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Invasive Cervical Cancer Treated Initially by Standard Hysterectomy[1]

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Ninety-two patients with invasive cervical cancer initially treated by standard hysterectomy were evaluated for features related to survival. The cell type included squamous cell (64) and adenocarcinoma (28). Posthysterectomy therapy included radiation therapy (78), pelvic lymphadenectomy (3), and radical parametrectomy (1). Hysterectomy was initially performed for the following indications: invasive lesion missed on cone biopsy, 17; hemorrhage at cone biopsy, 2; bleeding, 16; abnormal cytology, 13; presumed endometrial cancer, 9; known cancer, 7; pelvic relaxation, 5; planned therapy, 3; fibroids, 3; adnexal mass, 2; chronic discharge, 1; pyometra, 1; postpartum endometritis, 1. The cumulative 5-year survival for all patients was 68%, for squamous cell 80%, and for adenocarcinoma 41% ($P = 0.0001$). On postoperative evaluation 84 patients had presumed Stage I and 7 had parametrial involvement (Stage II). Patients with Stage I disease were then examined separately by cell type. Fifty-seven patients with squamous cell disease had cumulative 5-year survival of 85%. Radiation therapy in the immediate postoperative period produced a survival of 88%, compared to observation only with a 69% survival ($P = .10$). Patients with squamous cell disease and more than 50% cervical invasion had a 75% survival compared to a 96% survival for those with less than 50% ($P = .02$). The presence of disease at the surgical margins, grade, age, and increase in radiation therapy did not influence survival. Twenty-seven patients with presumed Stage I adenocarcinoma had a cumulative 5-year survival rate of 42%. Survival was significantly influenced by tumor grade ($P = .018$) and the amount of postoperative radiation therapy ($P = .03$), while age, amount of residual tumor, and presence of tumor at surgical margins did not influence survival. Patients with invasive squamous cell carcinoma treated by standard hysterectomy and postoperative radiation therapy have a prognosis similar to those treated initially by either radical surgery or radiation therapy. Patients with adenocarcinoma appear to have a significantly decreased survival when compared to patients with squamous cell disease and their prognosis is related to tumor grade and the amount of postoperative pelvic radiation. © 1990 Academic Press, Inc.

INTRODUCTION

Hysterectomy is the most common major gynecologic operation performed in the United States at the pesent time. It is performed for a multitude of indications with a low rate of morbidity and mortality. With the advent of cytologic screening and attention to the diagnosis of cervical disease, invasive malignancy is usually diagnosed preoperatively in the patient with cervical cancer. Occasionally, the diagnosis is made in the postoperative period and the question of adjuvant treatment then arises. Authors have suggested various forms of adjuvant therapy with ultraradical surgical procedures or radiation therapy being the usual methods [1–8]. Recently, radical parametrectomy with lymphadenectomy for the younger patient has been shown to provide excellent results [9]. With the large number of hysterectomies being performed, it is anticipated that this problem will continue to occur. This study was undertaken to combine the experience from three separate referral centers where radiation therapy has been the usual treatment of choice.

MATERIAL AND METHODS

Patients diagnosed with invasive cervical cancer treated initially by standard hysterectomy were reviewed from the University of Michigan Medical Center (UMMC), Puget Sound Oncology Consortium (PSOC), and The University of Virginia (UVA), Charlottesville, Virginia. Patients from the University of Michigan Medical Center covered the time period from 1963 through 1985; patients from the Puget Sound Oncology Consortium covered the period 1976 through 1987; and patients

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from the University of Virginia covered the time period 1968 through 1986. All records were reviewed for clinical characteristics and follow-up. Pathology was reviewed at the respective institutions' gynecologic tumor conference, and pathology results were recorded according to the pathology review by the gynecologic pathologist at the respective institution. Patients were considered to have a Stage IB squamous cell carcinoma of the cervix when pathology showed invasion greater than 3 mm in depth or angiolymphatic invasion was present. Patients with microinvasive squamous cell cervical cancer were not included in this study. Patients with adenocarcinoma of the cervix were included when the pathologic changes showed invasive adenocarcinoma regardless of the depth of invasion. All subtypes of adenocarcinomas were grouped under adenocarcinoma. Patients with questionable Stage II endometrial cancer were excluded and only those patients with a definite primary cervical lesion were included in the adenocarcinoma groupings.

