Can intermediate-risk node-negative patients with stage I corpus cancer do without posthysterectomy radiotherapy? Review of a 13-year experience

F. L. Ampil[1], *M.D.*; **G. Caldito**[2], *Ph.D.*; **J. Unger**[3], *M.D.*; **P. Connor**[3], *M.D.*; **R. Pelser**, *B.S.*

Departments of Radiology[1], *Biometry*[2], *and Obstetrics-Gynecology*[3]
Louisiana State University Health Sciences Center Shreveport, Louisiana (USA)

Summary

A retrospective comparative study of 41 patients with stage I corpus cancer, negative surgical staging, and adverse pathological features either treated or untreated by posthysterectomy radiotherapy (PHR) during a 13-year period was undertaken. The patients were matched for age, intermediate-risk classification, number of sampled nodes and the presence of coexisting illness. After complete follow-up, there was no significant difference in outcome between the patient groups. Unless it can be shown definitely that PHR is beneficial, its use in intermediate-risk node-negative stage I corpus cancer patients must be seriously questioned.

Key words: Lymph node sampling; Corpus cancer; Hysterectomy; Radiotherapy

Introduction

Can patients with stage I corpus cancer (SICC), negative lymph nodes, and additional histopathological features (e.g., grade 3 tumor, greater than one-third myometrial invasion) do without posthysterectomy radiotherapy (PHR)? A recent report [1] indicates that PHR may not be required in node-negative high-risk patients after hysterectomy for endometrial cancer. In contrast, another report [2] suggests that locoregional recurrence is reduced by PHR in select patients with negative surgical staging, grade 2 or 3 tumors and more than one-third myometrial invasion.

The purpose of this study was to evaluate the data from our institution to compare the survival, local recurrence and distant metastasis rates between intermediate-risk node-sampling-negative patients with SICC submitted and not submitted to PHR.

Materials and Methods

One hundred and fifty-five patients were evaluated for treatment of endometrial cancer during a 13-year period between 1984 and 1996. Case records and pathological reports were reviewed retrospectively to identify patients – women who underwent regional lymph node evaluations at the time of total abdominal hysterectomy and bilateral salpingo-oophorectomy for SICC and were found to be at an "intermediate-risk" – for inclusion in this analysis. The "intermediate-risk" individuals were those women with stage IA grade 3 tumor or stage IB/IC of all grades [3]. Information was obtained from available medical and tumor registry records.

This retrospective case-control study includes 41 node-negative SICC intermediate-risk patients whose ages ranged from 38 to 76 years. Twenty-one women did not receive PHR (NPHR group) since the attending staff did not believe PHR was indicated because of lack of proof of its value; we found 20 women with similar characteristics who were treated with radiation following hysterectomy (the historical control/PHR group), perhaps because "examinations in cervical cancer have shown that the risk of pelvic metastasis is considerably underestimated if only 20 lymph nodes are dissected; it can be suggested that this consideration is also true for endometrial cancer" [4].

The decision to perform selective pelvic and aortic lymphadenectomy was made in each case by the attending surgeon.

External beam pelvic irradiation from a 6 million volt linear accelerator (except for one patient who was treated using the cobalt-60 teletherapy unit) was administered to 15 patients. The technique of irradiation usually consisted of parallel opposed anterior and posterior as well as right and left lateral treatment portals; the mean total absorbed dose was 46 Gy (range 44 to 50 Gy). Fractional doses of 1.8 Gy to 2 Gy were delivered daily on five consecutive days each week. Vaginal cuff low-dose-rate intracavitary brachytherapy was applied in eight patients (including three women also treated by external beam radiation); the average vaginal cuff surface dose was 33 Gy (range 15 to 60 Gy).

The chosen endpoints for comparison were survival and failure patterns. All observed local and distant failures were histologically confirmed. Survival distributions were estimated using the product-limit method of Kaplan-Meier; when deemed appropriate, the 95% confidence intervals (±) were calculated. The chi-square test was used to examine the differences between categorical variables, the log-rank test for univariate analysis, and the Cox regression model for multivariate analysis.

Results

The clinical characteristics of patients in both groups are shown in Table 1. The average number of sampled lymph nodes from each group did not differ markedly; the para-aortic nodes were removed in ten women of the

Revised manuscript accepted for publication April 5, 2001

PHR group and in 11 patients from the NPHR set. Two women from the PHR group had endometrial cancer with a papillary serous or clear cell morphological appearance; the former patient is alive and well at four months from the time of diagnosis while the latter died without cancer five years later.

The estimated 5-year survival rates were 65% ± 22% and 52% ± 22% for the PHR and NPHR groups, respectively (Figure 1, $p > 0.40$). Other results can be seen in Table 2. The difference in follow-up time is statistically significant.

