Editorial Article

Management of endometrial carcinoma with cervical involvement. An unsettled issue

J. Menczer, *M.D.*

Department of Obstetrics and Gynecology, Gynecologic Oncology Unit, Edith Wolfson Medical Center, Holon, Sackler Faculty of Medicine, Tel-Aviv, University, Tel-Aviv (Israel)

Summary

The purpose of the present report is to review the various management options of endometrial carcinoma with cervical involvement. A Medline literature search for publications dealing with endometrial carcinoma (EC) with cervical involvement and treatment was made. Although many publications deal with EC with cervical involvement there is a lack of prospective controlled trials. Only one prospective randomized phase III trial has been published. The inaccuracies of clinical staging, the scarcity of reports with surgically staged patients, the multiple types of cervical involvement and prognostic indicators and the remarkable variations in treatment render it difficult to compare outcome results between publications. The small number of patients in many of these studies and their retrospective uncontrolled nature add to this difficulty. There are conflicting reports with regard to factors affecting outcome, also complicating the management issue of endometrial carcinoma with cervical involvement and comparison of treatment results. The optimal management of EC with cervical involvement remains to be established.

Key words: Endometrial carcinoma; Cervical involvement; Treatment.

Endometrial carcinoma (EC) is the most common malignant tumor of the female genital tract in developed countries [1] and its incidence seems to be rising [2, 3].

The great majority of the neoplasms are diagnosed in Stage I, and the survival of these patients is excellent except in undifferentiated tumors or in those deeply invading the myometrium. The adverse effect on outcome of cervical involvement in EC has long been recognized [4]. Since 1963 it has been taken into account in the Federation of Gynecology and Obstetrics (FIGO) staging [5] and is considered as Stage II.

The prevalence of patients with cervical involvement, based on clinical staging, is only about 10% [6] ranging in most series between 7% and 15% [7]. While the treatment of some Stage I EC patients is still controversial [8], the preferred management of EC with cervical involvement is even less clear.

The purpose of the present report is to review the various management options of EC with cervical involvement based on a Medline search that included the terms EC, cervical involvement, Stage II EC or neoplasm, and management or treatment.

Accuracy of cervical involvement diagnosed by fractional curettage

Previously, staging of endometrial carcinoma was clinical and involvement of the cervix was established mainly by fractional curettage. Determination of cervical involvement by this procedure was found to be very erroneous. Inaccuracies in clinical staging were found in up to 50%-60% of the cases [2, 9-12].

Endocervical curettage was also found to have a 13% false-negative rate [12]. Others stated that the absence of carcinoma in endocervical curettage is highly predictive of absence of cervical involvement by EC but the presence of tumor in the endocervical curettage was associated with true cervical involvement in only one-third of the patients [13]. In many series a large proportion of patients with clinical Stage II were either downstaged or upstaged. In a study based on a retrospective review of 156 EC patients diagnosed from 1978 through 1984 who underwent primary surgical evaluation, all cases were retrospectively restaged using the FIGO surgical staging system. Most patients had extrafascial total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) with a collection of peritoneal washings and retroperitoneal lymph node sampling. According to the preoperative FIGO clinical staging, 77.6% of the patients were in Stage I, 14.1% in Stage II, and the remaining patients were Stage III/IV or unstaged. Retrospective surgical restaging revealed 78.2% to be in Stage I, and 5.8% in Stage II. Thus surgical staging upstaged 12.4% of clinical Stage I and in clinical Stage II, 59.0% were downstaged while 27.3% were upstaged [14]. Similarly in a series of 70 patients with clinical Stage II who had primary surgery, only 37% of the patients had operative findings consistent with the preoperative clinical suspicion of Stage II disease; 41% were upstaged because of extrauterine disease and 22% downstaged to Stage I [15]. It is thus obvious that EC patients considered to have cervical involvement, i.e. clinical Stage II, on the basis of fractional curettage, were a heterogeneous group. This group included patients with and without cervical involvement, as well as patients with positive lymph nodes, positive peritoneal cytology and upper abdominal disease in addition to cervical involvement.

Parametrial involvement in EC patients with cervical involvement

On histological examination of resected parametria in 91 EC patients who underwent radical or modified radical hysterectomy with pelvic lymphadenectomy, parametrial involvement was found in three (11.5%) of 26 FIGO surgical Stage II patients. It was found in none of 48 Stage I and nine (52.9%) of 17 Stage III patients (16). Recently Sato *et al.* [17] reviewed the resected parametria from 269 EC patients who underwent radical or modified radical hysterectomy with pelvic lymphadenectomy. Parametrial histopathological spread was found in two (6.3%) of 32 patients with cervical involvement.

Lymph node involvement in EC patients with cervical involvement

Several studies have shown that cervical involvement correlates with lymph node involvement [4, 11, 18-20]. Larson *et al.* [19] cite older publications in which the rate of pelvic lymph node metastases ranges between 23% to 35% and that of paraaortic nodes randomly biopsied between 5% to 35%. Hirahatake *et al.* [21] detected positive pelvic lymph nodes in 31.4% and paraaortic lymph nodes in 15.7% in clinical Stage II EC patients. In contrast, Ayhan *et al.* [22] found that cervical involvement was a predictor of lymph node involvement in univariate but not in multivariate analysis.

