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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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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.

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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 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

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(Surveillance, Epidemiology, and End Results) database study from 1988 to 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 chi-square 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 covariate-adjusted 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 $\alpha = 0.0499$. 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