hysterectomy with lymphadenectomy, data are conflicting for locally advanced cervical AC/AS (FIGO stage IB_2-IVA) in terms of susceptibility to eradication using conventional multimodality therapy (i.e., chemoradiation + brachytherapy). Relative radioresistance as evidenced by lower response rates (RRs), increased time to response and significantly decreased overall survival (OS) of AC/AS compared with SCCA has been reported previously (Katanyoo *et al*, 2012; Rose *et al*, 2014).

When considering recurrent or persistent disease that cannot be resected and metastatic cervical carcinoma (FIGO stage IVB), the prognostic impact of histology is more problematic as this is a population for which treatment is essentially palliative, with cures being remote and/or near impossible. Chemotherapy doublets (primarily platinum based) constituted the standard of care until 2013 when it was reported that based on a second interim analysis, Gynaecologic Oncology Group (GOG) protocol 240 met one of its primary end points. The incorporation of bevacizumab, an antiangiogenic drug, with either a cisplatin–paclitaxel or topotecan–paclitaxel chemotherapy backbone significantly improved OS by 3.7 months (hazard ratio (HR) 0.71; 97% CI: 0.54, 0.94; $P = 0.0035$) (Tewari *et al*, 2014). The integration of antiangiogenesis therapy in this high risk poor prognostic population also led to statistically significant improvements in progression-free survival (PFS) and RR (Tewari *et al*, 2014). According to analyses of patient-reported outcomes using three previously validated instruments, these clinical benefits were not accompanied by a significant deterioration in health-related quality of life (Penson *et al*, 2015).

The GOG 240 results led first to United Kingdom Cancer Drug Fund approval of bevacizumab for women in England with advanced cervical cancer on 5 March 2014, and then to US FDA approval of both bevacizumab-containing triplet regimens on 14 August 2014. This was followed by Swissmedic approval of bevacizumab for cervical cancer on 22 December 2014, a Positive Opinion of GOG 240 issued by the Committee for Medicinal Products for Human Use on 27 February 2015, and finally European Medicines Agency approval for the European Union on 8 April 2015. Recently, the results of the protocol-specified analysis of OS confirmed a statistically significant survival benefit conferred by bevacizumab with extended follow-up (Tewari *et al*, 2017).

As a tertiary objective, GOG 240 prospectively validated the use of the Moore scoring criteria based on pooled clinical factors identified in prior phase III randomised trials led by the GOG in this patient population (Moore *et al*, 2010; Tewari *et al*, 2015). Importantly, tumour histology is not included in the Moore criteria, and in an analysis of GOG 240 prognostic factors, the benefit conferred by bevacizumab was not detected in AC/AS (Tewari *et al*, 2014). However, these histologies were found in only 27% of the study population and therefore GOG 240 was underpowered to draw any definitive conclusions concerning efficacy or lack thereof in AC/AS.

These observations led to two important questions. Specifically, does the difference in prognosis between SCCA and AC/AS previously reported in various studies of early-stage tumours and locally advanced disease apply to women struggling with advanced (i.e., recurrent or metastatic) disease? In other words, is survival following treatment with chemotherapy doublets different for SCCA and AC/AS? A second question was whether bevacizumab should be offered to women with AC/AS given the potential for improved OS despite the apparent lack of efficacy in GOG protocol 240 (underpowered for AC/AS) and known side effect profile of the drug (e.g., 8.6% fistula). While there was no clear way to directly address the second question, we approached the first question by increasing the sample size of advanced AC/AS to test our hypothesis that the behaviour of these histologic entities (i.e., SCCA vs AC/AS) in terms of survival parameters governing systemic therapy comprised of chemotherapy doublets would not differ.

MATERIALS AND METHODS

Cases were pooled from GOG phase III randomised trials in recurrent or persistent and metastatic cervical carcinoma, which permitted enrolment of patients with AC/AS histology. Each study was approved by the National Cancer Institute Central Institutional Review Board as well as the individual participating institutional local review boards and every patient provided written consent to these trials (Long *et al*, 2005; Monk *et al*, 2009; Tewari *et al*, 2014). This ancillary data study was approved by the GOG.

