RESEARCH ARTICLE

Lack of any Impact of Histopathology Type on Prognosis in Patients with Early-Stage Adenocarcinoma and Squamous Cell Carcinoma of the Uterine Cervix

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Abstract

Background: The aim of this study was to evaluate the prognosis of patients with stage IA-IIB cervical carcinoma and to investigate a possible correlation of histology with prognosis. Materials and Methods: Two hundred fifty one patients with adenocarcinoma and squamous cell carcinoma (SCC) histology for FIGO (International Federation of Gynecology and Obstetrics) stage IA-IIB uterine cervical carcinomas at the Radiation Oncology Clinic of GH Okmeydanı Training and Research Hospital between January 1996 and December 2006 were selected, analyzed retrospectively and evaluated in terms of general characteristics and survival. Disease-free survival (DFS) and overall survival (OS) was calculated using the Kaplan-Meier method and differences were compared with the log-rank test. Multivariate analysis using a Cox-proportional hazards model was used to adjust for prognostic factors and to estimate hazard ratio (HR) with 95% confidence interval (CI). Results: There was no differences between the two tumour types in age, stage, pelvic nodal metastasis, parametrial invasion, surgical margin status, DSI, LVSI, maximal tumor diameter, grade, and treatment modalities. 5-year OS and DFS were 73% and 77%, versus 64% and 69%, for SCC and adenocarcinoma, respectively (p> 0.05). Multivariate analysis revealed independent prognostic factors including pelvic nodal metastasis and resection margin status for OS (p=0.008, p=0.002, respectively). Conclusions: Prognosis of FIGO stage IA-IIB cervical cancer patients was found to be the same for those with adenocarcinoma and SCC.

Keywords: Adenocarcinoma - squamous cell carcinoma - uterine cervical carcinoma - histology - prognosis

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Introduction

Worldwide, the uterine cervical carcinoma is one of the most common malignancies and the second reason for cancer mortality in women. Each year, nearly 500,000 new cases are diagnosed. Most cervical carcinomas are diagnosed at an early stage due to PAP smear screening in developing countries (Monket al., 2007). SCC (squamous cell carcinomas) constitutes more than 75% of cervical cancers with decreasing frequency of SCC whereas the incidence of AC (Adenocarcinoma) has risen. Apprehensions have increased and the search for prognostic variables has accelerated due to the reports of rising incidence rates for cervical adenocarcinoma in young women (Peters et al., 1986; Vizcaino et al., 1998; Liuet al., 2001). In stage IB-IIA cervical carcinoma after either radiotherapy (RT) or radical hysterectomy with pelvic lymph node dissection, tumor control rate and prognosis are excellent with a 5-year overall survival ratio of 78-91 % (Landoni et al., 1997).

Some reports have shown that patients with adenocarcinoma have a poorer prognosis than SCC histology (Kleine et al., 1989; Eifel et al., 1990; Hopkins and Morley, 1991; Eifel et al., 1995; Irie et al., 2000; Nakanishi et al., 2000; Xie et al., 2012; Intaraphet et al., 2013). In another study, it was reported that the recurrence rate of the pure AC group was higher than in the SCC (Lee et al., 2011). Moreover, other reports determined no differences in prognosis between AC and SCC (Shingleton et al., 1995; Ayhan et al., 2004; Lee et al., 2006; Fregnani et al., 2008). One of those studies found that the AC histology showed less aggressive behavior histologically than did the SCC group, but disease-free survival rates demonstrated no difference (Fregnani et al., 2008).

The aim of this study was to estimate the prognosis of patients with stage IA-IIB cervical carcinoma and to

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investigate a correlation with histology on prognosis.

Materials and Methods

Patients

Two hundred fifty one patients with AC and SCC histology for FIGO (International Federation of Gynecology and Obstetrics) stage IA-IIB uterine cervical carcinoma at Radiation Oncology Clinic of GH Okmeydanı Training and Research Hospital between January 1996 and December 2006 were selected for the study and retrospectively analyzed. Survival and general characteristics of patients were assessed. Surgical and pathology reports, patient records, study and follow-up examination notes present in patient files in the clinical archives were reviewed and patients were assessed in terms of age, histopathologic diagnosis, grade, stage, tumor size, parametrial extension, lymphovascular space invasion (LVSI), presence of pelvic lymph node metastasis, surgical margin status, depth of stromal invasion (DSI), treatment modality, date of recurrence, date of metastasis and date of death or last follow-up.