Patients with microscopic disease extending to the surgical resection margin were considered to have Stage I disease when no gross tumor was described in the operative note and the postoperative pelvic exam was recorded as normal. Patients were assigned to Stage II if disease extension beyond the cervix was noted intraoperatively or if there was nodularity into the parametrium or other changes beyond those expected in the immediate postoperative period.

The amount of radiation therapy was not standardized among the institutions but tended to be standardized within each institution. All institutions gave radiation therapy, usually consisting of whole pelvis external radiotherapy and vaginal brachytherapy. Radiation therapy in earlier years was given by cobalt with anterior/posterior portals while in later years, this was given by the four field box technique, using linear accelerator. Vaginal cuff radiation consisted of either radium or cesium.

Biostatistical analysis was performed by the Department of Biostatistics, Department of Public Health, University of Michigan. Survival probability was plotted using the life tables of Kaplan and Meier [10]. The difference in survival amoung the various features was tested for significance using the Savage (Mantel–Cox) method [11,12].

RESULTS

A total of 92 patients (UMMC 52, PSOC 20, UVA 20) who had a standard hysterectomy as their initial therapy were identified. The clinical characteristics included married 93%, obese 26%, hypertension 33%, diabetes 6%, oral contraceptive usage 14%, smoking 47%. The age of diagnosis ranged from 25 to 89 years (mean 50.2, median 48). Symptoms related to the diagnosis included abnormal bleeding in 69% of the patients. Cervical cytology was not performed or not available in 33% of the patients, 21% had a normal cytology, and 46% had some type of abnormal cytology eventually leading to hysterectomy. Hysterectomy was initially performed for the following indications: invasive lesion not detected on cone biopsy, 17; hemorrhage at time of cone biopsy, 2; abnormal uterine bleeding, 16; abnormal cytology, 13; presumed endometrial cancer, 9; known cervical cancer, 7; pelvic relaxation, 5; planned as therapy for the invasive lesion, 3; leiomyoma, 3; adnexal mass, 2; chronic discharge, 1; pyometria, 1; postpartum endometritis, 1. Cone biopsy was nondiagnostic for invasive disease for the following reasons: pathology misinterpretation, 2; carcinoma *in situ*, margins negative, 4; carcinoma *in situ*, margins not reported, 5; microinvasive disease, 4. Two patients had repeat cone biopsies without finding invasive disease. Five patients underwent hysterectomy after colposcopic-directed biopsies showed carcinoma *in situ*. Three of these patients did not have an endocervical curettage.

Adjuvant therapy after standard hysterectomy included radiation therapy (78), pelvic lymphadenectomy (3), and radical parametrectomy (1). Pelvic lymphadenectomy was utilized in 2 patients with early squamous cell carcinoma lesions who refused radiation therapy and 1 patient with adenocarcinoma of the cervix who was initially treated with hysterectomy and lymph node sampling for a presumed endometrial cancer. Ten patients received no further therapy either by their own refusal or the lack of initial referral to one of the three institutions.

The cell type included squamous cell (64) and adenocarcinoma (28). The cumulative 5-year survival rate for all the patients was 68% and this was significantly related to the cell type, with the squamous type having an 80% and the adenocarcinoma a 41% cumulative survival (Fig. 1). Eighty-four patients had presumed Stage I disease, 7 had what was felt to be parametrial involvement (Stage II), and 1 patient had advanced Stage IVA disease. Four of the 6 patients with presumed Stage II squamous cell carcinoma died within 5 years, and 1 patient with Stage IVA squamous cell carcinoma died of disease within 1 year. Patients with Stage I disease were then further analyzed by cell type. Fifty-seven patients with squamous cell disease had a cumulative 5-year survival prediction of 85% (Fig. 2). Forty-five patients underwent radiation therapy in the immediate postoperative period and the cumulative 5-year survival in this group was 88%. One patient underwent a radical parametrectomy and 2 patients underwent pelvic lymph node dissections. The patient undergoing radical parametrectomy developed an isolated recurrence in the terminal ileum 4 months after parametrectomy. This was resected and she is currently

