The Role of Irradiation in Endometrial Cancer

By Perry W. Grigsby, MD

ABSTRACT

What are the indications for irradiation of patients with carcinoma of the endometrium? Carcinoma of the endometrium is the most common invasive gynecological neoplasm in women in the United States. The hallmark of its therapeutic management is hysterectomy. Although adjuvant irradiation has also been utilized, in contradistinction to carcinoma of the uterine cervix, for endometrial carcinoma, irradiation alone is not optimal therapy. The best clinical outcomes for patients with endometrial carcinoma seem to be achieved with either surgery alone or a combination of surgery and irradiation. When irradiation is administered, it is more often postoperative rather than preoperative therapy. Few prospective randomized studies have been performed for patients with endometrial carcinoma, until recently when randomized studies have attempted to answer questions regarding the best management for these patients.

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INTRODUCTION

In 1971, the Fédération Internationale de Gynécologie et d' Obstétrique (FIGO) defined a clinical staging system for endometrial carcinoma.[1] In 1989, it was revised into a surgical, rather than a clinical, staging system.[2] The rules of the clinical staging system implied that all patients underwent a dilatation and fractional curettage. The uterus was sounded and an examination under anesthesia was performed and 75–80% of patients were described as having clinical stage I disease. However, after pathologic evaluation of the surgical specimens, 10–15% of these patients were found to have tumor spread beyond the uterus. The current surgical staging procedure requires obtaining a peritoneal cytology specimen and sampling pelvic and para-aortic lymph nodes. Previously, these specimens were not routinely obtained from patients with endometrial carcinoma. With the advent of surgical staging, more patients are now found to have disease outside of the uterus. Hence, a smaller percentage of patients have true stage I disease. Without a consistent definition of patient populations, comparing the reported results of therapies for patients with endometrial cancer is difficult. Despite the current rules for surgical staging, not all of the required specimens are obtained for all patients. Recommendations for post-operative adjuvant therapy must be based upon information for each patient.

Outlined below are treatment recommendations for patients who undergo surgical staging and for those who undergo incomplete surgical staging. Recommendations are based upon the results of retrospective studies and the few prospective randomized studies that exist. The uses of irradiation as the sole therapy for patients with medically inoperable endometrial cancer and as postoperative treatment for recurrent endometrial cancer are also discussed, along with current prospective randomized studies.

STAGING METHODS

Complete Surgical Staging

Patients who have undergone complete surgical staging are administered postoperative adjuvant therapy on the basis of pathological risk factors identified by examination of the surgical specimens. Numerous risk factors have been identified for patients with endometrial carcinoma. In general, patients can be divided into one of three categories of risk for developing recurrent and metastatic disease: low risk, intermediate risk, and high risk. When a tumor is confined to the uterus, the primary risk factors for developing recurrent disease are tumor histology, tumor grade, depth of myometrial invasion, lymphovascular space involvement, and patient age. Depending on the risk factors present, patients with a tumor confined to the uterus can be classified as either at low risk or at intermediate risk for developing recurrent disease.

EDUCATIONAL OBJECTIVE

Learn treatment approaches for patients with various stages of endometrial carcinoma, including surgery, irradiation, and postoperative radiation.

TALKING POINTS Physicians Pharmacy Formulary Cancer Nurses

A recent study reports that preoperative irradiation provides a survival advantage for patients with deep myometrial invasion or grade 3 disease.

When a tumor is confined to the uterus, the primary risk factors for developing recurrent disease are tumor histology, tumor grade, depth of myometrial invasion, lymphovascular space involvement, and patient age.

Patients with grade 1 or 2 disease and less than 50% myometrial invasion have less than a 10% chance of having pathologically positive pelvic or para-aortic lymph nodes, and usually do not require postoperative adjuvant therapy.

Irradiation has been shown to be an effective therapy for palliation of symptoms from locally advanced, unresectable disease in the pelvis.

Dr. Grigsby is chief of the gynecological service of the Radiation Oncology Center of Washington University Medical School in St. Louis, MO.
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Patients with surgical stage IA, grades 1 and 2 endometrial adenocarcinomas are at low risk for developing recurrent disease if no postoperative adjuvant therapy is administered. No prospective randomized study of this patient population has been performed because the risk of recurrence is <10% and a Phase III study would require a prohibitively large number of patients to be enrolled in the study. Yet the results of numerous retrospective studies and pathological models of survival[3] demonstrate that postoperative adjuvant irradiation should not be routinely administered to these patients.