Eligibility. Patients with histologically confirmed advanced (stage IVB), recurrent, or persistent SCCA, AC, and AS carcinomas of the uterine cervix enrolled in the GOG Protocols 0179 (combination arm only), 0204 (all arms), and 0240 (non-bevacizumab arms) were included in this ancillary analysis of patients treated with platinum-based and non-platinum-based chemotherapy doublets. Patients receiving bevacizumab and those treated with single-agent cisplatin were excluded for purposes of this analysis, which was designed to evaluate survival of SCCA and AC/AS following treatment with chemotherapy doublets only.

The trial eligibility and exclusions for these three protocols have been previously reported (Long *et al*, 2005; Monk *et al*, 2009; Tewari *et al*, 2014). In brief, inclusion criteria were limited to stage IVB, recurrent or persistent cervical carcinoma with measurable disease and a performance status of 0, 1 (GOG 0204, 240) or 0, 1, or 2 (0179). Patients with previous chemotherapy for recurrence, concurrent or past malignancy, bilateral hydronephrosis unresolved with ureteral stents or percutaneous nephrostomy, and craniospinal metastatic disease were ineligible. All patients had to have measureable disease and all cases underwent GOG Pathology Committee review to assign histology.

Table 1. Clinical characteristics and response rates for the primary objective (SC *vs* AC + AS) and for the secondary objective (SC + AS *vs* AC)

	N	Primary objective			Secondary objective		
		SC N = *599(%)*	AC + AS N = *182 (%)*	*P*-value	SC + AS *N* = *661 (%)*	AC *N* = *120 (%)*	*P*-value
BMI (kg m^{-2})	779	26.6	27.7	0.13	26.7	27.8	0.20
Age (years)	781	46.6	48.0	0.31	46.5	49.6	0.03
Race/ethnicity	781			0.006			0.04
White		63.6	74.7		65.1	72.5	
Black		18.7	9.3		17.7	10.0	
Hispanic		13.7	9.3		13.2	10.0	
Asian		2.3	4.4		2.3	5.8	
Other		1.7	2.2		1.8	1.7	
Performance status	781			0.67			0.49
0		52.3	55.5		52.2	57.5	
1		46.1	43.4		46.1	41.7	
2		1.7	1.1		1.7	0.8	
Disease status	781			0.98			0.17
FIGO IVB		15.9	15.9		16.6	11.7	
Recurrent/persistent		84.1	84.1		83.4	88.3	
Tumour grade	781			<0.001			<0.001
Well (G1)		2.2	18.1		2.1	26.7	
Moderate (G2)		54.6	36.6		51.6	44.2	
Poor (G3)		42.2	42.9		45.2	26.7	
Ungraded		1.0	2.2		1.1	2.5	
GOG Protocol	781			<0.001			0.005
0179 Topotecan/cisplatin		21.2	10.4		20.0	11.7	
0204 All arms		55.1	53.3		55.4	50.8	
0240 No anti-VEGF		23.7	36.3		24.7	37.5	
Recurrence	781			0.80			0.64
No		17.9	17.9		17.4	19.2	
Yes		82.1	83.0		82.6	80.8	
Best response	781			0.07			0.065
Complete response		6.2	3.3		5.7	4.2	
Partial response		20.7	30.2		21.9	28.3	
Stable disease		46.4	44.0		45.8	45.8	
Progressive disease		19.5	17.0		19.7	15.0	
Not evaluable		7.2	5.5		6.8	6.7	

Abbreviations: AC + AS = adenocarcinoma plus adenosquamous carcinoma; BMI = body mass index; FIGO = International Federation of Gynaecology and Obstetrics; GOG = Gynaecologic Oncology Group; SC = squamous cell carcinoma; VEGF = vascular endothelial growth factor.

