Prognosis and treatment of primary adenocarcinoma and adenosquamous cell carcinoma of the uterine cervix

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Summary

Purpose: To evaluate a cohort of women with primary invasive carcinomas of the uterine cervix, and to compare the biological characteristics and behavior of a cohort of adenosquamous carcinomas with a cohort of adenocarcinomas and squamous cell carcinomas.

Methods: One hundred and fourteen cases of primary invasive cervical carcinoma presenting between 1 January 1987 and 31 December 1997 were studied. Sixteen (14%) women with adenosquamous cell carcinomas and eight (7%) adenocarcinomas were compared with 90 (79%) women with squamous cell carcinomas. Patients with Stage Ib and IIa were treated by radical hysterectomy and pelvic lymph node dissection. All patients with stage IIb and over were treated by radiation. Patients with bulky, large, barrel-shaped lesions were selected for treatment by a combination of radiation and extrapelvic hysterectomy.

Results: The corrected survival rate for stage Ib patients with adenosquamous cell carcinoma was only 27.2%, compared with a 92.2% corrected survival rate for squamous cell, and a 100% corrected survival rate for adenocarcinoma.

Conclusion: There is a higher proportion of adenosquamous cell and adenocarcinoma of the cervix than generally appreciated. The epidemiological risk factors associated with adenosquamous carcinomas of the cervix are more similar to those of squamous cell carcinomas than of adenocarcinomas. The survival difference between two groups is explained by effects of clinical stage, nodal spread, and vascular space involvement.

Key words: Adenosquamous cell carcinoma; Adenocarcinoma; Squamous cell carcinoma; Survival; Uterine cervix.

Introduction

In recent years the incidence of invasive pure adenocarcinomas and mixed adenosquamous cancer has risen in proportion to squamous cancers [1, 2]. Previous literature documented that 90-95% of primary tumors of the uterine cervix are classified as squamous cell carcinomas. Tumors with mixed squamous and glandular differentiation have been considered uncommon, comprising less than 5% of cases [3]. However, recent work has demonstrated the presence of stainable mucin in a significant proportion of cervical squamous carcinomas lacking architectural evidence of glandular differentiation [4, 5]. Although initially separated as ''mucin producing squamous carcinomas'', these tumors appear to share characteristics with conventional mixed tumors and so warrant inclusion as adenosquamous carcinomas [6]. Adenosquamous carcinomas are defined as tumors that contain an admixture of histologically malignant squamous and glandular cells [5, 7, 8]. In a recent WHO classification, the term mixed carcinomas was deleted and adenosquamous carcinomas are now classified under other epithelial tumors [9]. The prognosis of patients with adenocarcinoma of the cervix is worse than for patients with squamous cell carcinoma [10, 11]. However, the prognostic significance of adenosquamous tumors, including covert mucin-producing tumors, has not been established. Wentz and Reagan [12] suggested that patients with adenosquamous carcinoma have a relatively poor prognosis. Although a few reports agreed with their findings [8], Shingleton *et al.* [2] noted that adenosquamous cell carcinoma did not carry a poorer prognosis if compared stage for stage and tumor volume for tumor volume with other cervical cancers [13]. The current study reports on the biological behavior of a cohort of invasive carcinomas of the uterine cervix which included a significant group of adenosquamous tumors.

Materials and Methods

From 1 January 1987 to 31 December 1997, 114 primary cervical carcinomas, excluding microinvasive tumors, were diagnosed and treated at the Department of Gynecologic Oncology, Marmara University Hospital. The diagnoses of the diseases were made with punch or incisional biopsy and fractional curettage, and definitive therapy for all patients was carried out at the same hospital. Patients who had FIGO Stage Ib and IIa were usually treated by radical hysterectomy, pelvic lymph node dissection and para-aortic lymph node sampling as described by Piver and associates (Type III) [14]. Patients with bulky, large, barrel-shaped lesions were selected for treatment by a combination of irradiation and extrafascial hysterectomy as outlined by Nelson *et al.* [15]. All patients with Stage IIb or more were treated by radiation and the techniques used were the same as outlined by Fletcher [16]. In general, patients received average doses of 5,500 Gy externally through linear accelerator (6MV photon beam) and intracavitary insertions, usually two, delivered 4,000 to 5,500 to point A, depending on tumor stage (volume). The pathological specimens were investigated by the Department of Pathology of the same university hospital.