Mariani *et al.* [23] analyzed 112 patients with pelvic and/or paraaortic node involvement diagnosed at surgical Staging of EC patients. Metastases to common iliac nodes were significantly associated with cervical involvement. The most frequent site with metastatic lymph nodes in patients with cervical involvement was the external iliac chain (67%).

Extrauterine metastases have been documented in about 30% of patients with cervical involvement (24) and distant metastases in up to 20% of such patients [2, 24, 25].

Types of cervical involvement

Larson *et al.* [27] reviewed 58 EC patients with cervical involvement diagnosed by gross examination or endocervical curettage. He identified three clinicopathologic groups: gross cervical involvement (10 patients), occult stromal invasion (25 patients), and no evidence of stromal invasion (23 patients). It is not clear whether the latter group includes only patients with microscopic endocervical disease or also patients with gross tumor in the endocervix that was not identified on clinical examination. In a more recent retrospective study, Lanciano *et al.* [28] reviewed 184 patients with clinical or pathological Stage II EC. In this study cervical involvement was defined as gross involvement if a macroscopic lesion was seen on physical examination and as microscopic if, in the presence of normal cervical examination, the fractional curettage was positive for cervical involvement. It is obvious that the latter group included also patients with occult gross cervical involvement of the endocervical canal. It should be noted that the types of cervical involvement in both of these studies do not parallel the subdivision of the currently used FIGO surgical staging system.

Spread to the cervix

Cervical involvement in EC may be the result of contiguous or lymphatic spread.

Kadar *et al.* [10] thought that spread to the cervix in EC appears to be more frequent by tissue spaces or lymphatic channels than by contiguous surface extension, since in their series of 54 patients more patients had stromal than superficial involvement. However, in other series the number of patients with superficial and stromal involvement was equal [29] or there were more patients with superficial than with deep involvement [30-32].

The FIGO surgical staging system of endometrial carcinoma

In 1988 FIGO adopted the surgical staging system [33] that requires in addition to extrafascial hysterectomy and salpingo-oophorectomy (TAH/BSO), assessment of peritoneal fluid, of pelvic and paraaortic lymph nodes, and exclusion of upper abdominal disease. Accordingly, patients are initially operated on and cervical involvement is determined after histopathological examination of the excised uterus. This obviously overcomes the problem of establishing isolated cervical involvement and fractional curettage is actually not required. According to the new FIGO surgical staging system cervical involvement (i.e. surgical Stage II) is divided into Stage IIA when there is only endocervical glandular involvement and Stage IIB when there is invasion of the tumor into the stroma of the cervix.

Treatment of EC with cervical involvement

Only a few studies report results of one type of management. Most reports are retrospective and deal with the experience of single institutions with a variety of treatment methods. In the past, one of the most commonly used methods was preoperative external pelvic radiotherapy (ERT) or brachytherapy (BT) or both followed by TAH. In addition TAH followed by ERT or BT or both, radical hysterectomy or extended hysterectomy and bilateral pelvic lymphadenectomy alone or followed by irradiation and radiotherapy alone have also been used. Since the introduction of the surgical FIGO staging system, the tendency is to avoid preoperative radiation, to treat the patients with primary surgery and to surgically Stage all EC patients.

Many of the following reports dealing with treatment were published in 1988 or later, i.e. after the advent of the 1988 FIGO surgical staging system but they also comprise patients treated before 1988.

Preoperative irradiation followed by surgery

Boronow [34] was among the first to suggest preoperative pelvic irradiation and intracavitary radium in an attempt to overcome possible pelvic lymph node involvement in patients with cervical involvement.