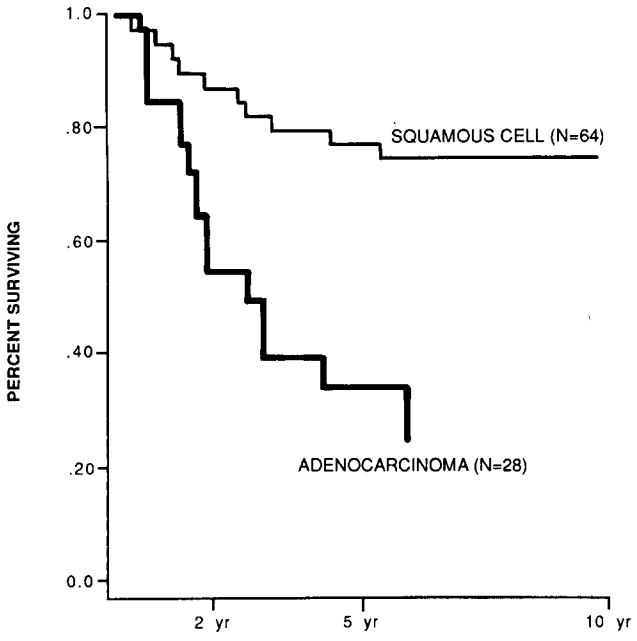

FIG. 1. Survival by cell type for all patients (P = 0.001).

undergoing chemotherapy. Nine patients underwent observation alone and 7 of these patients developed recurrent disease (mean 1.5 years, range 2 months to 3 years). In 6 of these patients, there was only local recurrence and in 1 patient there was local recurrence with distant metastases. All 6 patients with local recurrence underwent radiation therapy and only 2 patients are free of disease without further therapy. Three patients underwent pelvic exenteration after radiation therapy and 1 of these patients survives at 18 years from surgery. The total of 11 patients without parametrial treatment (the 9 untreated patients and the 2 patients with pelvic node dissection) had a cumulative 5-year survival of 69% (Fig. 3). The depth of cervical penetration was analyzed for patients with Stage I squamous cell cancer. Patients with <50% penetration had a 96% survival while those with >50% penetration had a 75% survival (P = 0.02) (Fig. 4). Factors that did not influence survival in Stage I squamous cell disease included the presence or absence of microscopic tumor at the surgical margins, tumor grade, and patient age.

There were 27 patients who had presumed Stage I adenocarcinoma of the cervix and these patients had a cumulative 5-year survival of 42% (Fig. 2). The survival was significantly influenced by the tumor grade (P = 0.018) in the adenocarcinoma group (Fig. 5). The depth of cervical penetration, patient age, and presence of microscopic tumor at surgical margins did not influence survival. One patient with presumed Stage IIB adenocarcinoma of the cervix died at 15 months. One patient treated with hysterectomy alone has died of disease. One patient treated with hysterectomy and lymph node sampling recurred at 18 months. She underwent radiation therapy and is now alive with disease.