Patients with surgical stages IB, IC, and IIA disease, grades 1, 2, and 3, are at intermediate risk for developing recurrent disease if no postoperative adjuvant therapy is administered. Only one prospective randomized study, the Gynecologic Oncology Group's (GOG) Phase III study (GOG-99)[4], has specifically addressed the issue of postoperative adjuvant radiotherapy for this patient population. Patients enrolled in the study were randomized to receive either surgery alone or surgery with postoperative pelvic irradiation. The surgery consisted of a transabdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO), pelvic and para-aortic lymph node sampling, and peritoneal cytology in all patients. All patients enrolled in the study had surgical stages I or IIA disease and negative lymph nodes. Postoperative pelvic irradiation treatment consisted of 50.4 Gray (Gy) delivered to the pelvis at 1.8 Gy per day. Vaginal cuff brachytherapy was not administered. A total of 392 patients were enrolled in the study. The stage distribution of patients enrolled in the study was 58% IB, 33% IC, and 9% stage IIA. Of the tumors, 82% were grades 1 or 2 and 18% were grade 3. The median follow-up period at the time of data analysis was 56 months. The results of the study demonstrated that the overall survival was 94% for the patients receiving irradiation and 89% for the patients receiving surgery only (P=0.09). Patients receiving irradiation had a 96% recurrence-free survival, significantly higher than the 88% for patients receiving surgery only (P=0.004). The recurrence rate in the pelvis was 2% for patients receiving irradiation, significantly lower than the 12% for patients receiving surgery only (P=0.001). Death from endometrial carcinoma occurred in 5% of patients receiving irradiation compared to 7% in patients receiving surgery only (data not shown). The complication rate was 15% for patients receiving irradiation, significantly higher than the 6% for patients receiving surgery only (P=0.007). The severe complication rate (grades 3 and 4) was also greater in patients receiving irradiation.

Most of the patients enrolled in the GOG-99 study had either stage IB disease or tumors that were grades 1 or 2. These patients are at low risk of developing recurrent disease. A subanalysis of the GOG-99 study indicated that significant risk factors for developing recurrent disease were advancing patient age, grades 2 and 3 histology, greater than 1/3 myometrial invasion, and the presence of tumor in the lymphovascular space. When patient survival was analyzed by these prognostic factors and stratified by patient age, significant differences in recurrence-free survival were observed. If patients were more than 70 years old with one of the prognostic factors, more than 50 years old with two of the prognostic factors, or any age with all three of the prognostic factors, then the recurrence-free survival was 87% for patients receiving irradiation, significantly higher than the 73% for patients receiving surgery only (P<0.01).

Patients with surgical stages IIB, III, or IV disease are at a high risk of developing

TABLE 1. TREATMENT GUIDELINES FOR PATIENTS AFTER SURGICAL STAGING

Stage	Postoperative Therapy
IA; G1, 2 IB; G1, 2	No further therapy
IA; G3 IB; G3 IC; G1, 2 IIA; G1, 2, 3[1]	Vaginal cuff brachytherapy
IC; G3 IIA; G1, 2, 3[2] IIB; G1, 2, 3 IIIA; G1, 2, 3[3] IIIB; G1, 2, 3[4] IIIC; G1, 2, 3[5] IVA; G1, 2, 3	External pelvic irradiation plus vaginal cuff brachytherapy
IVB; G1, 2, 3 (intra-abdominal) Any stage with papillary serous or clear cell histology	Whole abdominal irradiation, pelvic boost, and vaginal cuff brachytherapy

[1] With less than 50% myometrial invasion.
[2] With greater than 50% myometrial invasion.
[3] With positive cytology, whole abdominal irradiation in addition to pelvic irradiation and vaginal cuff brachytherapy.
[4] With groin irradiation if the disease involves the distal 1/3 of the vagina.
[5] With para-aortic irradiation if the para-aortic lymph nodes are positive.

G=grade.

