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Recurrence Patterns and Complications in Endometrial Adenocarcinoma with Cervical Involvement

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Background: Cervical involvement in endometrial carcinoma is a diverse entity, and the optimal management of these patients is not well understood.

Methods: Recurrence patterns and complications in 202 patients with histologically confirmed endometrial carcinoma with cervical involvement were retrospectively studied.

Results: The 5-year actuarial survival rate for all patients was 65%. Recurrences were documented in 80 (40%) of the patients, and the overall long-term survival rate in this group was 4%. Patients treated with radical hysterectomy (n = 33) had a 6% isolated pelvic recurrence rate and the lowest serious complication rate among the five treatment groups despite having the highest frequency of risk factors for recurrence among any of the groups studied. Patients treated with extrafascial hysterectomy alone (n = 37) had a 14% pelvic recurrence rate and very few complications. When radiotherapy preceded extrafascial hysterectomy (n = 37), the frequency of pelvic recurrences was 30%, and 19% experienced serious gastrointestinal or genitourinary tract complications. When radiotherapy followed extrafascial hysterectomy (n = 68), the pelvic recurrence rate was 24%, and 13% experienced serious complications. Overall, 24% of patients (49 of 202) had isolated pelvic recurrences, whereas 10% (21 of 202) had isolated distant recurrences and 5% (10 of 202) were simultaneously diagnosed with both pelvic and distant recurrences.

Conclusions: This large data base suggests that older conventional forms of therapy, particularly those using preoperative radiotherapy, subject the patient to significant morbidity over a 5- to 10-year period and, in terms of local control, are not necessarily superior to therapeutic modalities using primary surgical evaluation, such as radical hysterectomy. Consideration of primary surgery should be given in the appropriate situation, and radical hysterectomy should be considered when gross cervical involvement is encountered and intraoperative exploration does not show obvious extrauterine disease.

Key Words: Stage II endometrial cancer—Gross cervical involvement—Radical hysterectomy—Recurrence patterns—Complications—Primary surgical evaluation.

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The advent of surgical staging for endometrial cancer has drastically changed the approach to this disease (1). Surgical staging is particularly useful in stage II endometrial carcinoma, in which previous inaccuracies in the diagnostic techniques allowed for as few as 37% of cases to have surgical/pathologic findings consistent with the preoperative assessment (2). High rates of falsely positive endocervical curettage (ECC) results and low accuracy rates of preoperative predictions of extrauterine disease accounted for this discrepancy (3–6). Nev-

ertheless, when endometrial carcinoma is suspected to involve the cervix, the paracervical, paravaginal, and pelvic lymphatics are at risk for micro- or macroscopic metastases and must be treated. Since the early 1970s, preoperative radiotherapy (RT) followed by extrafascial hysterectomy has been recommended and accepted as the treatment of choice for this disease. However, when used to treat patients with a falsely positive ECC result and no surgical pathologic high-risk factors for recurrence, this treatment is clearly overly aggressive and a large percentage of patients are radiated unnecessarily. In addition, when disease has extended beyond the pelvis, when an endocervical primary tumor is diagnosed, or when the cervical involvement from the endometrial tumor is extensive, this modality may actually undertreat the patient and may compromise delivering adequate treatment. In the absence of a gross cervical lesion, primary extrafascial hysterectomy and selective lymph node sampling before RT also has been recommended to treat these patients and thus define the extent of extrauterine disease (7). In no prospective randomized trials has this modality been compared with more conventional forms of treatment—this type of study would be difficult because of the rarity of cervical involvement in endometrial cancer. Finally, various types of radical surgery, with and without radiation, also have been studied and found to be of benefit, especially in the presence of gross cervical involvement (2,3,8,9). However, radical surgery for endometrial cancer has been criticized in the past because of its high complication rate and technical difficulty in older, obese patients with endometrial cancer who have multiple medical problems.

Recently, we reported on the prognostic factors and survival in patients with endometrial cancer involving the cervix (3). Now, in an effort to help clear up some of the aforementioned problems, we report the recurrence patterns and complications among various treatment options in locally advanced endometrial carcinoma with cervical involvement.

