

Cancer of the cervix with endometrial extension treated by radiotherapy: A retrospective case-control study

F. L. Ampil¹, M.D.; G. Caldito², Ph.D.; J. B. Unger³, M.D.

Departments of Radiology¹, Biometry², and Obstetrics-Gynecology³
Louisiana State University Health Sciences Center, Shreveport, Louisiana, (USA)

Summary

Background: Studies determining prognosis of cancer of the cervix with endometrial extension (CCEE) in a case-control fashion are scant.

Methods: A case-control retrospective study of 20 women with CCEE and 16 patients with cervical cancer not extending to the endometrium (CCNEE) treated by radiation was undertaken. The patient groups were matched for age, disease stage, the presence of bulky/barrel-shaped tumor in the cervix, intercurrent illness, total radiation dose, and hemoglobin level. The overall mean follow-up was 54 months (range 8 to 218 months).

Results: The numerical rates of local and systemic failure as well as 5-year survival were worse for patients with CCEE versus CCNEE. However, the observed differences were not statistically significant.

Conclusion: Involvement of the endometrium by cancer of the cervix seems to confer a worse outcome among cervical cancer patients treated by radiation alone.

Key words: Cancer of the cervix; Endometrial extension; Radiotherapy.

Introduction

Owing to improved results from recent advances in the-rapeutics [1], clinicians are now able to better manage patients with locally advanced cancer of the cervix.

The prognosis of carcinoma of the uterine cervix is linked to tumor stage. Previous studies [2-4] have already demonstrated the adverse influence on outcome of involvement of the endometrium by cervical cancer, but controlled studies are few.

The purpose of the present study was to compare the results of radiotherapy (RT), especially prognosis, in cancer of the cervix with (CCEE) and without (CCNEE) endometrial extension.

Materials and Methods

A review was undertaken of all patients who had undergone radiation therapy (RT) for carcinoma of the uterine cervix between 1982 and 1998 at the Louisiana State University Health Sciences Center in Shreveport.

Patient selection for inclusion in this retrospective study was based on pathology reports showing cervical tumor and endometrial tissues and the completion of definitive RT alone for cancer of the cervix confined to the pelvic region. Sixty-seven individuals were identified after a review of pathology reports; 31 patients were excluded because of 1) total abdominal or radical hysterectomy with or without preoperative or postoperative RT; 2) Stage IVB – disseminated cervical cancer; 3) RT applied for local or regional recurrent tumor following initial curative surgery for carcinoma of the cervix; 4) patient non-compliance relative to completion of the prescribed full course of RT; 5) lack of patient follow-up information.

For the purpose of this study, we defined CCEE, through pathology reports, as squamous cell carcinoma of the cervix invading the endometrial stroma (20 patients). CCNEE indicates a report of cervical cancer and normal endometrial tissue (16 patients).

A full course of RT consisted of external beam pelvic teletherapy with one or two intracavitary (tandem and ovoids) brachytherapy applications; the details of irradiation technique have been described in a previous report [5]. One patient was treated with chemotherapy (Topotecan) and concurrent RT.

Survival was calculated using the Kaplan-Meier method. The Fisher exact, chi-square, 2-sample t, and Wilcoxon rank-sum tests were used in the comparative evaluations of the observed differences.

Results

The observations between the compared patient groups (except for age) were not meaningfully different (Table 1). Table 2 shows the outcome after definitive RT. Among the evaluable patients, the local failure rate in the CCEE group was (2/17) $12 \pm (95\% \text{ confidence interval}) 16\%$ and in the CCNEE patients (1/15) $7 \pm 13\%$ ($p > 0.99$); the corresponding distant failure rates were (5/17) $29 \pm 22\%$ and (1/15) $7 \pm 13\%$ respectively ($p = 0.18$). The cumulative survival rate at five years was $41 \pm 22\%$ for the CCEE patients and $75 \pm 22\%$ for the CCNEE individuals ($p = 0.16$). Admittedly, the poorer results seen in the CCEE group could perhaps be ascribed to the presence of advanced disease or other illnesses in more of the CCEE than CCNEE patients, and the lower administered radiation doses in some cases (the latter consideration having proved difficult to explain).

With respect to determination of possible prognostic factors, multivariate analyses revealed that the presence of bulky or barrel-shaped tumor in the cervix, other

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Table 1. — Demographic data.

Features	Cancer of the cervix		p value
	with (n=20) endometrial extension	without (n=16)	
Mean age (yrs)	54 ± *2	42 ± 2	< 0.002
Range	36-76	29-68	
≥ 65	15 ± 16%	6 ± 12%	0.61
Barrel-shaped/bulky cervical tumor present	30 ± 20%	44 ± 25%	0.39
Stage I-II disease	55 ± 22%	88 ± 16%	0.07
Other illness present	47 ^b ± 23%	25 ± 22%	0.17
Mean dose (Gy)			
RA ^c	72.6 ± 2.6	80.1 ± 0.8	0.11
LA ^c	72.5 ± 2.7	80.6 ± 0.6	0.07
Mean hemoglobin Level (Gm/dl)	10.9 ± 0.5	11 ± 0.6	0.87

*± = 95% confidence interval; ^b19 patients were evaluated; ^cRA = Point A, right; LA = Point A, left.