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Results

During the period of study, 114 patients were treated for primary invasive cervical cancer. Ninety (79%) patients had histologically documented squamous cell carcinoma, eight (7%) patients adenocarcinoma and 16 (14%) patients adenosquamous cell carcinoma (Table 1). The most commonly encountered type of cervical adenocarcinoma was the mucinous type [17]. They are composed of cells that have basal nuclei and abundant pale granular cytoplasm that stains positively with mucicarmine stains. Cells typically are stratified and there may be considerable nuclear atypia with variation in nuclear size, coarsely clumped chromatin, and prominent nucleoli. Mitosis usually are numerous (Figure 1). Adenosquamous carcinoma does not differ grossly from adenocarcinoma of the endocervix. The glandular component is usually poorly differentiated, showing minor degrees of mucinous differentiation in the form of cytoplasmic vacuolization and accumulation of mucin in gland lumens. The squamous component is poorly differentiated, showing little keratinization (Figure 2).

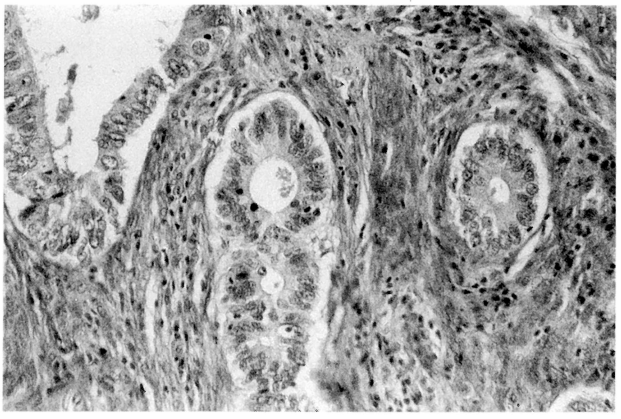

Figure 1. — Adenocarcinoma of endocervical type. Invasive glands surrounded by an altered, desmoplastic stroma (H&E x200).

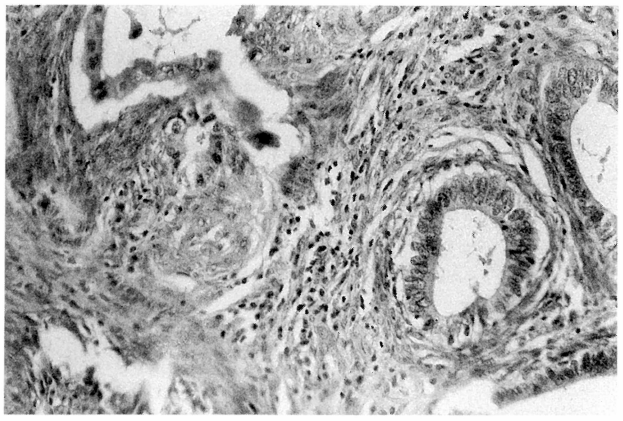

Figure 2. — Adenosquamous cell carcinoma showing admixture of glandular elements and solid squamous elements (H&E x200).

Table 1. — *Gross appearance and stage distribution of cervical carcinoma.*

State	Squamous cell ca n=90 (79%)	Adenocarcinoma n=8 (7%)	Adenosquamous cell ca n=16 (14%)
Normal	4 (4.4%)	2 (25%)	3 (18.75%)
Exophytic	52 (57.8%)	3 (37.5%)	7 (43.75%)
Endophytic	31 (34.5%)	2 (25%)	4 (25%)
Granular	3 (3.3%)	1 (12.5%)	2 (12.5%)
Stage Ib	64 (71.1%)	6 (75%)	11 (68.75%)
Stage II	22 (24.5%)	1 (12.5%)	4 (25%)
Stage III	3 (3.3%)	1 (12.5%)	1 (6.25%)
Stage IV	1 (1.1%)	0	0

Table 2. — *Survival by stage and cell type.*

Cell type	Stage	No. patients n=114	No. surviving n=87	Corrected survival 80.26%
Squamous cell	Ib	64	59	92.2
	II	22	18	81.8
	III	3	0	0
	IV	1	0	0
Adenocarcinoma	Ib	6	6	100
	II	1	1	100
	III	1	0	0
	IV	0	0	0
Adenosquamous	Ib	11	3	27.2
	II	4	0	0
	III	1	0	0
	IV	0	0	0