Treatment. While chemotherapy administration on the GOG 0179 combination arm included topotecan 0.75 mg m^{-2} intravenously on days 1, 2, and 3, followed by cisplatin 50 mg m^{-2} on day 1 every 3 weeks (Long *et al*, 2005), GOG 0204 was a trial of four cisplatin-containing doublet combinations (Monk *et al*, 2009). Patients on GOG 0204 received one of the following: paclitaxel 135 mg m^{-2} over 24 hours on day 1 and cisplatin 50 mg m^{-2} on day 2 every 3 weeks; vinorelbine 30 mg m^{-2} on days 1 and 8 + cisplatin 50 mg m^{-2} on day 1 every 3 weeks; gemcitabine 1000 mg m^{-2} on days 1 and 8 + cisplatin 50 mg m^{-2} on day 1 every 3 weeks; or topotecan 0.75 mg m^{-2} intravenously on days 1, 2, and 3, followed by cisplatin 50 mg m^{-2} on day 1 every 3 weeks (Monk *et al*, 2009).

Gynaecologic Oncology Group 0240 was a phase III trial of the incorporation of bevacizumab in advanced cervical cancer. As stated above, for purposes of our analysis, we included only the non-bevacizumab arms of this trial. Thus, patients received one of the following regimens: paclitaxel 135 or 175 mg m^{-2} + cisplatin 50 mg m^{-2} or paclitaxel 175 mg m^{-2} on day 1 and topotecan 0.75 mg m^{-2} intravenously days 1, 2, and 3 (Tewari *et al*, 2014).

Statistical considerations. The data abstracted included patient demographics, clinicopathologic features, chemotherapy regimens, and survival outcomes. Binary exchange analysis was performed to estimate OS and PFS for the primary objective comparing SCCA cases to all glandular cases, and for the secondary objective in which all squamous-containing histology (SCCA + AS) cases were compared with AC alone. An exploratory analysis was also undertaken to determine differences in survival of AC *vs* AS carcinoma.

Categorical variables were compared among the histology groups by the Pearson's χ^2 test and continuous variables by the Kruskal–Wallis test (Pearson, 1900; Kruskal and Wallis, 1952). Survival was estimated using the Kaplan–Meier method (Kaplan and Meier, 1958). The Cox proportional hazards model was used to evaluate independent prognostic factors (body mass index, age, race/ethnicity, performance status, disease status, and tumour grade) and to estimate their covariate-adjusted effects on PFS and OS (Cox, 1972). A correction for multiplicity of comparisons was made and nonlinearity of the effect of continuous variables was assessed using restricted cubic splines (Molinari *et al*, 2001). All statistical tests were two-tailed with the significance level set at $\alpha = 0.05$. We estimated from the known histologic distribution in the three studies that we would have roughly 80% power to detect a 20% difference in the hazard of death between different histologic groups in the primary objective. Statistical analyses were performed using the R programming language and environment (R Core Team, 2013).