The patients were clinically staged according to the FIGO staging criteria. All the patients that were included in this study were treated with simple, modified or radical hysterectomy with or without pelvic lymphadenectomy. After excluding ASC (Adenosquamous carcinoma) from the AC group, SCC with pure AC were compared in this study.

In the first year after treatment, all patients were followed-up every 3 months initially, then every 6 months for the next 3 years and after that every year until recurrence or death. The patients were followed up for a median of 76.0 months (standard deviation: 39.6 months), ranging from 6 up to 166 months.

Surgery

Almost all patients included in our study were treated with a Type I, II or III hysterectomy. One patient was treated with a type IV radical hysterectomy.

Radiotherapy

Whole pelvic radiation therapy was given using a 6 or 18 MV photon or cobalt 60 (when radiation oncologists had only cobalt 60) with 2 or 4-field box technique. Intracavitary brachytherapy was delivered to 180 patients by using HDR (High dose rate) or LDR (Low dose rate) applicators. The superior edge of external pelvic radiation field was set on the L4-L5 interspace, and the inferior edge was set 3 cm inferior to distal disease or below the obturator foramen. The lateral edge was placed to 1.5-2 cm lateral to the lateral margin of the bony pelvic wall. The anterior border of lateral field was the anterior appearance of the symphysis pubis and the posterior edge was posterior to the sacrum. External irradiation was delivered to the whole pelvic field at 1.8 or 2.0 Gy per fraction once daily, five days per week. The median dose to the whole pelvis was 50.0 Gy (range, 45.0-60.0 Gy). Twenty six patients received concurrent cisplatin-based chemotherapy and radiation therapy postoperatively.

Factors analyzed

Twelve potential prognostic variables were chosen based on the previously published clinical trials. The variables were divided into two or more categories; age (25-34, 35-44, 45-54, 55-64, ≥65), FIGO stage (IA,IB1,IB2,IIA,IIB), pelvic nodal metastasis (negative or positive), parametrial invasion (negative or positive), margin status (negative, positive, close margin), depth of stromal invasion (≥5mm or <5mm), LVSI (negative or positive), maximal tumor diameter (0-4cm, 4.1-6 cm, >6), grade (differentiated: grade I-II or undifferentiated: grade III-IV, treatment modality (postop-RT or postop-CCRT) and intracavitary brachytherapy (absent or present).

Statistical methods

Overall survival (OS) was defined as the time, in months, from the first day of treatment to the date of death, last follow-up and disease-free survival (DFS) was defined as the time, in months, from the date of treatment to the date of pelvic or distant recurrence. Data were analyzed using SPSS statistical software program package, version 12.0.1(SPSS Inc., Chicago, IL).OS and DFS were calculated using the Kaplan-Meier method. The log-rank test was used to compare differences in survival. Multivariate analysis was performed using the Cox proportional hazard regression model for prognostic factors and to estimate hazard ratio (HR) with ninety-five percent confidence interval (CI). Differences were assumed statistically significant when p values <0.05.

Results and Discussion

Two hundred fifty one patients with FIGO stage IA-IIB cervical cancer were admitted in this study. Two hundred eighteen patients (86.9%) had SCC and 33(13.1%) had AC.

Patient and tumor characteristics

Patient and tumor characteristics of 251 patients are displayed. Between patients with SCC or AC age, stage, pelvic nodal metastasis, parametrial invasion, surgical margin status, DSI, LVSI, maximal tumor diameter, grade, treatment modalities and intracavitary brachytherapy did demonstrate a statistical difference (p>0.05). Although the incidence of patients with stage IB1 and IIB in SCC was higher than that in AC (33.5% *vs* 11.8% and 26.1% *vs* 12.1%, respectively) this difference did not influence the other factors or the prognosis. In addition, the incidence of patients that LVSI and surgical margin were positive and maximal tumor diameter was 4.1-6 cm in SCC was higher than that in AC but these differences were not found to be statistically significant. The number of patients that received postoperative radiation therapy in SCC and AC groups was considerably higher (79.8% and

Table 1. Survival Outcomes According to the Histological Type

Treatment outcomes		SCC	AC	p value
5-year survival	DFS (%)	64	69	>0.05
5-year survival	OS (%)	73	77	>0.05

DFS, disease free survival; OS, overall survival

90.9%, respectively). Also, it was found that performing concurrent chemoradiotherapy postoperatively in SCC occurred more frequently than compared to AC (11.5% *vs* 3.0%, p>0.05, respectively).