Larson *et al.* [25] reported that of 83 clinical Stage II EC patients diagnosed between 1964 and 1983, cervical involvement was diagnosed by endocervical curettage in 51, by punch biopsy in 18 and by cone in two patients. Gross cervical involvement was present in 12 patients. Preoperative ERT followed by surgery was used in 64 (77%) of these patients. At surgery, 11 (17%) of these 64 patients had extrauterine metastases compared to four of ten (40%) without preoperative radiotherapy. The difference was statistically not significant. Four of 64 (6%) who had preoperative irradiation had pelvic metastasis compared to three of ten (30%) that did not. Five of 24 patients who had pelvic lymph nodes sampled had node involvement - one (6%) of 16 with and four (50%) of eight without preoperative radiotherapy ($p = 0.03$). In summary 20% had clinically occult extrauterine spread. Survival was similar in patients who did and did not have preoperative radiotherapy (64% and 60%, respectively). Pelvic recurrence was not observed in any of the 64 patients who received preoperative radiation but extrapelvic recurrence occurred in 17 (27%). In seven (11%) patients severe complications occurred after preoperative radiotherapy and two deaths could be attributed to treatment. Trimble *et al.* [35] reviewed the charts of 36 patients with clinical Stage II EC diagnosed over ten years. Fourteen patients were treated with a "standard" protocol involving ERT followed by cesium BT and then TAH. In 1981, a "modified" protocol was introduced, which called for TAH immediately following intrauterine and vaginal cesium. ERT was given only to those patients found to have deep myometrial invasion or residual cervical involvement. Of 14 patients treated by this protocol, seven had no surgical indication for postoperative external radiation. There was no increase in recurrence in these patients, and the five-year survival rate in these small groups of patients was 76% for patients treated with the modified protocol compared with 65% for those who had standard therapy. Morbidity related to ERT occurred in two patients with the standard protocol and one patient who received pelvic radiation on the "modified" protocol. According to the authors these results compare favorably with the best results obtained by other treatment methods. Podczaski *et al.* [36] treated from 1972 to 1987, 36 patients with clinical Stage II carcinoma of the endometrium with ERT, a single BT (cesium) application, and TAH, BSO. Patients were followed for a median of 54.4 months. Overall 2- and 5-year actuarial survival rates were 83 and 58%, respectively. Survival was analyzed in terms of independent variables such as surgical stage, presence of a gross cervical lesion, and residual disease within the myometrium or cervix. The 12 patients with a gross cervical lesion at clinical staging had a significantly worse prognosis, as compared to those without such a lesion ($p < 0.05$). Seven of these 12 (58%) demonstrated persistent or recurrent disease. The presence of extrauterine disease at surgery was a major prognostic factor in patient survival ($p < 0.01$). All six patients with extrauterine disease expired 2.3 to 53.0 months after surgery and two patients with persistence of disease expired 2.3 and 7.5 months after surgery. Eleven patients developed recurrent disease 2.1 to 56.5 months after surgery. All presented with distant metastases. Four of the 13 patients with persistent or recurrent disease had no residual tumor in the endometrium. Higgins *et al.* [37] reported 74 clinical Stage II EC patients diagnosed from 1967 to 1988 by cervical curettage or cervical biopsy and treated by a combination of preoperative radiation therapy followed in four to six weeks by TAH/BSO, and paraaortic lymph node sampling. All patients had histologically confirmed EC with involvement of the endocervix. Non-endometrioid EC was present in ten patients. Five patients (7.1%) had paraaortic lymph node metastases. Four were treated with extended-field radiation therapy and one with platinum-based combination chemotherapy. Eleven patients (15%) had recurrent cancer, with the vagina and upper abdomen being the most common sites of spread. The estimated 5-year and 10-year disease-free survival rates of these patients were 88% and 76%, respectively. The complication rate was only 5.4%. The authors concluded that the combination of preoperative radiation therapy and surgery produces excellent long-term survival in EC patients with cervical involvement. Reisinger *et al.* [38] reviewed 30 patients diagnosed from 1980 to 1987, with FIGO clinical Stage II EC. Patients in whom cervical involvement was based on fractional curettage or positive cervical biopsy with no gross disease, were treated by preoperative ERT. Patients with gross cervical disease received in addition BT. All patients were subsequently operated on. The 5-year actuarial survival for EC of endometrioid type was 82%. They concluded that preoperative ERT together with surgery offer excellent local control in all patients with clinical Stage II EC of endometrioid type. Zablow *et al.* [39] retrospectively reviewed 77 endometrial carcinoma patients with cervical involvement diagnosed by fractional curettage but confirmed pathologically. During one period patients were treated by ERT followed six weeks later by either radical or modified radical hysterectomy. During a second period preoperative ERT as well as BT were given followed after six weeks by simple TAH. The overall 5-year actuarial survival was 78% without a difference between the two treatment groups. Major complications (3%) were seen only in the radical surgery group. Maingon *et al.* [40] in a retrospective study of clinically staged patients diagnosed between 1976 and 1996, reported on two arms of preoperative radiotherapy. One arm included early stage, low-risk EC patients and the other included patients with grade 3 and 89 EC patients with cervical involvement diagnosed by deep endocervical biopsy. Of these, 13 had preoperative BT only and 73 had ERT combined with BT followed in six weeks by TAH/BSO. No disease was found in the cervix after the radiotherapy in about a third of these patients. Serious complications were observed in five patients: two fistulas (one rectovaginal and one vesicovaginal) where surgically corrected, one bowel obstruction required resection and end-to-end anastomosis and two instances of urinary incontinence. The 5-year survival for patients with cervical involvement was

84%. Of the total group, three had pelvic failures. They stated that preoperative radiotherapy is a safe and effective treatment method. In a previous paper this group reported six distant failures among 66 patients with cervical involvement [41].

The optimal method and dose of preoperative irradiation has not been defined but brachytherapy alone does not seem to deliver an adequate dose to control subclinical pelvic metastatic disease [25].

Primary surgery

Primary surgery and postoperative tailored radiotherapy has become the more commonly used treatment therapy for Stage I and II EC after the advent of surgical staging. However, in most of the reports dealing with primary surgery and published after 1988, no formal FIGO surgical staging was performed. Some of these because they comprise patients treated before it was introduced [15, 42] but some also comprise patients treated after its introduction [29, 43].

The type of primary surgery in most publications is not uniform even in the same institution. Thus, in one study [43] surgery consisted of TAH/BSO, of TAH/BSO and lymph node dissection, of radical hysterectomy with lymph node dissection and of vaginal hysterectomy without salpingo-oophorectomy (in one case).