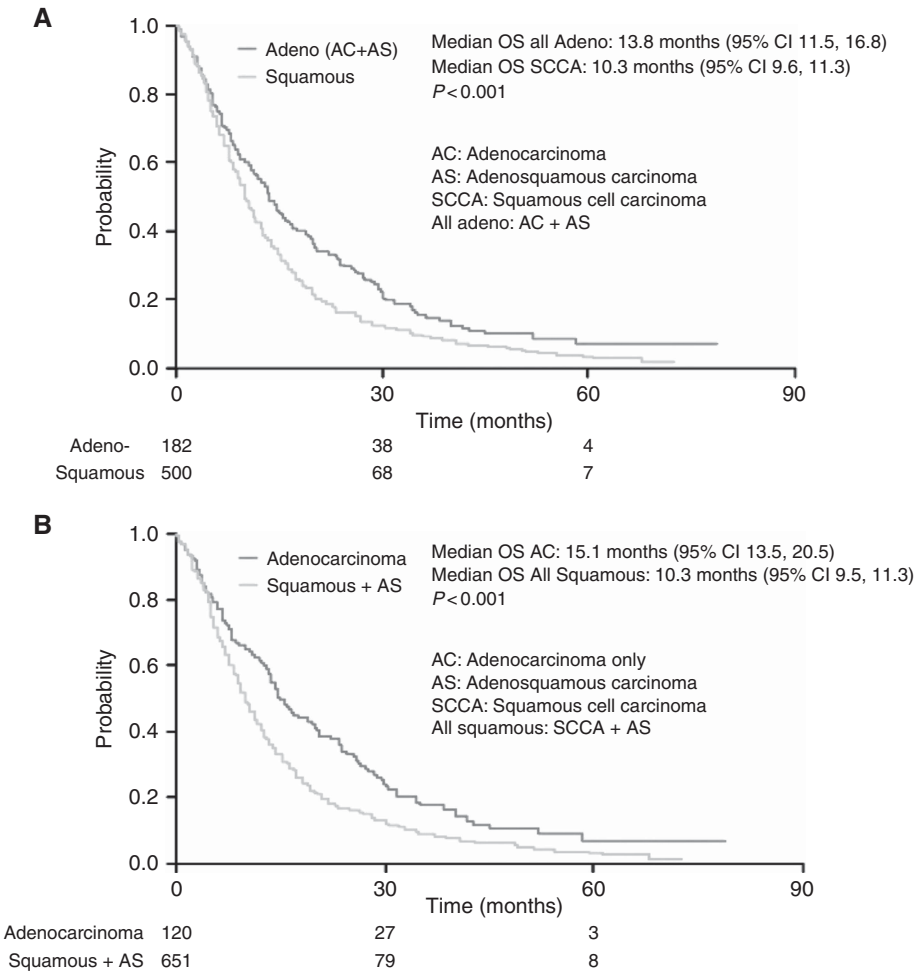

Figure 1. Kaplan–Meier curves of overall survival. (**A**) Primary objective (SCCA *vs* AC + AS carcinoma) and (**B**) secondary objective (SCCA + AS *vs* AC).

RESULTS

Seven hundred and eighty-one patients from GOG 0179, 0204, and 0240 met the inclusion criteria. Approximately 77% ($n = 599$) had SCCA, while the remaining 23% of patients ($n = 182$) had AC or AS carcinoma. The similarity of SCCA compared to all AC or AS patients regarding clinical-pathological characteristics, recurrence, and RRs are summarised in Table 1.

The median PFS for the SCCA patients compared to the AC + AS groups is 4.8 months (95% CI: 4.6, 5.3 months) *vs* 5.7 months (95% CI: 4.8, 7.1 months), $P = 0.27$, respectively, while the median OS is 10.3 months (95% CI: 9.6, 11.3 months) *vs* 13.8 months (95% CI: 11.5, 16.8 months), $P < 0.001$. The Kaplan–Meier curve for OS appears in Figure 1A.

Although on univariate analysis it appears that patients with glandular cancers experienced significantly improved OS compared to those with SCCA, this effect disappeared on multivariate analysis when the comparison is adjusted by other factors. Cox proportional hazards modelling demonstrates that SCCA had similar survival compared to AC or AS. While the adjusted hazard ratio (aHR) for disease progression in SCCA patients was 0.93 (95% CI: 0.77, 1.12, $P = 0.43$), the adjusted HR for death in SCCA patients was 1.13 (95% CI: 0.93, 1.38, $P = 0.23$). The Supplementary Table depicts the multivariate analysis for multiple prognostic factors.

In the secondary objective, all squamous cell-containing histology (SCCA and AS, $N = 661$; 85%) were compared to AC alone ($N = 120$; 15%). The clinical-pathological characteristics, recurrence, and RRs are also summarised in Table 1. The Kaplan–Meier curve for OS appears in Figure 1B. Similar to what was observed with our primary objective, the binary exchange analysis combining SCCA and AS did not show significant improvement in OS compared to AC alone on multivariate analysis (HR death 1.23, 95% CI: 0.97, 1.57, $P = 0.093$). The multivariate analysis of multiple prognostic factors also appears in the Supplementary Table.

Finally, we explored OS in patients with AC ($N = 120$; 66%) and compared them to those with AS ($N = 62$; 34%). The median PFS for the AC and AS groups is 6.4 months (95% CI: 5.2, 8.0) and 4.4 months (95% CI: 3.9, 6.4), respectively, log-rank test $P = 0.06$. The median OS for the AC and AS groups is 15.1 months (95% CI: 13.5, 20.5) and 10.1 months (95% CI: 8.5, 15.2), respectively, log-rank test, $P = 0.09$. On multivariate analysis, there was also no difference in survival (aHR death 1.19, 95% CI: 0.81, 1.74, $P = 0.38$).