Survival outcomes

The evaluated 5-year DFS rates in the SCC group and AC group were 64% and 69%, respectively (p>0.05). The evaluated 5-year OS rates for the SCC and AC histological studies were 73% and 77%, respectively (p>0.05) and there was a significant difference in neither OS or DFS rates between the two cell types (Table 1).

Prognostic Factor Analysis

Table 2 shows the results of the univariate analysis. Among the variables of the univariate analysis, two variables were identified to have prognostic significance: Pelvic nodal metastasis (p=0.006) and margin status (p=0.031).

Multivariate analysis included the two prognostic significance factors in univariate analysis. Multivariate analysis by Cox proportional hazard model showed that pelvic nodal metastasis and margin status considered independent prognostic factors for OS (p=0.016 and p=0.046, respectively). The results of multivariate analysis are shown in Table 3.

The incidence of AC has increased 20% during the last two decades (Smith et al., 2000; Visioli et al., 2004; Wang et al., 2004; Sherman et al., 2005; Gienet al., 2010). Although adenocarcinoma in cervical cancer patients has been increasing, it is controversial whether the histology of adenocarcinoma influences the prognosis in patients with early stage cervical carcinoma.

This study was designed to determine the outcome and clinicopathological characteristics of patients with stage IA-IIB cervical carcinoma and to investigate a possible influence of histology on survival of these patients. Surgical-pathological data from 251 patients with stage IA-IIB cervical cancer was analyzed retrospectively in this study. No significant difference between cell types in the incidence of age, stage, pelvic nodal metastasis, parametrial invasion, surgical margin status, DSI, LVSI, maximal tumor diameter and treatment modalities that may influence prognosis was detected. Cell type had no significant influence on DFS or OS. Pelvic nodal metastasis and margin status were independent prognostic factors in multivariate analysis.

Table 2. Univariate Analysis of Survival Time by Categorical Variable

Variable	Log-rank test value	Degrees of freedom	p value
Age	0.67	4	0.954
Stage	7.37	4	0.117
Pelvic nodal metastasis	7.49	1	0.006
Parametrial invasion	2.18	1	0.140
Margin status	4.67	1	0.031
Depth of stromal invasion	1.26	1	0.262
LVSI	1.034	1	0.309
Maximal tumor diameter	3,327	2	0.190
Treatment modality	0.698	1	0.404

Table 3. Multivariate Analysis of Prognostic Factors

Parameter	OR	95%CI	p value
Pelvic nodal metastasis	5.84	0.21-0.85	0.016
Margin status	3.99	1.01-3.99	0.046

In contrast to our study, some studies found that the prognosis of adenocarcinoma is worse when compared with squamous cell carcinoma(Kleine et al., 1989; Hopkins and Morley 1991; Eifel et al., 1995; Irie et al., 2000; Nakanishi et al., 2000; Lee et al., 2011; Huang et al., 2012). However, the majority of reports arguing that that AC has a poorer prognosis than SCC with regard to survival did not separate adenocarcinomas from those tumors with adenosquamous characteristics (Kleine et al., 1989; Hopkins and Morley 1991; Eifel et al., 1995; Irie et al., 2000; Nakanishi et al., 2000; Huang et al., 2012). In a prospective Gynecologic Oncology Group (GOG) study that enrolled patients with stage IB uterine cervical carcinoma, the effect of all three cell types (AC,ASC and SCC) on survival and recurrence-free interval (RFI) was compared and it was found that the presence of the adenosquamous cell type carried a poorer prognosis than other two cell types (Look et al., 1996). Thus, the poor prognosis of adenocarcinoma may be moderately derived from adenosquamous carcinoma being included in adenocarcinoma group. Cases of ASC were not combined with adenocarcinoma in our study. We compared prognosis of pure AC with SCC. This factor may expound why adenocarcinoma with squamous cell carcinoma had similar 5 year-OS rates in our study.

Similar to our study, some reports have shown that there is no significant difference between AC and SCC groups (Aoki et al., 2000; Ayhan et al., 2004; Chen et al. 2011; Katanyoo et al., 2012). Ayhan et al. found that OS and DFS were 84.0%, 87.7%, versus 83.1%, 86.4% for AC and SCC, respectively (p> 0.05) (Ayhan et al., 2004). Katanyoo et al. have reported in patients with locally advanced stages that AC had a worse response for RT/CCRT than SCC in terms of overall complete response (CR) and time to clinical CR. However, they could find no difference between both cell types in 5-year OS (Katanyoo et al., 2012). Chen et al. evaluated 2,362 patients with stage I cervical carcinoma and found no significant difference in survival between squamous cell carcinomas and adenocarcinoma when the primary treatment was surgery (Chen et al., 2011). Aoki et al. analyzed patients with stage IB-IIB had positive pelvic lymph nodes and reported that no difference was detected in survival between patients with SCC and nonsquamous cell types (AC and ASC). Even after exclusion of the patients with ASC, pure AC did not have an effect on prognosis in multivariate analysis in their study (Aoki et al., 2000).