METHODS AND MATERIALS

We examined the medical records of 202 patients with endometrial carcinoma and cervical involvement who were treated between January 1, 1972 and January 1, 1988. All patients were treated by members of the section of gynecologic oncology and/or radiation oncology of Rush Medical College, Chicago, Illinois. The patients were retrospectively assigned to have cervical involvement based on a review of the histopathology. Inclusion criteria included patients with FIGO clinical stage II endometrial carcinoma, the cervical involvement having been documented by ECC, cervical biopsy, or cone biopsy. Also included were patients with clinical stage I endometrial carcinoma where the cervical involvement was diagnosed on the basis of the hysterectomy histopathology. Patients with a diagnosis of leiomyosarcoma, malignant mixed mullerian tumor, or second primary malignancy diagnosed within the preceding 10 years were excluded from the study.

For the purposes of data analysis, patients were grouped into five treatment categories (groups 1–5). Statistical comparisons of recurrence rates among these treatment groups were purposely avoided because of the retrospective nature of the study, the selection bias created when choosing the treatment modality, and the disproportion of prognostic factors among the patients in each group. After opening the abdominal cavity, samples of pelvic washings were obtained and a thorough search of the abdomen, pelvis, and retroperitoneum was performed to rule out metastatic disease. The surgery included extrafascial hysterectomy or radical hysterectomy (RH) with removal of the adnexa and selective lymphadenectomy or complete lymphadenectomy, respectively. In selected patients, no lymph node dissection was performed. Patients in group 1 underwent an RH, bilateral salpingo-oophorectomy (BSO), and pelvic and aortic lymphadenectomies lymph node sampling (LNS) as part of their treatment (RH/BSO/LNS). In addition, six patients were subjected to whole pelvic RT (mean dose 48 Gy), three preoperatively and three postoperatively. Patients in group 2 were treated with extrafascial hysterectomy (TAH) and BSO (TAH/BSO). At the discretion of the primary surgeon, no patients in this group were subjected to lymph node sampling. Group 3 received whole pelvic RT (WPRT) with either cobalt-60, 4-MeV, or 8-MeV equipment delivered in fractions of 180–200 cGy/day (mean 49 Gy). Then a Fletcher-Suit afterloading device was placed, delivering a mean of 3,150 mg-hours to the uterus and a mean of 29 Gy to point A. Serious medical problems precluded surgery or more aggressive therapy in this treatment arm. Group 4 (RT/TAH/BSO ± LNS) was treated with WPRT delivered in fractions of 180–200 cGY/day to a total of 41 Gy. Next, intracavitary RT (ICRT) was delivered via a Fletcher-Suit afterload-

ing device, giving a mean of 3,180 mg-hours to the uterus and 30 Gy to point a. These patients (group 4) were then treated with TAH/BSO 6 weeks after RT. Selected patients in this group were subjected to LNS. A fifth treatment group (TAH/BSO/RT) was treated initially with TAH/BSO ± LNS followed postoperatively by WPRT (mean 49 Gy). Fifteen of these patients were given an additional boost to the vaginal mucosa with a Manchester cylinder (mean 55 Gy) and another three received a paraaortic boost (mean 45 Gy).

The records of each patient were reviewed for height, weight, age, and frequency of medical problems. Additionally, records were reviewed for traditional prognostic factors, perioperative and long-term complications including estimated blood loss, operative time, hospitalization length, and frequency of perioperative infection. An operative death frequency was calculated and defined as any death occurring within 30 days of the date of surgery. The frequency of bowel obstruction also was reviewed and was defined as a loss of bowel function documented by symptoms and/or abdominal x-ray and requiring enteral tube (nasogastric or cantor) placement. The frequency of gastrointestinal and genitourinary complications also were determined. Each was documented by clinical examination or by radiographic study. In addition, chronic complaints such as enteritis, proctitis, urinary dysfunction, and lymphedema were recorded. Recurrences were all documented by biopsy if pelvic in nature and radiographically or by biopsy if distant in nature.

Statistical computations and life table analysis were performed using an SPSS-X program (10). Student's *t* test was used to evaluate comparison of two means.

RESULTS

The clinical and histopathologic data reviewed identified 202 patients with endometrial carcinoma and cervical involvement. The mean age of the patients was 63 years, mean weight 67.5 kg, and mean parity 1.8. The physical parameters of each treatment group and the frequency of medical problems is shown in Table 1. Ninety percent gave a history of vaginal bleeding as their chief complaint. Extrauterine disease was documented in 27 of 84 of the patients (32%) whose primary treatment was surgical. In 93 patients (46%) less than half of the myometrium had been invaded by tumor, whereas in 109 (54%) more than half of the myometrium had been invaded by tumor. The distribution of tumor grade was 25%, 45%, and 30%, respectively, for grades 1 through 3. The mean follow-up time for all patients was 82 months.