Radiation therapy doses were calculated by combining the external whole pelvis radiation and the brachytherapy dosage. The whole pelvis radiation therapy during the study period was supervoltage given either by cobalt-60 or linear accelerator. Vaginal applicators consisted of

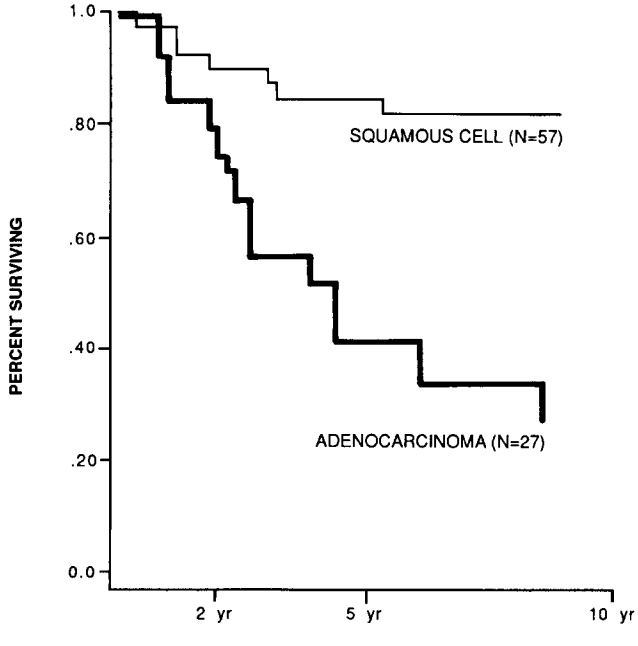

FIG. 2. Survival by cell type for patients with presumed Stage I disease (P = 0.001).

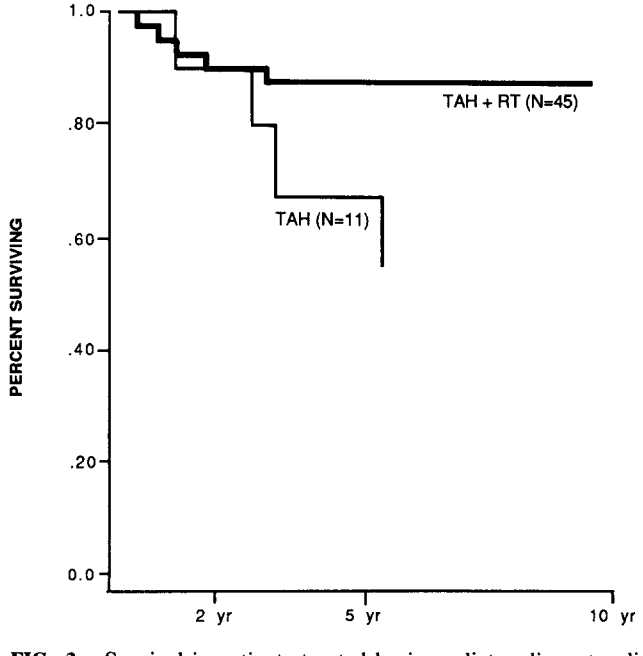

FIG. 3. Survival in patients treated by immediate adjuvant radiation therapy or no parametrial treatment (P = 0.10). TAH, total abdominal hysterectomy; RT, radiation therapy.

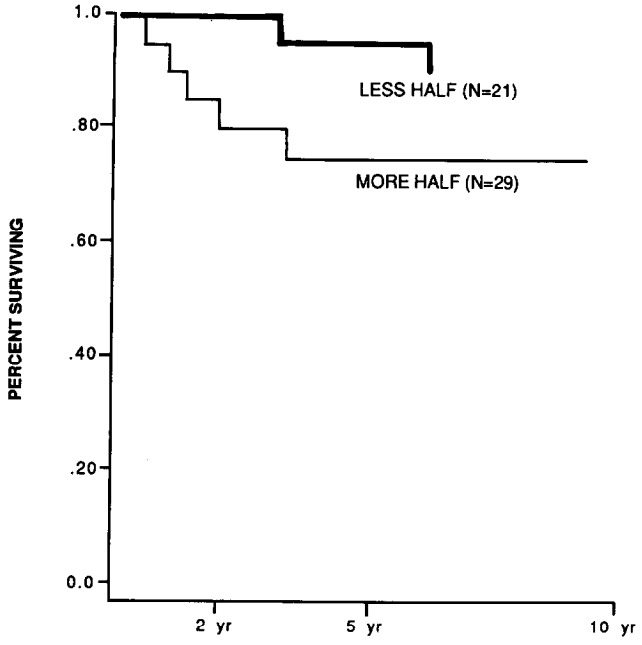

FIG. 4. Survival in patients with presumed Stage I disease by amount of cervical penetration (P = 0.02).