Table 2. — Outcome.

	Cancer of the cervix	
	with* (n=20) endometrial extension	without** (n=16)
Alive without cancer	(6)	(10)
Alive with cancer	(1)	—
Died without cancer	(4)	(3)
Died with cancer	(6)	(2)
Died, cancer status unknown	(3)	(1)

Follow-up of living patients (16 to 192 months*; 23 to 218 months**).

coexisting illnesses, and subsequent systemic failure profoundly influenced the prognosis in these patients with cervical cancer (Table 3).

The diagnoses of local recurrences (3 patients) and systemic failures (6 patients) were based on obvious clinical examination findings, histologic evidence, or imaging abnormalities (e.g., bilateral pulmonary masses present on chest radiograph, myelogram-shown cauda equina compression by osseous spinal metastases). Chemotherapy or RT was administered mostly for palliation of symptomatic distant metastasis. None of the eight persons who died with cancer survived for two years from the time of detection of recurrent tumor or the appearance of systemic disease; one patient was still alive at one month from diagnosis of local relapse. To our knowledge, none of the studied patients sustained a severe complication following therapy.

Table 3. — Prognostic factors*.

Variables	p value
Endometrial extension (absent vs present)	NS**
Age (yrs)	NS
Bulky/Barrel-shaped cervical tumor (absent vs present)	0.016
Disease stage (I vs II vs III vs IV)	NS
Other illness (absent vs present)	0.004
Local failure (absent vs present)	NS
Distant failure (absent vs present)	0.004

*Multivariate analysis; **NS = Not significant.

Discussion

A review of our 17-year experience of 1,163 cases of cervical cancer yielded 20 persons with CCEE (2%). This number may be an underestimation of the incidence of this particular histopathologic condition because there were undoubtedly other undiscovered patients with such lesions. The cases presently studied were identified after a review of only the pathology reports incorporated in the radiation oncology charts.

The current AJCC staging system does not greatly regard cervical carcinoma with extension to the corpus uteri [6]. In light of our findings, it seems clear that the CCEE condition is associated with a poorer outcome than cervical cancer without endometrial involvement, as other reports [2-4] have also purported. Perez and colleagues [2] reported on a larger population of Stage IB to III patients with CCEE and additional follow-up. In the group of 42 women with endometrial stromal invasion, the pelvic recurrence and subsequent extrapelvic (para-aortic nodal and/or distant) metastases rates were 24% and 31% respectively; in contrast, the corresponding failure rates in 397 patients without histologically documented neoplastic invasion of the endometrial stroma were 13% and 17%. Spanos *et al.* [3] assessed the effect of biopsy-determined endometrial involvement by squamous cell cancer of the cervix in 180 women with Stage IB to IIB disease. Fourteen individuals possessed CCEE while 45 patients were found "with fragments of squamous cell carcinoma, with separate endometrial stroma" — presumed cases without endometrial invasion by tumor. The local recurrence and distant metastasis rates in the CCEE group were 21% and 14%, respectively; the observed local relapse and systemic disease rates for the CCNEE women were 8% and 4%, respectively. Of interest is the fact that the majority of the studied patients in both reports [2, 3] were treated by RT alone; treatment (like ours) consisted of external beam pelvic irradiation and intracavitary brachytherapy applications. In another report of radiation treatment of CCEE [4], 150 patients with carcinoma of the cervix and a negative D & C were compared to 82 women with cervical cancer and positive D & C specimens. The investigators found observations similar to ours — a worse outlook for CCEE patients. However, it is possible that some of their CCEE irradiated women did not have true CCEE, (but rather, squamous cell cervical cancer contamination of the endometrial curettings). The criteria for a "positive D & C" specimen included "A) stromal invasion of endometrium by squamous cell carcinoma of the cervix; B) squamous cell carcinoma present in curettings with endometrial tissue; C) squamous cell carcinoma present without endometrial tissue".

It was not possible to give a satisfactory account for the inadequacy of radiation dose (by modern standards) in some of our CCEE patients. From the literature [7, 8], it is known that aggressive RT can favorably influence the outcome of women with non-disseminated cancer of the cervix.

Because CCEE is an uncommon problem, our study is necessarily retrospective, limited by the small numbers and its non-randomized nature. Also, patients with Stage III or IVA disease were included in the analysis (akin to that in another study [4]). Such extensive tumor could have truly affected patient outcomes, “masking the potential effect of endometrial involvement” [3]. We recognize that further trials involving larger numbers of patients with CCEE are needed to truly determine the impact on prognosis of corpus uteri invasion by cervical carcinoma. The findings from the present study prompt us to give foremost consideration to aggressive therapy – the application of curative doses of RT and concurrent administration of effective chemotherapeutic agents – as applicable to CCEE patients. This management plan, in our view, seems reasonable and presents hope for averting what may otherwise be a dismal outcome.

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Address reprint requests to:
 F. L. AMPIL, M.D.
 Division of Therapeutic Radiology
 Louisiana State University
 Health Sciences Center
 1501 Kings Highway
 Shreveport, Louisiana 71130 (USA)