TABLE 1. *Physical characteristics and medical problems among treatment groups*

	Mean age (yr)	Wt (kg)	Ht (cm)	% Medical problems (n)
Group 1: RH/BSO/LNS (n = 33)	65	67.4	155	48 (16)
Group 2: TAH/BSO (n = 37)	61	70.4	161.7	42 (15)
Group 3: RT (n = 27)	63	67.5	159.2	93 (25)[a]
Group 4: RT/TAH/BSO ± LNS (n = 37)	62	63.4	159.6	43 (16)
Group 5: TAH/BSO ± LNS (n = 68)	64	68.8	160.4	35 (24)

[a] $p < 0.0001$.

It is interesting to note that in patients who underwent a formal staging workup including a fractional dilatation and curettage before any RT, cervical disease could be confirmed at hysterectomy in only 51 of 79 patients (65%). Furthermore, only 24 (12%) of the original 202 patients had surgical stage II disease.

The frequencies of the various major prognostic factors and 5-year actuarial survivals within treatment groups are shown in Tables 2 and 3. There were 80 (40%) recurrences overall: in 49 of 202 (24%) the recurrences were isolated to the pelvis, whereas in 21 of 202 (10%) the recurrences were

TABLE 2. *Prognostic factors and long-term survival among surgical treatment arms in patients with endometrial cancer and cervical involvement*

Prognostic factor	Group 1 (n/%)	Group 2/ group 5 (n/%)[a]	Group 4 (n/%)
Gross cervical involvement	58/19	19/10	38/14
More than myometrial invasion	42/14	63/34	35/13
Grade III histology	30/10	24/10	27/10
Adnexal metastasis	18/6	15/8	16/6
Positive pelvic lymph nodes	21/7	19/8[b]	5/2
Positive aortic lymph nodes	9/3	10/4[b]	8/3
Positive peritoneal cytology	27/9	31/17	16/6
Actuarial survival	86/33	69/105[c]	65/37

[a] Fifty-four patients had histologically documented cervical involvement.
[b] Forty-two patients had formal lymph node dissection.
[c] One hundred five patients had clinical stage II endometrial adenocarcinoma initially evaluated by extrafascial hysterectomy.

TABLE 3. *Long-term survival in endometrial carcinoma with cervical involvement*

Treatment	No. of patients	5-year actuarial survival (%)
RH/BSO/LNS	33	86
TAH/BSO	37	77
RT	27	35
RT/TAH/BSO ± LNS	37	65
TAH/BSO/RT ± LNS	68	61
Total	202	65

distant and in 10 of 202 (5%) disease was diagnosed in the pelvis and distantly at the same time. However, if we exclude patients who did not have surgery (group 3), then 34 of 175 (19%) had pelvic recurrences. If all patients with pelvic recurrences are considered, isolated recurrences as well as pelvic and distant recurrences, then 59 of 202 (29%) had local recurrences.

Evaluation of recurrences by treatment shows that surgery, particularly radical surgery, plays an important role in local control (Table 4). The role of RT alone is less clear. Patients in group 1 (RH/BSO/LNS) had a pelvic recurrence rate of 6%. Three patients (9%) had distant recurrences, and one patient had both pelvic and distant recurrences diagnosed simultaneously. Nineteen of the 33 patients (58%) in this treatment arm had gross cervical involvement, and three (9%) had positive aortic lymph nodes (Table 2). Seven patients had cervical tumors that were large (>3 cm) before treatment and were treated by RH. Two of these patients had recurrences. One had a local recurrence and one a distant recurrence 18 and 26 months after diagnosis, respectively (Table 5). Treatment of bulky cervical disease with other treatment options was much less effective.

Five patients (14%) treated with a TAH and BSO (group 2) had isolated pelvic recurrences. Two patients in this arm had recurrences both in the pelvis and distantly, and four additional patients had distant metastases. Patients treated with RT alone (group 3) had an overall 5-year actuarial survival rate of 35%, and 15 of 27 (56%) had isolated pelvic recurrences. One additional patient had both a pelvic and a distant recurrence. Therefore, removal of the pelvic disease appears to be of utmost importance (Tables 3 and 4).