Local recurrence occurred in two patients at 23 months and 26 months after hysterectomy. In both patients, 34 lymph nodes were sampled including eight from the paraaortic region. The recurrences consisted of pelvic masses involving the vaginal cuff as demonstrated on computed tomographic imaging scans. The length of survival was nine months for both individuals. One patient was free of pelvic disease after aggressive salvage therapy (consisting of external beam pelvic irradiation and high-dose-rate intracavitary brachytherapy plus Megace/Tamoxifen treatment). The other woman died of disease despite Taxol chemotherapy.

Distant metastases were pleural-based in two women (and also in the supraclavicular fossa in one of the patients). The systemic lesions appeared within nine months after hysterectomy. Neither patient received treatment, and their survival was one month. An enterocutaneous fistula requiring remedial surgery developed in a woman 17 months following 45 Gy of external beam pelvic irradiation; the patient is alive and well 51 months later.

Univariate analysis in Table 3 shows improved survival in patients without local recurrence, concurrent illnesses or distant failure. However, on multivariate analysis, only the latter two variables proved to be truly independent prognostic factors.

Table 1. — *Demographic data*

Features	Posthysterectomy Radiotherapy (n=20)	Posthysterectomy No Radiotherapy (n=21)
Stage Ic, grades 1 to 3[a]	45% ± 22%	19% ± 18%
≥ 65 years of age[b]	45% ± 22%	38% ± 22%
Intercurrent illness present[c]	60% ± 22%	43% ± 22%
Mean number of sampled nodes[d]	9 ± 3 (range 1-28)	11 ± 5 (range 1-35)

[a]$p > 0.05$; [b]$p > 0.60$; [c]$p > 0.20$; [d]$p > 0.30$; [e]95% confidence interval.

Table 2. — *Results*

Rate	Posthysterectomy Radiotherapy (n=20)	Posthysterectomy No Radiotherapy (n=21)
Local failure[a]	0%	10% ± 14%
Distant metastasis[b]	10% ± 14%	0%
Complications[c]	5% ± 10%	0%
Follow-up (mos)[d]		
Median	70 ± 24	31 ± 10
Range	1-159	3-89

[a]$p > 0.10$; [b]$p > 0.10$; [c]$p > 0.20$; [d]$p > 0.001$; [e]95% confidence interval.

Table 3. — *Univariate and multivariate analyses of patient- and treatment-related factors in 41 intermediate-risk node-sampling-negative patients with stage I corpus cancer*

Variable	p value (Univariate analysis)	p value (Multivariate analysis)
Age[a]	NS*	NS
Race[b]	NS	NS
Tumor grade[c]	NS	NS
Stage I type[d]	NS	NS
Intercurrent illness[e]	< 0.01	< 0.05
Local failure[e]	< 0.01	NS
Distant failure[e]	< 0.01	< 0.01
Posthysterectomy radiotherapy[f]	NS	NS

*NS = Not significant; [a]<65 yrs vs ≥ 65 yrs; [b]African-American vs Caucasian; [c]Grades 1 and 2 vs grade 3; [d]Stage IA and IB vs Stage IC; [e]Present vs absent; [f]Applied vs not applied.

Table 4. — *Review of the literature about node-negative patients with corpus cancer*

Author	No. Patients	Follow-up	Failure Rate[a] Local	Failure Rate[a] Distant	Salvage Therapy success
A. Postoperative radiotherapy not administered					
Larson *et al.* [1]	(105)	Median 39 mos	(4) 4%	(4) 4%	(4/4)
This series	(21)	Median 31 mos	(2) 10%	0%	(1/2)
B. Postoperative radiotherapy administered					
Chadha *et al.* [22]	(38)	Median 30 mos	0%	(3) 8%	NS[c]
Cosa-Nz-UK Group [10]	(207)	36 to 120 mos	(9) 4%	(20)[b]10%	NS
This series	(20)	Median 70 mos	0%	(2) 10%	0/2

[a]Local = Vaginal or pelvic failure; Distant ≐ Extrapelvic failure and may include [b]groin failure; [c]NS = Not stated.