We reviewed several studies which analyzed both AC and SCC as presented in Table 4. Kleine et al. did not observe a significant difference in stage I and II patients treated by radical surgery. They found the most significant difference in prognosis when they evaluated the patients with stage I and II treated by RT. The five-year survival rate was 85.0% in SCC compared with 58.6% in stage I AC (Kleine et al., 1989). Huang et al. found that patients with AC/ASC of the uterine cervix had poorer outcome than those with squamous cell carcinoma when radiotherapy

Table 4. Studies which Compared between AC and SCC in Cervical Cancer

Ref	Year of enrolled patients	Stage	Number SCC:AC	5-year OS SCC	5-year OS AC	p value
Hopkins and Morley 1991	1970–1985	I	370:124	90.0%	60.0%	<0.001
		II	186:40	62.0%	47.0%	0.01
		III	114:25	36.0%	8.0%	0.002
		IV	57:13	NA	NA	NA
Eifel et al. 1995	1960-1989	IB	1538:229	81%	72%	<0.01
Nakanishi et al. 2000	1976-1995	IB	405:104	95.5%	88%	<0.001
Irie et al., 2000	1981-1996	IB-IIA	198:50	91.7%	77.9%	0.003
Ayhan et al., 2004	1980-1997	IB	454:67	87.7%	84.0%	>0.05
		IIB	170:85	70.8%	71.9%	>0.05
Katanyoo et al., 2012	1995–2008	IIIB/IVA	112:56	47.4%	41.1%	>0.05
This study	1996-2006	IA-IIB	218:33	73%	77%	>0.05

*Abbreviation: SCC, squamous cell carcinoma; AC, adenocarcinoma; NA, not available; OS, overall survival

was the primary treatment and the 5-year RFS (Relapse-free survival) rates for SCC *vs* AC/ASC patients were 86% *vs* 68% for Stage IB/IIA nonbulky, 74% *vs* 38% for Stage IB/IIA bulky, 70% vs. 49% for Stage IIB (Huang et al., 2012). Chen et al. showed that the survival rate was higher after primary surgery than after primary radiotherapy for cervical adenocarcinoma (Chen et al., 2011). These results suggested opinions that ASC/AC is more radio resistant than SCC for gross tumor and histology did not affect the outcome of patients performing radical hysterectomy. In the Cochrane review, in patients with stage I or IIA cervical AC and positive pelvic lymph node, Baalbergen et al. reported that five-year survival was 91% for patients treated by surgery alone but in spite of adjuvant RT, in the other group was only 34% (Baalbergen et al., 2013). The majority of patients included in our study were treated by radiation therapy or concurrent chemoradiotheraphy postoperatively. Preoperative RT was given only three patients with SCC and 18 patients received no treatment in addition to surgery. We did not detect any significant difference when compared treatment modalities in univariate analysis.

In a study evaluating patients with stage IB-IIB cervical carcinomas treated by surgery, Trattner et al. found only lymph node metastases and histopathological staging to be independent prognostic factors for OS in multivariate analysis (Trattner et al., 2001). In patients with stage IIB cervical carcinoma performed radical hysterectomy, Kasamatsu et al. found the presence of lymph node metastasis as an independent prognostic factor in multivariate analysis (Kasamatsu et al., 2009). Similarly, positive lymph node involvement was an independent prognostic factor in multivariate analysis for OS in our study.

Huang et al. found that one of the prognostic factors for local recurrence was positive resection margi (Huang et al., 2012). Similarly, in this study, the other independent prognostic factor, in addition to positive pelvic lymph node, was the resection margin status for OS in our multivariate analysis.

This study has some limitations. Firstly, the design of the study was retrospective. Secondly, the risk factors such as LVSI, DSI, margin status and grade status in most of the patients were unknown. Thirdly, we included very early stages in our study, such as IA1, IA2 or IB1 patients with tumor sizes of less than 2 cm and finally, because it was a very small number of patients with a very early stage, such as IA1-IA2, these substages could not be evaluated for survival separately.

In conclusion, to arrive at a more definitive conclusion regarding the prognostic importance of the AC histology, further research should be done prospectively, in the setting of a large-scale, randomized controlled study.

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