Andersen [42] analyzed 54 patients with clinical stage II EC determined by preoperative clinical examination, cervical biopsy and endocervical curettage, treated from 1974 to 1986. The majority of the patients (n = 34) were treated by TAH/BSO followed by combined ERT and BT. The remaining patients were treated by the same type of surgery but had preoperative BT and postoperative ERT (n = 8) or ERT and BT alone (n = 12). The highest cure rate (70.6%) was observed in patients treated with simple TAH/BSO followed by irradiation. Mannel *et al.* [15] reviewed retrospectively 70 EC patients with suspected cervical involvement based on a positive endocervical curettage or punch biopsy, diagnosed from 1977 to 1987 who were treated with initial surgery followed by tailored radiation or chemotherapy. Serous papillary carcinoma was encountered in 17 patients. Only 37% of the patients had operative findings consistent with the preoperative suspicion of cervical involvement. Postoperative therapy was determined by the extent of cervical involvement, depth of myometrial invasion, cell type, tumor grade, and the presence and location of extrauterine disease. Based on these parameters, 21 patients received no adjuvant therapy (90% 5-year survival); 38 patients received postoperative ERT (65% 5-year survival); and 11 patients received chemotherapy and/or extended radiation because of extrapelvic disease (no 5-year survivors). The overall survival of the 70 patients was 60%. They support this approach of initial surgery for EC with suspected cervical involvement because it permits accurate surgical staging under the new FIGO system, avoids radiotherapy in many patients whose disease is less extensive than suspected preoperatively, and can accomplish good local control with limited morbidity. Feltmate *et al.* [43] retrospectively reviewed 65 EC patients diagnosed from 1988 to 1996 who had various types of primary surgery and pathologically confirmed cervical involvement. Of 42 patients that underwent lymph node dissection, only 11 had also paraaortic lymph node dissection. Postoperative complications occurred in 12 patients including five severe complications (1 fatal myocardial infarction, 1 respiratory failure, 1 deep vein thrombosis and 2 ileus episodes requiring long hospitalization). Postoperative BT, ERT or both were given to 54 patients and four of these had severe complications. An overall survival rate of 78% and an excellent 5-year disease specific survival of 93% were observed in this series. A recurrence after primary surgery occurred in ten (15.4%) patients - four in the pelvis or vagina and six distant. Myometrial invasion to the outer one-third, postoperative ERT alone and vascular space involvement were found to be significant predictors of recurrence on univariate analysis. Vascular space involvement was found to be a significant predictor in multivariate analysis as well. Weis *et al.* [44] did not find any locoregional recurrence after treatment by TAH/BSO and adjuvant combined ERT and BT, in a retrospective analysis of 33 patients who had pathologically confirmed cervical involvement. Lymph nodes were not assessed in this study. The 5-year survival was 79%. Distant relapse occurred in three (9%) patients, all with grade 3 tumors. Forty-two EC patients with pathologically confirmed cervical involvement treated between 1987 and 1998 were reported by Jobsen *et al.* [29]. All patients underwent primary surgery but had no formal staging and received ERT postoperatively. Of the total group, 21 (50%) had cervical stromal involvement. The median follow-up was 62 months. Overall recurrences occurred in nine (21.5%) patients. Seven patients had distant metastasis, of which three also had locoregional recurrence. The presence of myometrial invasion (> 1/2) and/or lymph-angio invasion showed a significant relation with distant metastasis ($p = 0.01$). Patients with stromal involvement also had more recurrences (33%). There was a significant different 5-year disease specific survival for those without and those with stromal involvement (95% and 74%, respectively; $p = 0.03$). Patients with cervical stromal involvement and grade 3 disease showed a significantly poorer 5-year survival (48.6%; $p = 0.003$). They concluded that the results obtained in this series are in accordance with the literature and that their treatment policy seems justified, except for patients with stromal involvement and grade 3 disease, in which a more aggressive treatment should be considered. Mariani *et al.* [32] reported the results of 57 EC patients with histologically documented cervical involvement FIGO surgical Stage II-III. Of these, 34 were Stage II (24 were IIA and 10 IIB). In patients treated before 1988, stage was determined retrospectively but not all patients had pelvic and paraaortic lymph node assessment. Surgery included simple TAH, wide TAH and radical hysterectomy. Adjuvant radiotherapy, namely ERT or BT or both, was administered to 38 (67%) of the total group of patients. The disease-related and the recurrence-free survival in Stage II patients was 91% and 88%, respectively. The 5-year disease-free survival for Stage II patients who underwent radical hysterectomy (n = 19) and

simple TAH (n = 15) was 100% and 73%, respectively. In patients with surgical Stage II disease who underwent radical hysterectomy no recurrences were observed irrespective of adjuvant radiotherapy while in patients who underwent simple TAH, adjuvant radiotherapy improved local control. Distant failures were observed in four (12%) of the 34 surgically staged Stage II patients. Sartori *et al.* [45] retrospectively reviewed the impact on outcome of two different surgical approaches (simple TAH vs. radical hysterectomy) and the effect of adjuvant radiotherapy on recurrence and survival in five Italian hospitals from 1980 to 1995. Of 1,606 EC patients, 203 (12.6%) had pathologically confirmed cervical involvement. Simple TAH was performed in 135 (66%) and radical hysterectomy in 68 (34%) of the patients. All patients in the radical hysterectomy group and 97 (72%) in the simple TAH group had pelvic lymph node dissection but paraaortic lymph node dissection was not done. Therefore these patients were not true FIGO surgical Stage II patients but should be considered as patients who were at least Stage II. Sixty-six (59%) of 111 of Stage IIA and 67 of 92 (73%) of Stage IIB patients underwent adjuvant ERT. The difference in actuarial 5-year survival rates for patients with Stage "IIA" and Stage "IIB" was statistically not significant (86% and 74%, respectively; $p = 0.072$). The 5-year survival rates were better in the radical hysterectomy group than in the simple TAH group (94% and 79%, respectively; $p < 0.05$). Local and distant recurrences were also less frequent in patients who underwent radical hysterectomy. The recurrence rate was 18.6% in the observation group and 11.3% in the ERT group with an overall rate of 13.8%, but the survival in the two groups was not different. Most of the relapses were regional in the observation group and distant in the ERT group. These authors found a very wide range (26% to 91%) of survival rate in various previous publications dealing with EC patients with cervical involvement treated by primary surgery and adjuvant radiation therapy. A survival advantage for patients treated by radical surgery as compared with simple TAH or combined treatment with radiation and surgery, especially in patients with numerous high-risk factors and patients with gross cervical involvement, has also been reported by Boente *et al.* [24].

