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The prognostic significance of histologic type in early stage cervical cancer – A multi-institutional study

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HIGHLIGHTS

- Historically, cervical adenocarcinomas (ADC) have been viewed as more aggressive than squamous cell carcinoma (SCC).
- Overall, ADC's tended to be smaller tumors at diagnosis but higher grade and stage when compared to corresponding SCCs.
- Comparing early stage disease ADC and SCC suggests that these patients have equivalent recurrence risk and overall survival.

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ABSTRACT

Background. Cervical adenocarcinomas (ADC) have been viewed as more aggressive than squamous cell carcinoma (SCC). We analyzed an international cohort of early stage cervical cancer to determine the impact of histologic type.

Methods. Retrospective analysis of patients with SCC (148 patients) and ADC (130 patients) stages IA1-IB2 who underwent surgery at our three institutions (two from Detroit, one from Mexico) from 2000–2010 was performed for: age, stage, tumor size, lymphovascular invasion (LVI), invasion depth, lymph node status (LN), recurrence and survival. Pathologic review proceeded inclusion.

Results. In the Latino population, ADC's tended to be higher grade ($p = 0.01$), while SCC's were larger with deeper invasion ($p < 0.001$). LVI and LN were not significantly different. Recurrence rate (RR) was 8% (8/101) in ADC and 11.8% (9/76) in SCCs. 5 year survival (OS) was equivalent (98.2% and 95.2% for ADC and SCC respectively, $p = 0.369$). In the Detroit cohort, we noted no difference in size, grade, depth of invasion, LVI, LN. RR was 8/72 (13.7%) for SCC and 4/29 (13.7%) but not statistically different between the tumor types ($p = 0.5$). 5 year survival was 91% and 92% for ADC and SCC, respectively. In this population 33% of the patients with SCC and 34% of the patients with ADC received adjuvant chemo-radiation ($p = 0.4$). Histologic type demonstrated no significant outcome difference for any type of adjuvant therapy.

Conclusion. Comparing early stage disease cervical ADC and SCC suggests equivalent recurrence and survival. Therefore, the paradigm of more aggressive management of early stage cervical ADC warrants further investigation.

Introduction

Approximately 580,000 cases of cervical cancer are diagnosed worldwide each year. In the United States ~12,400 new cases are diagnosed with ~4,000 disease related deaths [1]. Squamous cell carcinoma (SCC) accounts for 65–85% of all diagnosed cancers with

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adenocarcinoma (ADC) accounting for ~15–25%. ADC has increased in incidence over the last ten years in some estimation by as much as 32% [2–5]. Historically, ADC of the cervix is viewed as more aggressive in nature than corresponding SCC; however, active debate continues with studies, large and small, both affirming and arguing against this contention. These studies have generally been limited either in regional or institutional scope [6–12]. In addition, few studies have examined the outcome of patients after hysterectomy in this patient population. Many institutions continue to treat early stage ADC based on the supposition of worse outcomes. Adjuvant therapies, such as chemoradiation, are often associated with significant morbidity. Therefore, we undertook to study, in two different patient populations, the importance of histologic cervical cancer type, specifically SCC versus ADC, in early surgically staged cervical cancer.

Methods

Patients from 2000–2010 from three inner city academic institutions (Mexican Oncology Hospital, Mexico City, Mexico; Karmanos Cancer Center, Detroit MI; and Henry Ford Hospital, Detroit, MI) who had undergone surgery for clinical stage IA1-IB2 SCC or ADC of the cervix were eligible for inclusion in the present study. All pathology slides were reviewed and diagnosis of adenocarcinoma and squamous cell carcinoma were confirmed by a GYN Pathologist prior to inclusion in the study; all cases of adenocarcinoma and squamous cell carcinoma *in situ* were excluded. Pathologic variables – including stage, grade, presence of lymphovascular invasion (LVI), tumor size (greatest diameter), depth of invasion, lymph node involvement were abstracted from the Pathology records as determined by the original GYN pathologist who reviewed the case and also reevaluated prior to inclusion in the current study by a GYN Pathologist. Clinical and demographic variables – including age, recurrence, survival and treatment modalities – were abstracted from the clinical charts as well as Pathology records where applicable. Categorical variables were analyzed by chi square and continuous variables with one-way ANOVA and t-test analysis. Overall survival (OS) and recurrence free survival (RFS) were analyzed via Kaplan Meier (KM) analysis. All analyses were performed utilizing the Statistical Software Package for Social Sciences Version 21.0 (SPSS/PASW, Inc. Chicago, IL). Patient cohorts were analyzed both individually by hospital/regional site and as a unified study cohort.