TABLE 4. *Sites of recurrence in endometrial carcinoma with cervical involvement*

	Pelvic (n/%)	Distant (n/%)	Both (n/%)	Total (n/%)
RH/BSO/LNS (group 1; n = 33)	2/6	3/9	1/3	6/18
TAH/BSO (group 2; n = 37)	5/14	4/11	2/5	11/30
RT (group 3; n = 27)	15/56	3/11	1/3	19/70
RT/TAH/BSO ± LNS (group 4; n = 37)	11/30	3/8	0/0	14/30
TAH/BSO/RT ± LNS (group 5; n = 68)	16/24	8/12	6/9	30/44
Total (n = 202)	49/24	21/10	10/5	80/40

Interestingly, of the patients treated with conventional preoperative RT followed by TAH (group 4) 11 (30%) had local recurrences, whereas three (8%) had distant recurrences. The tumor burden was significant in this group because 14 patients (38%) had gross cervical involvement (Table 2). In six the tumor was >3 cm; their 5-year survival rate was exceptionally poor at 18%. In addition, three patients in this group had aortic lymph nodes that tested positively for disease. Each of these patients died from their disease despite adjuvant extended-field RT. Two patients (5%) had pelvic lymph nodes that tested positive for disease despite having undergone preoperative RT. One of these patients died 11 months later with a pelvic recurrence.

In the fifth study arm, patients treated primarily by TAH followed by RT, 16 (24%) had pelvic recurrences, eight had distant recurrences, and six demonstrated both pelvic and distant disease at the time of the diagnosis of their recurrence. Four patients in this group had aortic lymph nodes that tested positive for disease (Table 2). Three of the four received RT (45 Gy) to the aortic region. The other patient was treated with chemotherapy. All four patients died from recurrent disease in the abdomen. Together, groups 2 and 5 had eight patients (19%) with pelvic lymph node metastasis, and four of these had a pelvic recurrence despite postoperative RT. Fifteen patients also were given a vaginal mucosal boost. Three patients within this subset had recurrences in the upper vagina and pelvis despite this therapy.

TABLE 5. *Long-term survival in patients presenting with large cervical disease (>3 cm)*

Treatment	No. of patients	5-year acturial survival
RH/BSO ± RT (group 1)	7	74%
RT (group 3)	3	0%
RT/TAH/BSO (group 4)	6	18%

No patients with cervical disease >3 cm were treated initially with hysterectomy.

The mean time from diagnosis to recurrence in all 202 patients was 32 months, and the mean time from recurrence to death was 9 months. Survival in patients diagnosed with recurrences was dismal. Three patients (4%) remained alive without evidence of disease 32, 76, and 93 months after their recurrences were diagnosed and subsequently treated (Fig. 1). Each of the survivors was diagnosed with a local pelvic recurrence and was treated with a combination of whole pelvic and vaginal RT. None of the three survivors had been treated with previous RT. One had been treated with radical surgery and two with TAH.

Treatment-related complications also were studied in each of the five treatment groups (Table 6). It should be noted that in several cases, especially in group 3 patients, it was very difficult to ascertain between complications that were secondary to recurrent disease or were treatment related. The radical surgery patients (group 1) experienced very little serious morbidity. Despite concomitant use of RT in six patients, no major injuries to the gastrointestinal or genitourinary tracts were noted. Four patients experienced minor complications: chronic bladder dysfunction in two patients and radiation proctitis in two. Each was managed with conservative therapy.

The only perioperative death in the study occurred in group 2. She died of congestive heart failure 14 days after undergoing TAH/BSO. Three patients in group 3 experienced partial small bowel obstruction, although operative intervention was not performed in any patient. In addition, four patients in this arm encountered enteric fistulae as complications of their RT and/or progressive disease. Three were rectovaginal, and one was vesicovaginal. Because of the poor medical condition of this subgroup of patients, each of these complications was managed conservatively. In addition, 21% of these patients complained of chronic pain secondary to rectal stricture, radiation enteritis or proctitis, or urinary dysfunction requiring conservative medical management.