It should be noted that in most of the patients included in the above-mentioned series no formal surgical staging according to current FIGO criteria was done, therefore the true extent of their disease is actually not known.

Only very few authors have reported treatment results of patients who had full surgical staging according to FIGO rules. Eltabbakh *et al.* [31] retrospectively reviewed 48 consecutive Stage II EC patients treated between 1984 and 1998 who were surgically staged. Surgical staging was defined as exploratory laparotomy, hysterectomy with salpingo-oophorectomy peritoneal washings and bilateral pelvic and periaortic lymphadenectomy or sampling. The main line of treatment for patients in whom cervical involvement was known before surgery (n = 11) was radical hysterectomy and the main line of treatment in those in whom it was diagnosed postoperatively (n = 20) was TAH followed by both ERT and vaginal BT. None of the patients treated by radical hysterectomy recurred while three of 17 (17.6%) patients treated with TAH followed by either ERT (n = 13) or vaginal BT (n = 4) had tumor recurrence. The difference between these two groups was statistically significant ($p = 0.02$). The estimated 5-year overall survival and disease-free survivals were 92.1% and 89.9%, respectively. There was no difference in survival among women who underwent radical hysterectomy and those who underwent simple TAH with postoperative combined ERT and BT. Morbidity secondary to therapy was mild. They concluded that survival of women with surgical Stage II endometrial cancer is excellent especially among those treated with TAH followed by both ERT and vaginal BT or by radical hysterectomy.

In a recent study Cornelison *et al.* [46] analyzed the Surveillance, Epidemiology, and End Results (SEER) data from 1988 to 1994 in order to estimate whether primary treatment differences using simple primary TAH (n = 365) or primary radical hysterectomy (n = 377), with or without postoperative radiation, altered disease-free survival of FIGO surgical Stage II EC. An overall 83.1% 5-year survival rate was estimated. The 5-year cumulative survival rate for patients who received simple hysterectomy and radical hysterectomy was 84.3% and 92.9%, respectively ($p < 0.05$). Survival for patients who received primary surgery followed by combination radiation therapy was 82.7% with simple TAH and 88% with radical hysterectomy ($p < 0.05$). There was no significant survival difference for radiation versus no radiation in either surgical group. They concluded that radical hysterectomy is associated with better survival when compared to simple TAH for FIGO surgical Stage II EC. Because the SEER 1988 guidelines do not subcategorize cervical involvement into IIA and IIB, separate results for these substages could not be given.

Greven *et al.* [30] concurred with previous studies showing that, in the presence of cervical involvement, combined ERT and BT are superior to postoperative BT alone, but in only about half of their 64 patients were lymph nodes and peritoneal cytology evaluated. In contrast, good results of postoperative low-dose rate BT [47] or high-dose rate BT without ERT, namely a survival of 84%-97%, and a low recurrence rate has also been reported in series of intermediate risk EC that included small numbers of surgically-staged Stage II patients [48, 49]. The survival of Stage II patients was not analyzed separately in these reports. In addition Ng *et al.* [50] recently found that postoperative vaginal vault BT brachytherapy is associated with minimal morbidity and excellent survival of Stage II (occult) EC patients who underwent extended surgical staging.

In this context, the only prospective randomized phase III study of the effect of postoperative radiotherapy in 392 surgically staged women with intermediate risk EC (FIGO Stages IB, IC, II occult), is noteworthy [51]. In this recently published Gynecologic Oncology Group study a distinction between a high intermediate risk subgroup (HIR) and a low intermediate risk subgroup (LIR) was made. The HIR subgroup included patients: 1) with moderately to poorly differentiated tumors, presence of lymphvascular space and outer third myometrial invasion; 2) aged 50 or greater with

any two risk factors listed above; 3) aged 70 with any risk factors listed above. Patients were randomized to either no additional postoperative treatment (NAT, n = 202) or postoperative ERT (n = 190). A non-significant 4-year survival difference was observed between the NAT and ERT groups (86% and 92%, respectively). The estimated 2-year cumulative incidence of recurrence was 12% in the NAT arm and 3% in the ERT arm (p = 0.007). This treatment outcome was even more evident in the HIR subgroup (26% and 6%, respectively). Regretfully, separate results for the 37 Stage II (occult) patients are not given separately.