Discussion

This retrospective study highlighted several important features with respect to the care and management of the particular subjects of this report. First, there is a large variability in the number of nodes removed per patient or per station. In our 20 patients comprising the PHR group, the frequency of pelvic relapse was 0% at a median

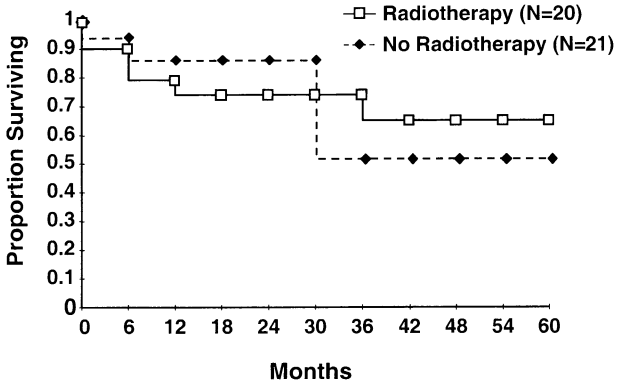

Figure 1. — Estimates of survival of node-sampling-negative intermediate-risk patients with stage I corpus cancer submitted and not submitted to posthysterectomy radiotherapy.

follow-up of 70 months and an average of nine removed, negative nodes. By way of comparison, in a reported study of 295 patients [5], recurrence was not observed in any patient with a negative selective lymph node dissection that included bilateral pelvic and para-aortic sites; the mean number of excised nodes was nine and the median follow-up, 39 months. On the other hand, the relapse rate was 11% despite the finding of negative pelvic and para-aortic nodes in another series of 222 patients [6]; the nodes removed during the staging procedure numbered 15 to 30 and the average follow-up was 36 to 72 months. In both studies, high-risk women received postoperative radiotherapy or chemotherapy. Second, admittedly our patient series was quite small but we found (as others [7] have) that the prognosis of pelvic relapse is not always dismal; we acknowledge the fact that successful salvage of recurrences depends greatly on the extent of disease at the time of failure. Corpus cancer may recur in the vaginal cuff, pelvic cavity, or at an extrapelvic location. Since the oncologist cannot predict the site of subsequent treatment failure, it is important to recognize that pelvic teleirradiation uniformly treats the pelvic cavity while the scope of brachyradiotherapy is limited.

It is known from the literature [6, 8] that patients without pelvic and/or para-aortic nodal metastatic disease have lower recurrence and higher survival rates than women with nodal metastases. Thus, in many surgically staged patient series [6, 8-12] PHR has been used when pelvic nodal metastases have been documented in an attempt to improve patient outcomes. However, the value of PHR in this particular clinical situation remains to be ascertained since a prospective, randomized and controlled trial has not yet been undertaken; this study may be hard to perform because allowing half of these node-positive women to remain untreated might prove difficult for physicians and patients to accept.

The frequency of surgically staged node-negative women with SICC far outnumbers that of patients with nodal metastases [5, 9, 10, 13]. Also, the incidence of "intermediate-risk" patients was 75% and 89% in some studies [5, 14]. We reviewed our experience because it was not clear to us whether intermediate-risk node-negative women with SICC need PHR. Several reports [5, 6, 9, 11, 14-19] indicate that endometrial cancer patients who underwent disease staging and were at "higher risk" received adjuvant postoperative radiotherapy; it seems that the finding of negative nodes did not affect the postoperative management plan of irradiation. In the 1996 survey of American gynecologic oncologists which assessed the practice of surgical staging and its impact on adjuvant treatment in patients with stage I endometrial cancer, recommendations for PHR were reduced but not completely omitted when the pathologic status of lymph nodes was negative [20]. We believe that the possible rationale for the use of PHR in node-negative patients with high-risk features such as deep myometrial invasion and a grade 3 tumor rests in the reported relapse risks of 32% to 46% and 33% to 42% associated with such pathological findings, respectively [6, 21]; these features have been reported to be independent risk factors for recurrence and reduced survival [2].

A review of the literature (with this series included) displayed in Table 4 [1, 10, 22] shows that local and distant failure rates have not exceeded 4% to 10% in node-negative patients with or without the application of postoperative radiotherapy. It is difficult to justify PHR to reduce the incidence of local relapse in women with SICC when deaths due to recurrent disease are infrequent [23]. The value of PHR in cases of intermediate-risk node-negative women with SICC has yet to be proven by a randomized trial. Such a study will require a large number of patients "since the risk of recurrence is less than 7% when lymph nodes are negative and there is no extrauterine disease at laparotomy" [23]. In the recently completed phase III GOG 99 randomized study of surgery versus surgery plus adjuvant pelvic irradiation among women with intermediate-risk endometrial cancer, the use of PHR decreased the risk of relapse but did not have a significant effect on overall survival because the pelvic recurrences were often effectively treated [24]; most of the accrued patients had disease with low histologic grade and shallow myometrial penetration, perhaps due to the reluctance of the investigators to enroll patients with more high-risk features [25]. Moreover, nodal status in these surgically staged women was presumably negative.

Certainly the issue of PHR in this select group of women (intermediate-risk node-negative patients with SICC) deserves further investigation. Until the results of such a study are known, individualization of therapy should be practiced and "clinicians must decide if selection of postoperative therapy," especially PHR, "is appropriate or not. This occurs whether the patients have been surgically staged or not" [21].

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