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recurrent disease if no postoperative adjuvant therapy is administered. Pathological factors associated with a high risk of recurrence are cervical involvement and tumor spread beyond the uterus, or both. This includes patients with including involvement of the uterine serosa, adnexa, fallopian tubes, ovaries, and pelvic and para-aortic lymph nodes, as well as positive peritoneal cytology and upper abdominal metastasis.

Few prospective studies to evaluate adjuvant therapy in patients with high risk factors for recurrence have been conducted. The Italian Cooperative Group[5] randomized 340 patients with stages IC, IIA, and IIB (grade 3) and stages IIIA, IIIB, and IIIC (grades 1, 2, and 3) to receive postoperative irradiation or chemotherapy. All patients initially underwent a TAH/BSO and selective lymph node sampling. The 165 patients receiving irradiation were treated with 45 Gy to the pelvis without brachytherapy. The 175 patients receiving chemotherapy were treated with five cycles every 4 weeks of cisplatin (50 mg/m^2), adriamycin (45 mg/m^2), and cyclophosphamide (600 mg/m^2). The rate of recurrence in the pelvis or a distant site was 27% for patients receiving irradiation and 29% for those receiving chemotherapy (not significant). The rate of recurrence in the pelvis alone was 5% for patients receiving irradiation and 10% for those treated with chemotherapy (P=0.09). The overall survival and progression-free survival rates were not reported for this study. A subgroup analysis of the data indicated that the most significant prognostic factors for the development of recurrent disease were patient age, grade 3 tumor histology, and the depth of myometrial invasion by the tumor. Lymphovascular space involvement was not evaluated.

Also at high risk for developing recurrent disease are patients with papillary serous and clear cell histology. Traditionally, patients with this tumor histology have a poor outcome irrespective of the surgical stage of the disease. The GOG evaluated these patients in a prospective phase II study, GOG-94[6], a single-arm study in which patients with stages I to IV papillary serous and clear cell carcinoma of the endometrium and stages III and IV endometrioid endometrial carcinoma were all treated with irradiation of the entire abdomen. The total dose to the entire abdomen (no liver shielding, 5 HVL PA kidney blocks) was 150 Gy (30 Gy/day). The para-aortic lymph nodes were treated with 45 Gy only if they were pathologically positive. The total dose to the pelvis was 50 Gy. Brachytherapy was not administered. In all, 165 patients were enrolled in the study. The 5-year survivals were 65% for those with stages I and II papillary serous and clear cell carcinoma, 33% for those with stages III and IV papillary serous and clear cell carcinoma, and 31% for those with stages III and IV endometrial adenocarcinoma. The chronic bowel toxicity from irradiation to the entire abdomen was 7%, similar to previously reported results.[7]

After completing this study, the GOG initiated a prospective randomized Phase III two-arm study, GOG-122, with about 150 patients enrolled in each arm. Eligible patients had surgical stages III and IV endometrial carcinoma of any histology, including papillary serous and clear cell carcinoma. The patients were randomized to receive irradiation of the entire abdomen (as in GOG-94) or postoperative chemotherapy consisting of eight cycles, at 3-week intervals, of doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2). The results of this study are pending. However, the GOG has recently begun a subsequent two-arm study, GOG-184, to evaluate this same patient population, in which all patients undergo a TAH/BSO, lymph node sampling, and debulking (to < 2 cm) of abdominal disease. The patients then receive postoperative pelvic irradiation of 50.4 Gy and if the

TABLE 2. TREATMENT GUIDELINES FOR PATIENTS AFTER INCOMPLETE SURGICAL STAGING (NO LYMPH NODE EVALUATION)

Stage	Postoperative Therapy
I; G1, 2 (less than 50% myometrial invasion)	No further therapy
I; G3 (any myometrial invasion) I; G1, 2, 3 (more than 50% myometrial invasion) II; G1, 2, 3 III; G1, 2, 3	External irradiation plus vaginal cuff brachytherapy
Any stage with papillary serous or clear cell histology; positive cytology	Whole abdominal irradiation, pelvic boost, and vaginal cuff brachytherapy
IVA; G1, 2, 3	External pelvic irradiation plus vaginal cuff brachytherapy
IVB; G1, 2, 3 (intra-abdominal)	Whole abdominal irradiation, pelvic external irradiation, and vaginal cuff brachytherapy

G=grade.