Patients with squamous cell carcinoma had a mean age of 49 years. During the same period the mean ages for patients with adenocarcinoma, and adenosquamous cell carcinoma were 52 and 42 years, respectively. The age range was the same for both adenocarcinoma and squamous cell carcinoma of the uterine cervix. Marital status and parity of our patients were of predominantly married and parous groups, a finding that relates them closely with women affected by both adenocarcinoma and adenosquamous cell carcinoma of the cervix. Bleeding from the vagina was almost universal and was the reason most of these women sought medical help. Since most of the patients had symptomatic tumors, one would anticipate the finding of a cervical mass, a feature of 98 cases (Table 1). Twenty-four percent of the patients with adenosquamous cell carcinoma had a negative smear. No cervical lesions were noted in 25% of the adenocarcinomas and in 18.75% of the adenosquamous cell carcinoma patients on speculum examination (Table 1). However on bimanuel examination all of these patients had suspicious cervical induration and thickening. Twenty-seven of the 114 patients with cervical cancer are dead of disease. All living patients have been followed at least four years for an overall corrected survival rate of 80.26% (Table 3). The corrected survival rate of Ib patients with adenosquamous cell carcinoma is only 27.2%, compared with a 92.2% corrected survival rate for squamous cell, and a 100% corrected survival rate for adenocarcinoma. But this observation was based only on six patients and may

not be significant. Comparing all stages of cervical cancer, there is a statistically significant decrease in survival in patients with adenosquamous cell carcinoma as compared with squamous cell and adenocarcinoma. Of the 71 patients with Stage Ib lesions treated by radical hysterectomy, none had positive nodes and all had clear margins in the removed specimen. The remaining ten patients with Stage Ib had positive nodes and were treated by external irradiation, four of them died from distant metastases. Five patients with bulky, barrel-shaped lesions had positive para-aortic lymph nodes discovered at planned extrafascial hysterectomy after irradiation. All patients with stage IIb or more advanced lesions were treated with irradiation. None survived (Table 2).

Adjunctive chemotherapy with cyclophosphamide, adriamycin, and cisplatinum was used in three patients with metastatic extrapelvic disease. There was only one patient with partial response. Lung metastases were most common (55%), but liver and other intra-abdominal organs were often involved.

Discussion

Histogenetically, lesions with mixed patterns of epithelial differentiation are thought to arise from the pluripotential subcolumnar reserve cells of the endocervical mucus membrane and represent biphasic differentiation [17]. Therefore, differentiation towards squamous, glandular or a mixed pattern is not surprising. Traditionally, mixed cervical carcinomas were relatively uncommon; however, as confirmed by the current study and others [2, 8, 18, 19] a relative increase in the number of patients with adenosquamous cell carcinoma of the cervix has been found. Studies regarding the aggressiveness of adenosquamous cell cancers are conflicting [8, 19]. The postulated poor prognosis has been disputed by Shingleton *et al.* [3]. The current report emphasizes that adenosquamous cell cervical carcinoma is more aggressive with a poorer survival rate and atypical presentation than squamous or adenocarcinoma tumors. The mean age of patients with adenosquamous cell carcinoma in the present study was 42 years of age, and one half of the patients were under 40. Survival rates in these patients were very low. Studies by different authorities have all reported a decreased survival in patients with cervical cancer who were less than 35 years of age [20]. Cervical lesions greater than 4 cm in diameter have been related to a propensity towards local treatment failure, distant metastases, and a lowered survival rate [21]. In the present report 48% of the patients with Stage Ib adenosquamous cell carcinoma who died had cervical lesions less than 4 cm in diameter, and 26% had occult lesions. There were no survivors in the Stage III adenosquamous cell group. This was also true of Stage III and IV adenocarcinomas and squamous cell carcinomas of the cervix during the study years. Cervical cytologic smears are not always effective in diagnosing invasive carcinoma of the cervix. Berkowitz *et al.* [20] diagnosed only 37% of patients with invasive cervical cancer based on cervical cytology. In the present study 60% of patients with adenosquamous cell carcinoma who had lesions greater than 2 cm had negative cytologic smears. These lesions may arise from high in the endocervical canal, preventing early detection by usual cervical cytologic smear methods.

The majority of mixed carcinomas of the cervix are not amenable to radiation treatment even locally, and this is more pronounced the less mature they are. Combined surgical and radiotherapeutic treatment gives better results, except for the immature type, which thus far has resisted all methods of treatment used [18].

Conclusion

There is a higher proportion of adenosquamous cell and adenocarcinoma of the cervix than generally appreciated. Small components of one kind frequently appear in growths of the other, and occasionally the cancerous tissues are blended in almost equal proportions. When compared with squamous cell carcinoma, women with adenosquamous cell and adenocarcinoma of the cervix have a significantly higher rate of local tumor recurrence, distant metastasis, and poorer survival. The survival difference between the two groups is explained by effects of clinical stage, nodal spread, and vascular space involvement.

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