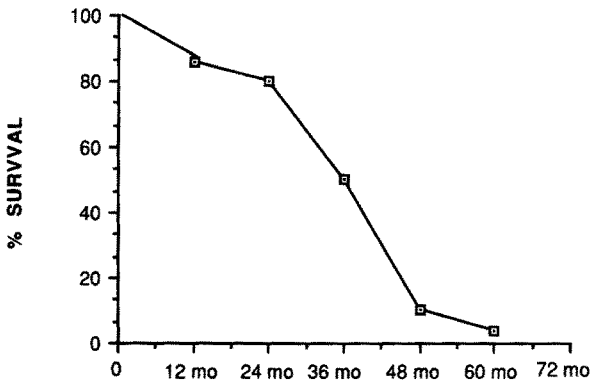

FIG. 1. Overall survival in 80 patients with documented recurrences in endometrial carcinoma with cervical involvement. Three patients (4%) achieved long-term survival with salvage therapy.

TABLE 6. *Treatment complication (%) in endometrial carcinoma with cervical involvement*

Treatment	SBO	GI/GU fistula	Chronic enteritis, proctitis, and urinary dysfunction	Death
RH/BSO/LNS (group 1)	0	0	12	0
TAH/BSO (group 2)	0	0	0	5
RT (group 3)	11	13	21	0
RT/TAH/BSO ± LNS (group 4)	19	0	5	0
TAH/BSO/RT ± LNS (group 5)	13	0	15	0

In Group 4, where external RT and ICRT preceded the surgical treatment, seven of 37 patients' courses (19%) were complicated by small bowel obstruction over a 10-year period. Two of these patients required operative intervention (Table 6). When RT was given postoperatively after simple hysterectomy (group 5), nine patients (13%) experienced complete or partial small bowel obstruction. Two of these cases required operative intervention. Ten patients in this group had chronic problems such as radiation enteritis/proctitis or unexplained pain.

Overall, the mortality rate related to treatment was minimal (0.05%), but significant morbidity occurred in groups 4 and 5. Most of the complications were managed conservatively, but 15% (16 of 105) required surgery to correct the problem. The mean blood loss, operating room time, infection rate, and mean length of hospital stay for the five treatment groups are shown in Table 7. Significant differences were noted between the RH group and the other treatment group in terms of estimated blood loss ($p < 0.05$), operative time ($p < 0.05$), and length of hospitalization ($p < 0.05$).

DISCUSSION

The grave implications of cervical involvement in endometrial carcinoma can be seen in 5-year survival rates of 57% in clinical stage II disease compared with 74% for clinical stage I disease as re-

TABLE 7. *Surgical factors in various treatment modalities for endometrial carcinoma with cervical involvement*

Treatment group	Estimated blood loss (ml)	Operative time (min)	Infectious morbidity (%)	Hospitalization time (days)
RH/BSO/LNS	1,150[a]	215[a]	4	10.0[a]
TAH/BSO	400	110	1	5.0
RT	NA	NA	7[a]	NA
RT/TAH/BSO ± LNS	800	150	5	7.8
TAH/BSO/RT ± LNS	550	120	4	6.3

[a] Statistically significant complications.

ported by Kottmeier (11). Similarly, we report a 61% survival rate with surgically confirmed cervical involvement and a 65% survival rate for the entire group of patients. Despite aggressive treatment, the local recurrence rate remains high (24%). Patients treated with RT alone had a particularly high pelvic recurrence rate (56%). It is now recommended, although not universally practiced, to surgically stage these patients before administering RT (1,2,5,7). Although we believe that initial TAH, BSO, and staging treatment offers the benefit of defining the extent of extrauterine disease and prevents overaggressive treatment postures in the setting of a falsely positive ECC result, we have found that any treatment short of radical surgery in the presence of gross cervical disease, especially in the setting of bulky (>3 cm) cervical disease, does not provide adequate local control. It should be clear from the results presented here that RH should be strongly considered when gross cervical involvement is present. Despite suggestions in the past that older, obese patients could not tolerate this radical procedure, our results and the results of others suggest otherwise (12).