DISCUSSION

Although the impact of histology on survival in recurrent or persistent and metastatic (stage IVB) cervical cancer has not been previously addressed in the literature, our analyses suggest that response to systemic therapy and survival rates following treatment with chemotherapy doublets in this population are not different for SCCA and AC/AS carcinoma. Furthermore, when 'squamous' tumours were combined (i.e., SCCA + AS) and compared with

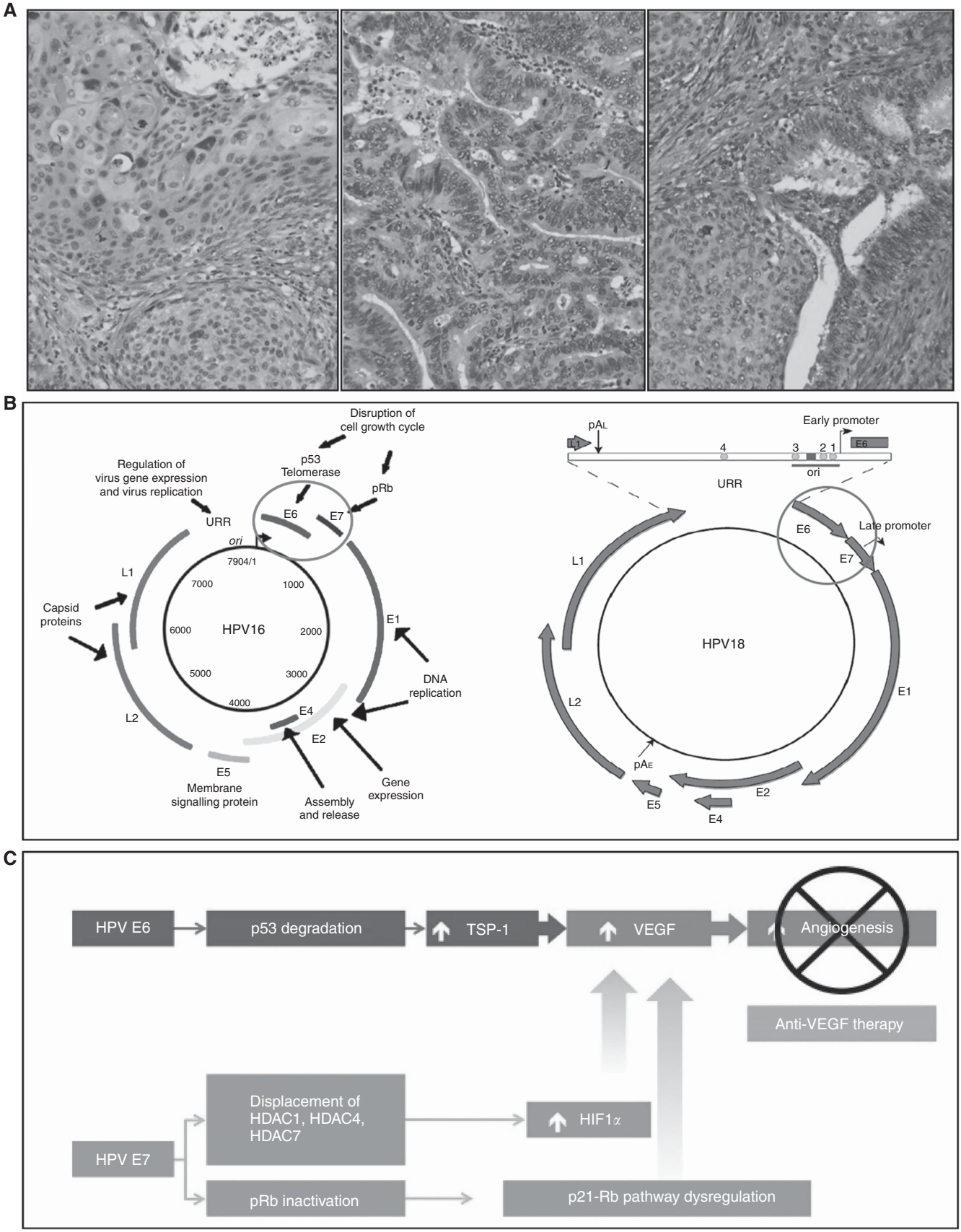

Figure 2. Squamous cell carcinoma *vs* AC *vs* AS of the uterine cervix: different diseases? (**A**) Histologic appearance of SCCA (left), AC (centre), and AS (right). (**B**) Human papillomavirus 16 genome (left) and HPV 18 genome (right). (**C**) Proposed molecular cascade through which tumour hypoxia and HPV oncogenes *E6* and *E7* drive angiogenesis.