Comparison between pre- and postoperative radiotherapy

Retrospective comparisons between pre- and postoperative radiotherapy have also been made. It must of course be taken into account, that the results are based on retrospective reviews of mostly clinically staged patients in various institutions. Lanciano *et al.* 1993 [52] analyzed 184 consecutive patients with clinical or pathologic cervical involvement. Only a minority of the patients underwent formal FIGO staging. Distant metastases after pre- and postoperative radiotherapy were diagnosed in 13% and in 4% of the groups, respectively, and pelvic failure occurred in 11% and 4%, respectively. They found no significant difference in 5-year disease-free survival between patients who had preoperative and those that had postoperative radiotherapy (77 and 87%, respectively). In other studies reported between 1979 to 1990, i.e. mainly in the presurgical staging era, the range of 5-year actuarial survival for pre- and postoperative radiation therapy was similar ranging from 57% to 85% and from 52% to 87%, respectively [6, 25, 28, 36, 53, 54].

In one study a comparison between patients who had pre- and postoperative BT only was made. Calais *et al.* [55] has retrospectively analyzed results of treatment of clinically staged 121 EC patients treated with preoperative BT and then radical hysterectomy (Group 1), and of 63 patients treated with radical hysterectomy and then postoperative BT (Group 2). BT consisted in both groups of 60 Gy. Thirty-three patients in Group 1 and 14 patients in Group 2 were in clinical Stage II. The remaining patients had Stage I disease. The 5-year actuarial survival for clinical Stage II patients was about 61% with no significant difference between the groups. The late severe complication rate was 14% in Group 1 and 7.9% in Group 2, a difference that was also not statistically significant. They concluded that since no differences were observed between the two techniques, vaginal BT should be given postoperatively when surgery is the primary treatment in patients with Stage I or II, grade 1 or 2, disease and with no deep myometrial invasion.

Ahmad *et al.* [6] summarized 32 reports published till 1989 of EC patients with cervical involvement treated by all methods including a combination of radiation therapy either before ore after surgery and found an average survival of 74% ranging from 44% to 91%.

Radiation therapy alone

Many EC patients are elderly with multiple medical problems and are therefore not suited for surgical treatment. Such patients may be treated by radiation therapy only. Cardiovascular disease, diabetes, age greater than 80 and morbid obesity are the most common indications for this treatment modality. These patients also frequently die of intercurrent disease. Patients receiving primary radiotherapy constitute 4 to 9% of EC patients [56].

In reports published mostly before 1980 and cited by Boothby *et al.* [7] the 5-year survival of these patients ranged from 29% to 77%. Ahmad *et al.* [6] reported a five-year actuarial survival of 16 patients treated with radiation therapy alone that was similar to patients treated with pre- or postoperative radiotherapy, namely 74.5%. He found that the survival of patients treated by radiotherapy alone in 18 reports published between 1963 and 1985 ranged between 0 to 91%. Lanciano *et al.* [28] reported a 5-year disease-free survival of 77% that was similar to their other modalities of treatment. Others reported survival rates of only 26% to 56% [42, 53, 57, 58].

Rose *et al.* [56] conducted a case-controlled analysis comparing corrected survival of 64 patients treated with primary radiation to patients, matched by clinical stage, tumor grade, and time of diagnosis, treated with surgical therapy with or without radiation therapy. Primary radiation therapy was used to treat 9.0% of the patients with endometrial carcinoma during the study period. Ninety percent of patients had either clinical Stage I or II disease. Forty-eight of the 64 patients (75%) completed treatment that included both ERT and BT. Ten patients received BT only. Twelve complications, both acute and chronic, occurred in 11 patients (17%). Intercurrent disease accounted for 13 (36%) of the 36 of the deaths. Although primary radiation therapy alone is generally considered inferior to a surgical approach for patients with EC, this case controlled study of clinical Stage I and II patients treated by primary radiation therapy matched to surgically treated controls showed no statistical difference in survival.

Adjuvant chemotherapy

The Gynecologic Oncology Group conducted a prospective randomized study on the use of adjuvant doxorubicin after surgery and radiation of EC with clinical Stage I or II (occult) who after surgery had risk factors for recurrence [59]. After surgical pathological evaluation, patients were randomized to receive doxorubicin (60 mg/m^2 starting dose to a maximum cumulative dose of 500 mg/m^2) bolus therapy (n = 92) or no doxorubicin chemotherapy (n = 89). There was no statistically significant difference between the two arms with regard to survival, disease-free survival or recurrence pattern.

Adjuvant hormonal therapy has also been tried. In a prospective randomized trial 388 Stage I and II EC patients

received adjuvant medroxyprogesteron acetate or tamoxifen or were observed only. This series included 66 patients with clinical Stage II disease who postoperatively received ERT. No survival difference was observed between those treated with medroxyprogesterone acetate and controls. However, an improved survival was observed in those treated with tamoxifen [60].

Factors affecting recurrence and survival

The great majority of recurrences (about 70% to 100%) occur during the first two to three years after therapy [7, 31, 45, 61, 62]. The overall pelvic and distant recurrence rate ranges in most series between 9% and 30% [7, 25, 32, 36-38, 43, 45, 61].

Boente *et al.* [61] retrospectively, studied the recurrence patterns and complications in 202 patients with histologically confirmed EC with cervical involvement but who did not undergo surgical staging, The 5-year actuarial survival rate for all patients was 65%. Treatment consisted of radical hysterectomy, simple TAH and pre- or postoperative radiotherapy. Patients treated with radical hysterectomy (n = 33) had a 6% isolated pelvic recurrence rate and the lowest serious complication rate. Patients treated by preoperative radiotherapy (n = 37) had the highest pelvic recurrence rate (30%). Serious gastrointestinal or genitourinary tract complications were experienced by 19% of the patients. Overall, 24% of the patients had isolated pelvic recurrences, 10% had isolated distant recurrences and 5% were simultaneously diagnosed with both pelvic and distant recurrences. While the database of this series of EC patients with cervical involvement is quite large the recurrence and serious complication rates seem to be extremely high.