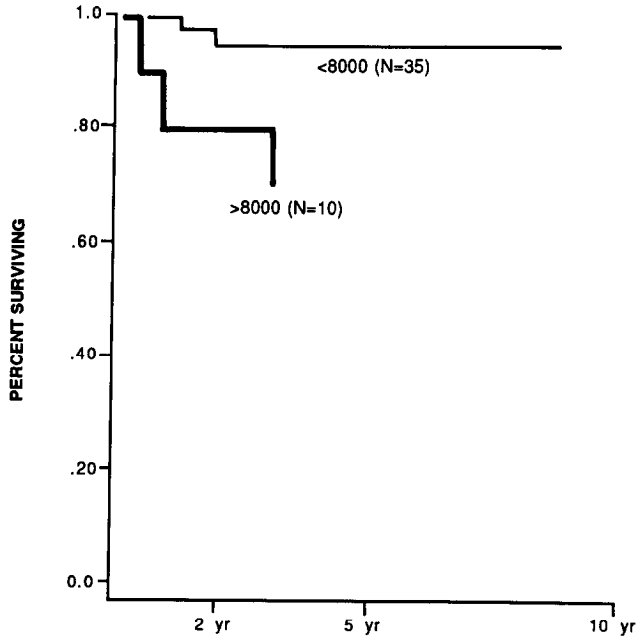

FIG. 6. Survival by amount of adjuvant radiation for patients with Stage I squamous cell cancer of the cervix (P = 0.03).

either radium or cesium and were calculated in milligram hours. All radiation therapy given at the University of Michigan Medical Center during this period was given to doses of approximately 4000–4500 rad pelvic irradiation and 2800–3000 mg hr for a total of approximately 7000 rad vaginal surface dose. Patients treated from the Puget Sound Oncology Consortium received combined doses of approximately 6500–7000 rad. Patients treated at the University of Virginia received somewhat higher doses with 65% of their patients going beyond 8000 rad combined dose. The survival effect was analyzed by cell type for those patients receiving less than 8000 rad combined dosage compared to those receiving more than 8000. In patients with squamous cell disease, 35 patients received less than 8000 while 10 received more than 8000. Those receiving the lesser radiation had a 94% 5-year survival compared to a 70% survival for the 10 patients receiving more than 8000 (P = 0.03) (Fig. 6). In patients with Stage I adenocarcinoma of the cervix, 20 patients received less than 8000 with a 36% cumulative survival while 5 patients received more than 8000 with an 80% survival (P = 0.03) (Fig. 7). The majority of the patients receiving the higher doses of radiation were treated at one center.

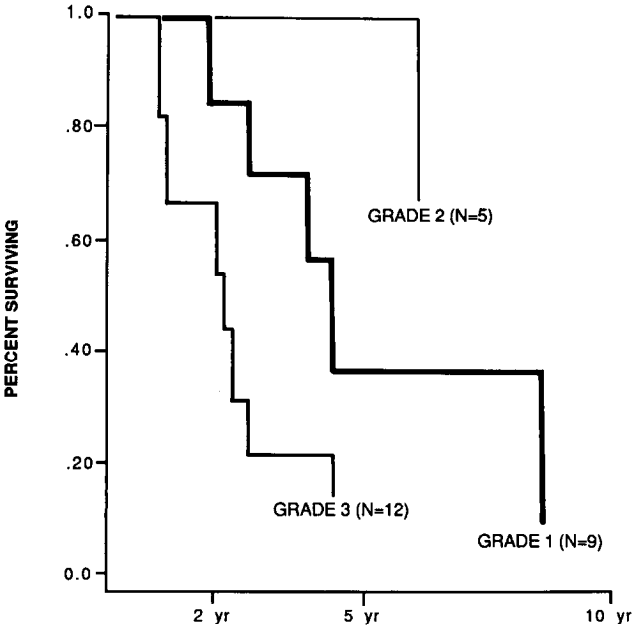

FIG. 5. Survival by tumor grade for patients with adenocarcinoma of the cervix (P = 0.02).