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para-aortic lymph nodes are pathologically positive, the patients receive pelvic para-aortic irradiation of 45 Gy. For those patients with cervical involvement, deep invasion, or lower uterine segment involvement, intracavitary vaginal cuff irradiation is also administered. After irradiation is completed, patients are randomized to receive one of two chemotherapy regimens: six cycles, at 3-week intervals, of doxorubicin (45 mg/m^2) and cisplatin (50 mg/m^2) or six cycles, at 3-week intervals, of doxorubicin (45 mg/m^2), cisplatin (50 mg/m^2), taxol (160 mg/m^2), and G-CSF (5 mcg/kg on days 3–12).

Incomplete Surgical Staging

Before adoption by FIGO of the surgical staging system for patients with endometrial carcinoma, lymph node sampling was rarely performed. Most published retrospective studies report the results of patients who did not undergo lymph node sampling. A recent survey performed by the American College of Surgeons indicated that 70% of patients undergoing surgery for endometrial carcinoma do not undergo pathologic lymph node evaluation (Taylor, personal communication). Therefore, the decision for postoperative adjuvant therapy is based on incomplete information. However, without lymph node sampling, patients can still be divided into groups at low, intermediate, or high risk for developing recurrent disease based upon the grade of the tumor, the depth of myometrial invasion, the presence of tumor in the lymphovascular space, lower uterine segment involvement, cervical involvement, upper abdominal involvement, and positive peritoneal cytology.

Patients with grades 1 or 2 endometrial adenocarcinoma with less than 50% myometrial invasion have a 5-year survival rate greater than 90% if the disease is confined to the uterus.[8] This correlates with the incidence of lymph node metastasis found by Creasman and colleagues in a GOG surgical staging study.[9] The results of the GOG surgical staging study revealed that patients with grades 1 or 2 disease and less than 50% myometrial invasion had less than a 10% chance of having pathologically positive pelvic or para-aortic lymph nodes. These patients usually require no postoperative adjuvant therapy.

Patients who are at intermediate risk of developing recurrent disease following surgery are those with grade 3 disease and less than 50% myometrial invasion, and those with grades 1 or 2 disease with greater than 50% myometrial invasion. These patients have 5-year survivals ranging from 70% to 85%.

A recent prospective randomized phase III study performed by Creutzberg and colleagues addressed postoperative adjuvant therapy in this group of patients.[10] In this study, patients underwent a TAH/BSO with no lymph node sampling or dissection. Patients were grouped on the basis of their surgical findings; patients who were eligible for the study were those with grade 1 disease with more than 50% myometrial invasion, patients with grade 2 disease and any degree of myometrial invasion, and patients with grade 3 disease and less than 50% myometrial invasion. Patients with grade 3 disease and deep myometrial invasion were not eligible for the study. Patients were randomized to receive either postoperative pelvic irradiation (46 Gy) or no further therapy. The study enrolled 715 patients and the median follow-up was 52 months. The results of the study demonstrated that the actuarial 5-year pelvic recurrence rates were 4% in the radiotherapy group and 14% in the control group (P<0.001). The actuarial 5-year overall survival rates were 81% for the radiotherapy group and 85% for the control group (P=0.31). Deaths due to endometrial cancer occurred in 9% of the patients treated with irradiation and in 6% of the control group (P=0.37). Complications of any severity were reportedly 25% in patients receiving irradiation and 6% in patients in the control group (P<0.001). Grades 3 and 4 complications occurred in only 7 of the 715 patients; six of the seven complications occurred in patients who received irradiation. A Cox multivariate regression analysis revealed that the prognostic factors for pelvic recurrence or death were patient age greater than 60 years old, greater than 50% myometrial invasion, and grade 3 histology. Lymphovascular space

TABLE 3. PREOPERATIVE IRRADIATION

Clinical Stage	Preoperative Therapy
IA, B; G3	Preoperative brachytherapy
II; G1, 2, 3 (Microscopic cervical involvement)	
II; G1, 2, 3 (Gross cervical involvement)	Preoperative external pelvic irradiation and intracavitary brachytherapy

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invasion was not evaluated. Patients with grade 3 histology and less than 50% myometrial invasion had a risk of locoregional recurrence similar to that of patients with tumors of grades 1 or 2 and greater than 50% myometrial invasion, and the risk of death was greatest for those with grade 3 tumors.