Some authors reported that depth of myometrial invasion [2, 29, 37, 53, 63], age of more than 59 years [42] and high grade [28, 38, 39, 53, 63] were significant prognostic factors. On the other hand, Eltabach *et al.* [31], found that depth of myometrial invasion, tumor histology and grade were not significantly related to recurrence in surgically-staged Stage II patients. In one study [63] extent of involvement in the endometrial cavity was found to have a statistically significant influence on survival.

The effect of residual tumor after preoperative radiotherapy on survival is controversial [40, 53, 64]. Its presence may be influenced by the radiation dose, the radiotherapy method and by the time interval to surgery. Paradoxically Larson *et al.* [64] found that while the recurrence rate among 20 patients with no residual disease and 48 patients with residual disease was not significantly different (25% vs 21%, respectively), the actuarial 5-year survival rate was significantly lower in patients with no residual than in patients with residual disease (53% vs 78%, respectively; $p < 0.05$).

With regard to vascular space involvement, no discordant reports were encountered. In two publications it was found to have an adverse effect on outcome [29] and to be a predictor of recurrence [43].

Effect of cervical involvement-type on outcome

Opposite reports exist with regard to the effect of cervical involvement-type on treatment outcome. In some studies no survival difference was found between microscopic or occult and gross cervical involvement [7, 27, 28, 43, 45]. Larson *et al.* [27] stated that although the presence of cervical involvement in endometrial carcinoma is an important prognostic factor, the extent of cervical involvement does not appear to be of significant prognostic value. On the other hand a survival difference between microscopic and gross cervical involvement (61% vs 48%) that did not reach statistical significance was found in one study [65] while in others the survival difference between these two types of cervical involvement was statistically significant [11, 24, 36, 39, 66]. Similar conflicting results have been reported with regard to the effect on outcome of glandular and stromal involvement (Stage IIA and IIB). No difference in survival between these substages has been reported in some studies [10, 30, 45] while others [29, 42, 67, 68] found a statistically significant adverse effect of stromal involvement on survival. Jobsen *et al.* [29] reported a significant different 5-year disease specific survival for Stage IIA and IIB (95% and 74%, respectively; $p = 0.0311$) in patients who had pathologically confirmed cervical involvement but who were not surgically staged. They also found that Stage IIB showed more recurrences than Stage IIA. The poorest results in this series were obtained in patients with a Stage IIB grade 3 tumors (5-year survival of 48.6%; $p = 0.003$). Mariani *et al.* [32] noted that the association between cervical stromal invasion and distant failure was of borderline significance while Reisinger *et al.* [68] found that Stage IIA had a distant metastases rate of 14% whereas 44% of patients in Stage IIB developed distant disease ($p = 0.06$) at five years.

Discussion

Surgical staging of EC has several advantages over clinical staging. It overcomes the inaccuracy of the diagnosis of cervical involvement based on fractional curettage, establishes an accurate histological grade, provides a more precise assessment of depth of myometrial invasion and of the presence of extrauterine disease and allows tailored postoperative treatment and a more predictive prognosis [14, 52, 69].

However, it should be noted that today the preoperative diagnosis of cervical involvement can be made with great certainty. Obviously, when cervical involvement is established by biopsy of a gross cervical lesion or by conization, it is much more accurate than when it is based on fractional curettage. Some institutions have used cervico-hysteroscopy for the diagnosis of cervical involvement [45, 70]. Attempts of establishing preoperatively cervical involvement by imaging methods such as ultrasound, computed tomography and magnetic resonance have also been made. Magnetic resonance is

probably the most appropriate imaging method for this purpose [71]. Recently positron emission tomography has been used for follow-up in EC patients [72]. It could also be used for the preoperative diagnosis of cervical involvement.

It is beyond the scope of this review to deal with details of preoperative radiotherapy but it differs greatly in dose as well as in technique in the various publications [2, 37, 53].

If surgical staging is to be performed then preoperative irradiation should not be used anymore even if the diagnosis of cervical involvement has been preoperatively definitively established. However, survival data of EC patients with cervical involvement indicate a favorable outcome in patients treated by preoperative irradiation. The main objections to this treatment method is that many patients may be overtreated, that it makes the pathological examination of the uterus more difficult with regard to the determination of grade, depth of myometrial invasion and pelvic node involvement. As already pointed out, the above-mentioned modern means can today accurately establish cervical involvement even when it is occult on clinical examination. Extrauterine disease can often also be detected by modern imaging methods. It has been shown that irradiation is adequate to eradicate occult pelvic metastases [25, 73]. In addition, the presence of paraaortic node involvement can be established even after preoperative irradiation. Therefore patients so afflicted can still have postoperative extended field irradiation and or chemotherapy when necessary. Surgical staging, including the determination of the depth of myometrial invasion and of the tumor grade prior to preoperative radiation should not be a purpose in itself. Obviously, it is of great prognostic importance but a favorable treatment outcome may be of greater value to the individual patient. Thus preoperative radiation followed by simple hysterectomy can still be a treatment option for some patients. A fitting example is those patients who, to begin with, are not candidates for full surgical staging because of age-related co-morbidity.