Significant complications related to radiation therapy occurred in 11 of 78 patients (14%). Five of the 61 patients (8%) receiving less than 8000 rad had the following complications: vesicovaginal fistula (2), small bowel obstruction (2), enteritis (1). Six of 17 patients (35%) receiving more than 8000 rad developed the following complications: enteritis (5), lympyhedema (1). There was a significant difference in the complication rate between patients treated with the lower and higher doses of radiation therapy (P = 0.005).

DISCUSSION

The treatment of cervical cancer historically has been either radical surgery for early stage disease or radiation

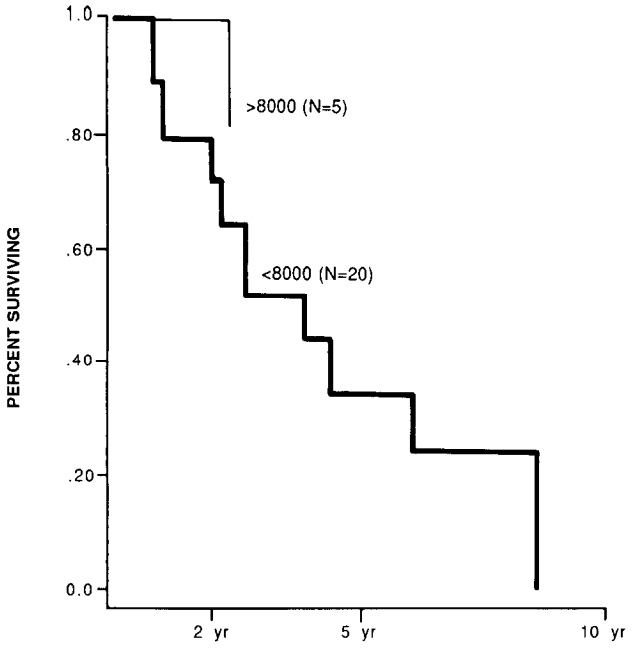

FIG. 7. Survival by amount of adjuvant radiation for patients with adenocarcinoma of the cervix (P = 0.03).

therapy for both early and late stage disease. These approaches have produced favorable results and with the advent of improved surgical techniques and modern radiotherapy, the complications have been reduced. The diagnosis of an invasive cervical lesion after a standard hysterectomy has been performed implies that the primary malignancy has been insufficiently treated. Earlier reports suggested that no follow-up therapy leads to an unacceptable universal mortality. In this same study, radiation therapy produced a 30% 5-year survival while radical follow-up surgery produced a 67% survival. These results led Green and Morris in 1969 to recommend follow-up radical surgery for this clinical situation [1]. At approximately the same time, Durrance reported excellent results with adjuvant radiation therapy [2]. The results reported here for squamous cell disease are very similar to his survival results. Durrance reported a 92% survival when hysterectomy margins were free of disease and adjuvant radiation therapy was used. Microscopic disease at the surgical margins did not appear to influence survival in his report. Importantly, all patients recurred where adjuvant radiation therapy was delayed for more than 6 months. Andras *et al.* in a follow-up to Durrance's initial work reported a 96% 5-year survival when tumor was microscopic and confined to the cervix. When gross tumor was present or the margins were not free, survival dropped to approximately 85%. This survival decreased even further to 47% when obvious residual pelvic tumor was present [3]. Cosbie reported a 71% survival when no residual disease was present with a decrease in survival to 20% when residual disease was present [5]. This group of patients with residual tumor would be similar to the group that we consider to be Stage II and their survival rates are similar to those of this report. Davy reported a 77% survival when margins were free and 38% survival when margins were involved. For patients where therapy was delayed beyond 6 months, survival was reduced to 20% [6]. Heller recently reported on 18 patients with presumed Stage I disease and this group had a 78% survival when treated in the immediate postoperative period. Seven patients with presumed Stage II disease had a 67% survival [8]. Our report is similar to previous reports suggesting that radiation therapy in the immediate postoperative period provides excellent results for patients with squamous cell disease. Patients with small early invasive lesions appear to have an excellent prognosis and the 96% survival reported here would be similar to that for the group reported by Andras *et al.*, where patients with microscopic disease confined to the cervix also had a 96% 5-year survival. The survival does appear to decrease when a greater volume of tumor is present (deep cervical penetration) but acceptable survival results are obtainable with adjuvant radiotherapy.