These data demonstrate the low frequency (6%) of pelvic recurrences in patients treated with radical surgery despite the fact that a large percentage of these patients had gross cervical involvement and extrauterine disease (Tables 2 and 4). Others have confirmed the excellent survival rates and infrequent pelvic recurrence rates using RH in stage II endometrial carcinoma, but these studies lack substantial numbers of patients with bulky cervical disease (2,9,13). Larson et al. reported no pelvic recurrences in 69 patients who received pelvic irradiation and surgery (14). However, only 12 patients (14%) of the entire group had gross cervical involvement. No patients in that study had undergone primary radical surgery. It is not clear what proportion of these patients were in the group undergoing both RT and surgery. Trimble et al. also reported excellent local control with a modified combined radiotherapeutic/surgical approach in which only preoperative cesium (30 Gy) was given before TAH. The WPRT is held until the prognostic factors are defined surgically (15). Again, the limiting factor in their review was that only one patient had gross cervical involvement. Rubin et al. recently reported on 71 patients treated with preoperative WPRT followed by a modified RH and BSO, as well as postoperative vaginal brachytherapy. They reported excellent local control with this regimen, and the treatment was well tolerated. Again, although this regimen appears to work well in patients with occult cervical involvement, only a small percentage of the patients (16%) had gross cervical involvement, and these patients had a 39% 5-year rate of survival (16). Others have reported on the use of radiation in combination with surgery, but very few patients underwent RH (17). In contrast, we have recently reported a 75% long-term survival rate in patients with gross cervical involvement treated primarily by radical surgery (3).

Aside from the argument regarding local control of the tumor, the previous criticisms of radical surgery included high rates of urinary tract injuries, chronic urinary dysfunction, and the general assumption that elderly, obese, hypertensive, and diabetic patients would not tolerate the radical procedure. In the data presented here, we see that the majority of serious complications (e.g., bowel obstruction, fistula formation) occurred in groups other than those treated with RH. The frequency of bowel obstruction (13–19%) in groups 4 and 5 is in agreement with that reported in the literature by Larson et al., in which 12% had serious gastrointestinal or genitourinary problems. To reiterate, no gross disproportion of height, weight, age, or frequency of medical problems was detected among groups 1, 2, 4, and 5. However, the patients undergoing radical surgery did have an increased amount of blood loss, operative time, and hospital stay as compared with the other groups. The excellent recovery of the patients undergoing RH is no doubt due to careful patient selection and overall improvement in care in the past decade, including improved anesthetic techniques and thromboembolism and antibiotic prophylaxis, as well as improved surgical techniques. A recent review of 70 patients with suspected cervical involvement confirmed a low morbidity rate using a modified RH as the primary treatment modality. We are aware of the differences in

radicality between type II and type III RH; however, we have not seen the traditional high complication rates with the latter in the past decade.

Several questions are still unanswered. What is the appropriate therapeutic modality for occult cervical involvement? We have previously reported an overall 68% 5-year survival rate with occult cervical involvement in clinical stage II disease. We also have shown that the extent of occult involvement correlates with prognosis (3). Homesley et al. confirmed this concept in a review of 90 patients from Memorial Sloan Kettering Cancer Center, where those with occult cervical involvement had a 61% 5-year survival rate, and five of 24 (21%) of the recurrences in patients with occult cervical disease were local in nature.

Creasman et al. in the Gynecologic Oncology Group's series of 150 patients with occult stage II disease, reported a 20% and 11% frequency of pelvic and aortic lymph node metastasis, respectively. It is readily apparent that these data are not identical to those of stage I endometrial cancer and these patients therefore should not be treated as such. It also has been suggested, although in a retrospective fashion, that the timing of RT is not an independent predictor of outcome (18). Therefore, because of the increased risk of extrauterine disease when the cervix is suspected to be clinically involved in endometrial carcinoma, we believe that an operative assessment is indicated so that the RT can be tailored to the individual patient's needs. It is not clear whether a TAH or a type II or type III RH is indicated in the presence of occult disease, but a prospective randomized trial comparing different types of surgery has never been performed. A type III RH in this series provided excellent local control and long-term survival with minimal morbidity in patients with gross cervical involvement and is on recommendation in this clinical area.

Because of its rarity, stage II endometrial carcinoma should be studied in a multicentered, prospective, randomized, controlled fashion. The present and past data would indicate that initial therapeutic options of radical surgery, TAH, and pre- and postoperative RT are some of the important controversies that need to be evaluated. However, over the past 25 years, trends toward more or less aggressive therapy have not significantly altered overall survival. Patients with the aforementioned poor prognostic factors such as bulky cervical disease and/or extrauterine disease, because of their high local and distant recurrence rates, are candidates for adjunctive therapy in the form of combinations of chemotherapy, RT, hormonal therapy, and biologic response modifiers.

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