Results

278 patients were included in the present study. Specifically, 148 patients with SCC and 130 patients with ADC were analyzed. 101 patients were included from the two Detroit, MI hospitals and 177 patients from the Mexican Oncology hospital (see Tables 1 and 2). Initially, the Mexican cohort was examined independently. The majority of the patients included stage IB1 (71% vs. 95% SCC vs. ADC). While ADC's tended to be higher grade than SCC (31% G3 vs. 6%, $p = 0.01$), SCCs tended to be larger on diagnosis (2.81 vs. 2.05, $p < 0.0001$) and more invasive (1.45 vs. 1.4, $p = 0.01$). There was no significant difference between SCC and ADC for lymph node involvement (17% vs. 16%) or LVI (22% vs. 25%). When the clinical data was reviewed, the follow-up for both ADC and SCC was five years with similar outcomes for both recurrence (8% vs. 11.8%) and survival (two deaths vs. four) with mean OS about 8.88 years ($p > 0.5$) and mean RFS 8.3 years for ADC and 7.5 years for SCC ($p = 0.783$) with five year OS >95% and five year RFS >90% for both histologic types, (see Fig. 1). While there was no difference in clinical outcomes, the ADC patients received significantly more adjuvant chemoradiation than their SCC counterparts (71% vs. 17%, $p = 0.001$). As this adjuvant therapy may have biased the clinical outcomes, we then explored an additional patient population in Detroit, MI. In the Detroit cohort there was no significant difference

Table 1
Comparison of Mexican and Detroit Cohorts by Cervical Carcinoma Type.

	Mexican Cohort			Detroit Cohort		
	Adenocarcinoma (n = 101)	Squamous (n = 76)	p-value	Adenocarcinoma (n = 29)	Squamous (n = 72)	p-value
Age (median)	51 (35–75)	51 (22–86)	NS	42 (30–63)	42 (27–70)	NS
Stage			NS			NS
IA1	3 (3%)	13 (17.1%)		0 (0%)	8 (11.1%)	
IA2	1 (1%)	0 (0%)		3 (10.3%)	5 (6.9%)	
IB1	96 (95%)	54 (71%)		25 (86.2%)	47 (65.3%)	
IB2	1 (1%)	9 (11.9%)		1 (3.4%)	12 (16.7%)	
Lymph node status			NS			NS
Positive	16 (15.8%)	13 (17.1%)		4 (13.8%)	17 (23.6%)	
Negative	85 (84.2%)	63 (82.9%)		25 (86.2%)	47 (65.3%)	
Not Performed	-	-		-	8 (11.1%)	
Grade			p = 0.01			NS
1	19 (18.8%)	26 (34.2%)		6 (19.4%)	7 (9.7%)	
2	50 (49.5%)	45 (59.2%)		13 (41.9%)	41 (57.0%)	
3	32 (31.7%)	5 (6.6%)		6 (25.8%)	16 (22.2%)	
Not mentioned in Path report				4 (12.9%)	8 (11.1%)	
LVI			NS			NS
Positive	26 (25.7%)	17 (22.4%)		10 (34.5%)	35 (48%)	
Negative	75 (74.3%)	59 (77.6%)		19 (65.5%)	37 (52%)	
Tumor largest diameter (mean cm)	2.05 (1–4)	2.81 (1–6)	p < 0.0001	2.48 (0–7)	2.61 (0–13)	NS
Invasion depth (mean cm)	1.4 (0.3–1.9)	1.45 (0–2.4)	p = 0.01	0.98 (0–3.0)	0.95 (0–3.5)	NS
Treatment			p = 0.001			NS
Radical hysterectomy/BSO/PLND	29 (28.7%)	65 (82.7%)		19 (65.5%)	48 (66.7%)	
Radical hysterectomy/BSO/PLND + RT	72 (71.3%)	11 (17.3%)		10 (34.5%)	24 (33.3%)	
Recurrence			NS			NS
Yes	8 (8.0%)	9 (11.8%)		4 (13.7%)	8 (11.1%)	
No	92 (91.1%)	67 (88.2%)		25 (86.3%)	64 (87.5%)	
Missing	1 (0.9%)	-		-	-	
Survival (overall)			NS			NS
Alive	94 (93.1%)	66 (86.8%)		26 (89.7%)	62 (86.1%)	
Alive with disease	4 (4.0%)	6 (7.9%)		-	2 (2.8%)	
Dead	2 (2.0%)	4 (5.3%)		3 (10.3%)	8 (11.1%)	
Missing	1 (0.9%)	-		-	-	
Follow-up (median in years)	5 (1–9)	5 (2–9)	NS	5 .1(1–11)	5.8 (1–16)	NS