The popularity of preoperative irradiation has declined but some groups still use it.

In 2001 Thomas *et al.* [74] published clinical practice guidelines for radiotherapy of EC in France. Once the guidelines were defined, the document was submitted for review to independent reviewers, and to the medical committees of the 20 French Cancer Centers. With regard to EC with cervical involvement these guidelines state that treatment can be preoperative when Stage II disease has been suggested by positive endometrial curettage. Curiously, the diagnosis of cervical involvement is based on fractional curettage although these guidelines were published about 13 years after the introduction of the new FIGO surgical staging system.

Some authors [61] strongly oppose preoperative ERT because according to them it may subject the patients to significant morbidity over a 5- to 10-year period and, in terms of local control, is not necessarily superior to therapeutic modalities using primary surgical evaluation, such as radical hysterectomy. Others oppose it because they are convinced that all patients should undergo surgical staging [75]. It is noteworthy that there is no proof of improved survival in surgically-staged Stage II patients.

Results with regard to primary surgery are also conflicting and difficult to compare. This can be attributed mainly the fact that many reports comprise clinically staged patients, i.e. series with a high proportion of under or overstaged patients [27, 28], others comprise patients with pathologically confirmed cervical involvement but without formal staging [24, 43 ,61] and only few comprise patients with true surgical Stage II disease [31, 46, 48].

Radical hysterectomy in EC patients was once considered to be associated with considerable morbidity [76] but this has not been confirmed in more recent studies [31, 45] probably due to more careful selection and general improvement in postoperative care. Radical hysterectomy seems to be a very effective treatment for patients with FIGO Stage II patients. Magino *et al.* [70] collected data by means of a questionnaire, concerning specific diagnostic and therapeutic options, sent to 115 leading centers for gynecological oncology in Western Europe. According to the 82 responses received, 79.5% of Stage II EC patients underwent radical hysterectomy. This rate of radical hysterectomy seems very high when the frequent co-morbidity of EC patients is considered. It is not clear how Stage II was established in these patients.

In some studies no significant differences in survival have been found between radical hysterectomy and simple TAH followed by irradiation [43]. Others reported a better survival [24, 45, 46, 61] and local control [23, 45] after radical hysterectomy than after simple TAH and postoperative radiation. In addition a selection bias exists since it may be assumed that patients who underwent radical hysterectomy were most probably younger and medically uncompromised.

Although the necessity of adjuvant irradiation after radical hysterectomy in many of surgically-staged Stage II is not certain, some authors have supported postoperative irradiation to improve survival, independently of the type of hysterectomy performed [31]. The technique and dose of postoperative irradiation also varies. Even in patients treated in the same institution the mode of postoperative irradiation is not uniform. Thus in one recent study postoperative radiotherapy consisted of ERT, of BT only or of both [43]. Again, results are difficult to compare because of the variation in operative procedure and postoperative irradiation details. In addition all the studies are non-randomized and retrospective. It should be mentioned that therapeutic doses of radiation therapy after surgery may be associated with bowel enteric complications particularly if the small bowel becomes adherent to the vaginal cuff [37, 43, 62].

Some authors have emphasized the therapeutic importance of parametrial [31, 32, 46] and lymph node dissection. Mariani *et al.* [77] even suggested a potential therapeutic role for formal paraaortic lymph node dissection in EC patients.

Many reports usually contain a small proportion of non-endometrioid EC as well [7, 15, 29, 31, 32, 37, 38] further confounding the interpretation of treatment results. Although it is well known that the survival of some non-endometrioid types of EC is low, few reports give separate results for these tumors. Reisinger *et al.* [38] reported that the 5-year actuarial survival for EC with cervical involvement of eight patients with non-endometrioid EC was only 38% as compared to 82% in the endometrioid type and concluded that additional treatment options should be considered for patients with non-endometrioid type EC because of their poor survival and high failure rate in the upper abdomen.

The inaccuracies of clinical staging, the multiple types of cervical involvement and prognostic indicators and the remarkable variations in treatment, render it difficult to compare outcome results between publications. The small number of patients in many of these studies and their retrospective uncontrolled nature add to this difficulty.

There are conflicting reports with regard to factors affecting outcome such as age, myometrial invasion, grade, as well as with regard to type of cervical involvement, i.e. gross vs occult or microscopic disease, superficial vs deep cervical involvement, Stage IIA vs IIB, also complicating the management issue of EC with cervical involvement and comparison of treatment results.

These multiple variables make it extremely difficult to group publications into a table and to derive definitive conclusions or recommendations.

Reviewing the literature on management of EC patients with cervical involvement is confusing and frustrating. Feltmate *et al.* [43] stated in 1999 that most recommendations for treatment of EC with cervical involvement come from studies of clinical Stage I disease with only a few studies that consider clinical Stage II and essentially no studies that consider only surgical Stage II disease. To a great extent this still holds true.

The optimal management of EC with cervical involvement remains to be established.

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Address reprint requests to:
J. MENCZER, M.D.
Gynecologic Oncology Unit
Department of Obstetrics and Gynecology
E. Wolfson Medical Center
Holon (Israel)