The results of the above study are similar to the findings of Grigsby and colleagues in their retrospective study of 858 patients with clinical stage I endometrial adenocarcinoma.[11] These investigators found that the 5-year survival results for clinical stage I patients (determined without lymph node dissection or sampling) were greater than 90% for patients with grades 1 and 2 histology and less than 50% myometrial invasion. Patients with grade 3 disease and less than 50% myometrial invasion, and those with grades 1 and 2 histology and greater than 50% myometrial invasion, had 5-year survivals ranging from 69–85%. Conversely, patients with deep myometrial invasion and grade 3 histology had a 5-year survival of only 42%.

TREATMENT WITH IRRADIATION

Preoperative Irradiation

Primary surgery is the most commonly employed initial therapy for patients with endometrial carcinoma. However, some physicians prefer preoperative irradiation as the primary approach for its resulting tumor shrinkage before surgery and reduced incidence of subsequent distant metastasis.

Preoperative irradiation can be delivered through external irradiation, intracavitary brachytherapy, or a combination of the two. Preoperative intracavitary brachytherapy, first described by Heyman, has produced results that suggest it generates longer survival and fewer complications than postoperative irradiation.[12]

Clinical Stage I

Sause and colleagues reported that preoperative irradiation provides a survival advantage for patients with deep myometrial invasion or grade 3 diseases.[13] A retrospective analysis from the Mallinckrodt Institute of Radiology demonstrated a dose-response relationship for patients undergoing preoperative brachytherapy.[8] Patients had a 5-year progression-free survival rate of about 90%, regardless of tumor grade, with preoperative irradiation of greater than 3,500 mgh delivered to the uterine fundus. However, patients with grades 1 or 2 tumors did not exhibit a dose-response relationship.

Preoperative external irradiation has also been performed. Weigensberg[14] reported the results of a prospective Phase III clinical trial in which patients were randomized to receive either external pelvic irradiation or brachytherapy before surgery. This study demonstrated that patients who received preoperative brachytherapy with an intracavitary implant experienced longer survival and fewer local recurrences than patients who received preoperative external irradiation.

The complication rates in the Weigensberg study were 3% for patients receiving brachytherapy and 11% for those receiving external irradiation. Grigsby and colleagues reported no complications associated with preoperative brachytherapy performed in 334 patients.[8]

Clinical Stage II

Many treatment centers commonly provide preoperative irradiation for patients with clinical stage II endometrial cancer, through an intracavitary implant, external irradiation, or both. No prospective randomized studies have been performed for these patients, but retrospective studies indicate that survival rates for this group of patients range from 70–85%.[15] Preoperative irradiation may be the best approach for patients with gross cervical involvement; however, a radical hysterectomy has been advocated for patients with clinical stage II disease in lieu of preoperative irradiation.[16]

TABLE 4. IRRADIATION ALONE (MEDICALLY INOPERABLE ENDOMETRIAL CARCINOMA)

Stage	Therapy
IA, B; G1, 2 (less than 50% myometrial invasion by MRI and radiographically negative lymph nodes)	Intracavitary brachytherapy
IA, B; G1, 2 (more than 50% myometrial invasion by MRI) IA, B; G3 II; G1, 2, 3 III; G1, 2, 3 IV; G1, 2, 3	External pelvic irradiation and intracavitary brachytherapy
Any stage; positive pelvic lymph nodes	External pelvic irradiation and intracavitary brachytherapy
Any stage; positive para-aortic lymph nodes	External pelvic irradiation and intracavitary brachytherapy, plus para-aortic irradiation

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"Irradiation for pelvic recurrences is most successful as combined external irradiation and intracavitary or interstitial brachytherapy."