Table 2. Molecular aberrations between SCCAs and ACs of the uterine cervix

Validated mutations detected by histologic subtype[a]				
Gene	**Total, N = *80***	**SCCA, N = *40***	**AC, N = *40***	***P*-value**
Any *KRAS* mutation	7 (8.8)	0 (0.0)	7 (17.5)	0.001
G12A	1 (1.3)	0 (0.0)	1 (2.5)	
G12D	3 (3.8)	0 (0.0)	3 (7.5)	
G12V	2 (2.5)	0 (0.0)	2 (5.0)	
G13D	1 (1.3)	0 (0.0)	1 (2.5)	

Recurrent somatic mutations in cervical carcinomas[b]							
Gene	**Non-silent mutation**	**Relative frequency (%)**	**Patients**	**Unique sites**	**Silent mutation**	**Indel + null**	***q*-value**
SCCA (*N* = 79)							
FBXW7	12	15	12	8	0	2	4.03E − 12
PIK3CA	11	14	10	5	0	1	< 9.08e − 12
MAPK1	6	8	6	3	0	0	0.000671
HLA-B	7	9	6	7	1	3	0.00169
STK11	3	4	2	2	0	1	0.012
EP300	13	16	12	13	1	4	0.354
NFE212	3	4	3	2	0	0	0.0597
PTEN	5	6	5	5	0	3	0.0693
AC (*N* = 24)							
ELF3	3	13	3	3	0	3	0.03
CBFB	2	85	2	2	0	1	00342

Abbreviations: AC = adenocarcinoma; SCCA = squamous cell carcinoma.
[a]Adapted with permission from: Wright AA, *et al. Cancer* 2013; 119: 3776–3783.
[b]Adapted with permission from: Ojesina AI, *et al. Nature* 2014; 506: 371–375.

pure glandular lesions (i.e., AC), survival was not significantly different. Finally, our study suggests that advanced cervical AC behaves clinically analogous to advanced cervical AS when treated with chemotherapy doublets.

Molecular, pathologic, and some clinical evidence, however, supports the contention that despite having many shared risk factors, including high-risk HPV infection (Silcocks *et al*, 1987; Green *et al*, 2003; Berrington de Gonzalez *et al*, 2004), AC/AS and SCCA of the cervix are two different diseases (Figure 2A). There appears to be a higher prevalence of HPV subtype 18 infection in AC compared with SCCA (Figure 2B) (Fujiwara *et al*, 2014). In addition, the development of SCCA appears to be driven primarily by HPV 16 and a wider diversity of the relatively uncommon oncogenic HPV subtypes (Figure 2B). Of particular relevance is that both HPV 16 and 18 genomes contain the *E6* and *E7* oncogenes, which have downstream effects on a final common pathway towards virally mediated tumour angiogenesis (Figure 2C). Other epidemiologic differences include smoking (strongly implicated in SCCA *vs* AC) as well as nulliparity and obesity (more commonly seen in ACs) (Fujiwara *et al*, 2014).

A systematic molecular analysis of cervical cancers has shown that ACs ($n = 40$) have distinct oncogenic mutations compared to SCCA ($n = 40$) (Table 2) (Wright *et al*, 2013). In particular, *KRAS* mutations are observed only in ACs (17.5 AC *vs* 0% SCCA, $P = 0.01$) and *EGFR* mutations are not detected (0 AC *vs* 7.5% SCCA, $P = 0.24$). In another report, the molecular profiles of 79 SCCA and 24 ACs were considered (Table 2) (Ojesina *et al*, 2014). In addition to uncovering new genomic alterations in SCCA *(E1A binding protein p300, F-box and WD repeat domain containing 7, major histocompatibility complex, class I, B, mitogen-activated protein kinase 1, nuclear factor, erythroid 2-like 2)*, two genes with somatic mutations observed only in ACs were identified, *E74-like factor 3* and *core-binding factor, β-subunit* at a frequency of 13% and 8%, respectively.