Patients with an adenocarcinoma of the cervix treated in this fashion had a markedly altered survival in this series. The majority of the literature addresses this problem in squamous cell disease and this is probably related to the preponderance of squamous cell disease when compared to adenocarcinoma of the cervix. Heller reported 5 patients with an adenocarcinoma of the cervix with 1 dying of disease. Andras reported on 19 patients with results that were similar to those for squamous cell disease. A previous evaluation from the University of Michigan suggested that patients with an adenocarcinoma of the cervix treated by standard hysterectomy and external radiation therapy had an ominous prognosis and the poor survival is confirmed in this report [13]. It is interesting to note that in this report, the survival in patients with adenocarcinoma was significantly influenced by the amount of adjuvant radiotherapy. Dosages that exceeded a combined total of 8000 rad improved survival. All of these patients did have negative cervical margins and other factors did not seem to influence survival. It is possible that the adenocarcinoma type requires doses beyond those necessary for squamous cell disease. It is also interesting to note that in patients with adenocarcinoma, the tumor grade influenced survival. Similar results were reported in patients treated in a standard fashion [13]. Increasing doses of radiotherapy in patients with squamous cell disease did not influence survival and in fact, this particular group had a decreased survival when compared to those where lower doses were given.

The number of patients seen among the three institutions as well as the continuing referral of patients di-

agnosed postoperatively suggests that this problem will continue to occur. The most common reason for a hysterectomy in this report was a presumed intraepithelial process while the invasive lesion was, in fact, not detected on cone biopsy. This is similar to the report of Heller *et al.*, where 60% of patients had intraepithelial neoplasia, leading to the hysterectomy [8]. The second most common indication in this report was abnormal bleeding, suggesting that a complete and thorough evaluation of the cervix had not been performed prior to the procedure. Abnormal cytology was the third most common indication for hysterectomy, also suggesting that a complete and thorough evaluation of the cervix was not undertaken. Thirteen patients with a variety of other indications for the surgery had an unsuspected lesion of the cervix and this does call attention to the absolute necessity for an evaluation of the cervix prior to a planned hysterectomy. Seven patients had a known cancer and the operating surgeon simply performed the wrong operation. Three patients had the hysterectomy as planned therapy with the full knowledge that postoperative radiotherapy would be added. This was planned because of inadequate geometry for intracavitary placement in two patients and a tuboovarian abscess in one patient. With the poor response to radiotherapy in adenocarcinoma, alternative therapies should be considered for this tumor type. Nine patients had a presumed endometrial cancer that were then found to have an adenocarcinoma of the cervix in the postoperative period when the entire uterus was analyzed. This highlights the necessity of an adequate and thorough pathologic examination prior to surgery. When necessary, a narrow deep cone biopsy can be performed as it is critical to delineate an adenocarcinoma of the cervix from an endometrial cancer.

Patients with invasive squamous cell carcinoma treated by standard hysterectomy and postoperative radiation therapy have a prognosis similar to that for those treated initially by either radical surgery or radiation therapy. Patients with adenocarcinoma have a significantly decreased survival when compared to patients with squamous cell disease and their prognosis is related to tumor grade and the amount of postoperative pelvic radiation therapy.

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