Irradiation Alone

Some patients with clinical stage I endometrial cancer present with advanced age and severe comorbidities that preclude surgical staging or hysterectomy. With irradiation alone, these patients may have an expected survival of several years despite their severe illnesses. Most of these patients may be treated with either brachytherapy alone or combined external irradiation and brachytherapy based upon tumor grade, depth of myometrial invasion, and lymph node status. Grigsby and associates[17] demonstrated that the 5-year progression-free survival rates for clinical stage I disease were 94% for patients with grade 1 tumors, 92% for grade 2 tumors, and 78% for grade 3 tumors if patients received both external irradiation and intracavitary brachytherapy. Overall survivals are in the range of 70–80% for this elderly group of patients with medically inoperable endometrial carcinoma. Both tumor grade and magnetic resonance imaging (MRI) of the pelvis are used to determine the depth of myometrial invasion and to estimate the probability of lymph node metastasis.[18]

The complication rate after a low-dose-rate intracavitarydevice is implanted in severely ill patients with medically inoperable endometrial carcinoma is not as high as might be expected. In an evaluation of brachytherapy-related complications in patients with medically inoperable stage I endometrial carcinoma, Chao and colleagues[19] demonstrated a mortality rate of 2.1% (two deaths in a study population of 96, one from a myocardial infarction and one from a pulmonary embolus) and a life-threatening complication rate of 4.2%. Similar complication rates after high-dose-rate (outpatient) brachytherapy for patients with medically inoperable endometrial carcinoma have been reported.[20-22]

Patients with clinical stage II endometrial carcinoma that is medically inoperable are usually treated with combined external irradiation and intracavitary brachytherapy. The 5-year survival rates for these patients range from 50–60%,[15,23,24] inferior to the results of combined preoperative irradiation and surgery.[15]

Clinical stage III endometrial carcinoma occurs in 5–10% of patients and is treated with irradiation alone or combined irradiation and surgery. This treatment group consists of patients with clinical findings of tumor involvement of the vagina or parametria and should not be confused with patients with surgical stage III endometrial carcinoma. The 5-year survival rates for patients with clinical stage III disease treated with external irradiation and intracavitary brachytherapy range from 16–42%.[25-28] Because the survival rate for these patients is poor with irradiation alone, clinical practice currently is to perform surgical debulking when possible, followed by postoperative irradiation. However, no significant body of published data exists to support this approach.

Stage IV endometrial carcinoma is found in less than 5% of patients. When the disease is confined to the bladder or rectum, then irradiation alone may be used, but long-term survivors are uncommon. Goff and colleagues evaluated the use of cytoreductive surgery for patients with stage IV disease and reported a median survival of 18 months for those patients undergoing cytoreductive surgery compared to 8 months for those who did not undergo surgery.[29] Irradiation has been shown to be an effective therapy for palliation of symptoms from locally advanced, unresectable disease in the pelvis. Spanos and colleagues have reported a safe and effective accelerated, hyperfractionated pelvic irradiation schedule for patients with advanced and recurrent endometrial carcinoma.[30] Common tumor sites outside the pelvis that may also be treated with palliative irradiation are bones, lungs, and lymph nodes.

Postoperative Irradiation

Patients with recurrent endometrial cancer after surgery should be fully evaluated to determine all sites of recurrent and metastatic disease. Those who are found to have recurrent disease in the pelvis with no evidence of distant metastatis should be treated with irradiation. The use of combined irradiation and chemotherapy in this patient population is unstudied.

Pelvic recurrence may present as vaginal cuff recurrence only, pelvic nodal disease only, or a combination of the two. Isolated distal suburethral recurrences are very rare (<0.5%).[8] Kuten and associates[31] determined the prognostic significance of recurrence site in their retrospective study of 51 patients with locoregional recurrent endometrial carcinoma. They found a 5-year disease-free survival of 40% for patients with an isolated vaginal cuff recurrence;[32-35] this falls within the 20–50% range previously reported. No patients with pelvic lymph node recurrences survived beyond 1.5 years.

Irradiation for pelvic recurrences is most successful as combined external irradiation and intracavitary or interstitial brachytherapy. Total irradiation doses should approach 75–85 Gy, depending upon tumor size.

SUMMARY

The treatment of patients with endometrial carcinoma has evolved over the past several years to employ surgery, irradiation, or both. Recommendations for adjuvant irradiation are based upon individual patients' risk factors, which must take into account whether the patient has had complete surgical staging (only performed in a minority of patients in the United States). Treatment guidelines shown in Tables I–IV are recommendations for the general patient population; therapy for a given patient must be individualized.[36] OS

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