The molecular data reviewed above further highlight differences between AC and SCCA and suggests possibly new targets for combating cervical cancer. However, before our current analyses, it was unknown if histologic subtype impacts clinical outcomes following chemotherapy treatment for recurrent or persistent or metastatic disease. The pooled data of three large phase III randomised trials in this high-risk cervical cancer population were obtained from the reliable, prospectively maintained GOG database. The analyses are unique as such a large cohort of AC/AS is not likely to be obtainable anywhere else in the world. Accordingly, given that the existing literature on tumour histology as an independent prognostic factor in cervical cancer has focused on early-stage and locally advanced disease, our study fills an important void that some investigators would be surprised to find still exists despite years of study.

Based on subsequent studies by the GOG, including the phase II trial of bevacizumab monotherapy in which single agent activity in heavily pre-treated, recurrent cervical cancer was reported (GOG 227C; Monk *et al*, 2009) and the previously discussed randomised phase III trial of chemotherapy doublets with and without bevacizumab (GOG 240; Tewari *et al*, 2014), the standard of care for advanced cervical cancer has shifted from chemotherapy doublets alone to chemotherapy doublets + bevacizumab. In point of fact, both triplet regimens studied in GOG 240 (i.e., cisplatin–paclitaxel–bevacizumab and topotecan–paclitaxel–bevacizumab) are listed as Category 1 in the National Comprehensive Cancer Network Cervical Cancer Treatment Guidelines. In GOG 240 the survival impact conferred by bevacizumab was not observed in AC, either due to underpowering of AC cases or reduced activity of bevacizumab in cervical AC or both. The question on the table is whether anti-vascular endothelial growth factor (VEGF) therapy can improve survival in women with advanced cervical AC/AS. Although our analyses suggest that SCCA and AC/AS behave similarly when treated with chemotherapy doublets, it is not possible from these data to infer any equivalence of activity of antiangiogenesis therapy between advanced cervical SCCA and AC/AS.

Table 3. Activity of bevacizumab in non-cervix adenocarcinoma

Author	Disease	Regimens	PFS	OS
Hurwitz *et al*	Colorectal ECOG PS 0–1 First line Metastatic	ILF + placebo	6.2 m	15.2 m
		ILF + Bev	10.6 m HR 0.54; 95% CI: 0.45, 0.66	23.8 m HR 0.66; 95% CI: 0.54, 0.81
Sandler *et al*	Non-SCCA NSCLC ECOG PS 0–1 First line, met Loc adv, recur	Carb/Pac + placebo	4.8 m	10.3 m
		Carb/Pac + Bev	6.4 m HR 0.65; 95% CI: 0.56, 0.76	12.3 m HR 0.80; 95% CI: 0.69, 0.93
Miller *et al*	Breast ECOG PS 0–1 Loc recur, met	Pac + placebo	5.8 m	24.8 m
		Pac + Bev	11.4 m HR 0.42; 95% CI: 0.34, 0.52	26.5 m HR 0.87; 95% CI: 0.72, 1.05
Burger *et al*	Ovary GOG PS 0–2 First line FIGO stage III/IV	CP + placebo – placebo	10.3 m	39.3 m
		CP + Bev – placebo CP + Bev – Bev	11.2 m 14.1 m HR 0.717; 95% CI: 0.63, 0.82	38.7 m 39.7 m HR 0.915; 95% CI: 0.73, 1.15

Abbreviations: Bev = bevacizumab; Carb or C = carboplatin; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; GOG = Gynaecologic Oncology Group; HR = hazard ratio; ILF = irinotecan, fluorouracil, and leucovorin; m = months; non-SCCA NSCLC = non-squamous cell carcinoma non-small-cell lung cancer; OS = overall survival; Pac or P = paclitaxel; PFS = progression-free survival; PS = performance status.

These data do allow for some speculation concerning the incorporation of antiangiogenesis therapy for advanced cervical AC/AS. Not only are RRs and survival similar between advanced cervical SCCA and AC/AS treated with systemic therapy (specifically, chemotherapy doublets), but the molecular aberrations in predominantly HPV16-driven cervical SCCA and the predominantly HPV 18-induced cervical AC/AS both favour a proangiogenic tumour environment. Although the biologic rationale for targeting the VEGF-dependent angiogenesis pathway in cervical cancer is complex, a mechanistic rationale has been proposed (Eskander and Tewari, 2014). The HPV *E6* and *E7* oncogenes affect downstream angiogenic pathways. E6 mediates p53 degradation with subsequent increase in thrombospondin-1 leading to increase in VEGF and thus promotion of angiogenesis (Figure 2C). Human papillomavirus E7 inactivates pRb causing p21-Rb pathway dysregulation triggering VEGF production. Additionally, E7 displaces HDAC1 (histone deacetylase), HDAC4, and HDAC7 initiating a cascade that increases hypoxia-inducible factor 1α (Figure 2C). A rationale that cervical SCCA and AC/AS will have a similar response to VEGF inhibition is supported by both tumour histologies being driven by viral E6/E7 with induction of the VEGF-dependent tumour angiogenesis.

Tumours of similar histology arising in different organs appear to respond to similar therapy. Examples of this phenomenon are found in the response of malignant germ cell tumours of the testis and ovary to the bleomycin–etoposide–cisplatin regimen (Mann *et al*, 1989) as well as the reported efficacy of the cisplatin–etoposide doublet in small-cell carcinoma of the lung and cervix (Hoskins *et al*, 2003). In point of fact, the demonstrable activity of bevacizumab in other ACs including colorectal, lung, breast, and ovarian cancer provides support for consideration of bevacizumab efficacy in AC of the cervix (Table 3) (Hurwitz *et al*, 2004; Sandler *et al*, 2006; Miller *et al*, 2007; Burger *et al*, 2011). It is noteworthy that because of concerns for catastrophic pulmonary haemorrhage associated with centrally located SCCA lung tumours, bevacizumab is only approved by the US FDA for ACs of the lung.

It should be emphasised that our data concerning the response and survival associated with chemotherapy doublets has not been prospectively validated. Given the relative infrequency of glandular tumours of the cervix and the change in standard of care from chemotherapy doublets to bevacizumab-containing triplet therapy, a clinical trial to answer this question may not be feasible. Ultimately, the emergence of validated predictive biomarkers for targeted therapy will determine whether SCCA and AC/AS should be treated with different drugs, particularly those that may be governed by SCCA- and/or AC/AS-specific mutations. In this regard, treatment algorithms for SCCA and AC/AS are likely to diverge. However, given the wide net cast by antiangiogenesis therapy, including its activity in the tumour microenvironment, until distinct histologic-driven therapies emerge, patients with recurrent or persistent and metastatic cervical AC/AS should be counselled regarding the known toxicities of anti-VEGF therapy and lack of proven efficacy against AC of the cervix, balanced with the potential benefits, which may include a significant survival advantage.

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CONFLICT OF INTEREST

All the authors cite no relevant conflicts of interest related to this manuscript, except as noted below: Dr(s) Tewari (study chair/principal investigator for GOG 240), Penson (quality of life chair for GOG 240), Oaknin (Spain chair through GEICO for GOG 240), and Monk (senior author of GOG 240 and chair of the Cervix Cancer Committee of the NRG Oncology Cooperative Group and co-chair of the Gynaecologic Cancer Intergroup) were members of the scientific steering committee that conducted GOG 240. To participate in the regulatory discussions through which bevacizumab could potentially be approved for women struggling with advanced cervical cancer, these authors as well as author Eisenhauer participated on 1-2 advisory boards held by Roche/Genentech. Monk, Penson, and Tewari subsequently joined the Roche/Genentech speaker's bureau to help review appropriate patient selection and management of bevacizumab-related adverse events with the oncology community. The institutions where Monk, Oaknin, and Tewari practice have contracted research grants with Roche/Genentech to conduct trials evaluating the anti-PD-L1 agent, atezolizumab. Roche/Genentech contracted research with institution: Monk, Oaknin, Tewari; Roche/Genentech Advisory Boards participation: Monk, Penson, Eisehauer, Tewari; Roche/Genentech Speaker's Bureau: Monk, Penson, Tewari.

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