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A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study

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Abstract

Background. Despite their low risk for recurrence, many women with endometrial adenocarcinoma receive postoperative radiation therapy (RT). This study was developed to determine if adjunctive external beam irradiation lowers the risk of recurrence and death in women with endometrial cancer International Federation of Gynaecology and Obstetrics (FIGO) stages IB, IC, and II (occult disease).

Methods. Four hundred forty-eight consenting patients with "intermediate risk" endometrial adenocarcinoma were randomized after surgery to either no additional therapy (NAT) or whole pelvic radiation therapy (RT). They were followed to determine toxicity, date and location of recurrence, and overall survival. A high intermediate risk (HIR) subgroup of patients was defined as those with (1) moderate to poorly differentiated tumor, presence of lymphovascular invasion, and outer third myometrial invasion; (2) age 50 or greater with any two risk factors listed above; or (3) age of at least 70 with any risk factor listed above. All other eligible participants were considered to be in a low intermediate risk (LIR) subgroup.

Results. Three hundred ninety-two women met all eligibility requirements (202 NAT, 190 RT). Median follow-up was 69 months. In the entire study population, there were 44 recurrences and 66 deaths (32 disease or treatment-related deaths), and the estimated 2-year cumulative incidence of recurrence (CIR) was 12% in the NAT arm and 3% in the RT arm (relative hazard (RH): 0.42; $P = 0.007$). The treatment difference was particularly evident among the HIR subgroup (2-year CIR in NAT versus RT: 26% versus 6%; RH = 0.42). Overall, radiation had a substantial impact on pelvic and vaginal recurrences (18 in NAT and 3 in RT). The estimated 4-year survival was 86% in the NAT arm and 92% for the RT arm, not significantly different (RH: 0.86; $P = 0.557$).

Conclusions. Adjunctive RT in early stage intermediate risk endometrial carcinoma decreases the risk of recurrence, but should be limited to patients whose risk factors fit a high intermediate risk definition.

Keywords: Uterine cancer; Endometrial adenocarcinoma; Radiation therapy; Radiation therapy for endometrial adenocarcinoma; Intermediate risk endometrial adenocarcinoma; Phase III study of radiation therapy for endometrial adenocarcinoma

Introduction

Every year more than 36,000 women are diagnosed with adenocarcinoma of the endometrium [1]. Historically, many of these women have received postoperative radiation based

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on the belief that this treatment would decrease relapses [2–5]. Data supporting this routine treatment are largely from single-institution retrospective reports [6,7]. There seems to be increasing agreement that women presenting with noninvasive endometrial adenocarcinoma are at such a low risk of recurrent disease that radiation therapy (RT) should not be included in their treatment plan. The use of radiation therapy for International Federation of Gynaecology and Obstetrics (FIGO) stages IB, IC, and II (occult) remains controversial in endometrial adenocarcinoma [10,11]. Creutzberg et al. [8] examined this question in a prospective randomized study. Their data suggested that postoperative radiation therapy reduces locoregional recurrence in stage I endometrial carcinoma but is not indicated in women under 60 years and those with grade 2, superficially invasive tumors. Analysis of their study is limited as complete surgical staging was not an entry requirement and the actual number of women with FIGO stage I endometrial adenocarcinoma remains unclear. To address the utility of postoperative radiation therapy in women with stage IB, IC, and II (occult) endometrial cancer, the Gynecologic Oncology Group (GOG) initiated this study.

Materials and methods

For this study, intermediate risk endometrial adenocarcinoma was defined based on data from a surgical staging protocol (GOG # 33) [9]. These data suggested that all women found to have any degree of myometrial invasion with adenocarcinoma of any grade and no evidence of lymph node involvement (International Federation of Gynaecology and Obstetrics [FIGO] stage IB, IC, IIA (occult), and IIB [occult]) should be considered as a member of the intermediate risk group, expected to have a 5-year recurrence rate of 20–25% with nearly all of the recurrences occurring within 24 months of diagnosis. This definition is similar to the one used in a review reported by Kadar et al. [12]. Additionally, clear cell and papillary serous adenocarcinomas of the endometrium were associated with a relatively high risk of recurrence. Patients with these cell types were excluded from the intermediate risk group.

The Gynecologic Procedures Manual of the GOG outlined minimum surgical requirements for study entry and included a total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective bilateral pelvic, and para-aortic lymphadenectomy with removal of any enlarged or suspicious nodes. If none was seen, nodal tissue from the distal half of each common iliac artery, anterior and medial tissue from the proximal half of the external iliac artery, and vein as well as the distal half of the obturator fat pad were all removed as pelvic nodes; tissue from the inferior mesenteric artery to the mid common iliac artery was removed as para-aortic nodes. Patients undergoing laparoscopic procedures were not eligible and lymph node counts were not required.

Additional eligibility requirements included: WBC = 3000/mm^3; platelets = 100,000/mm^3; creatinine = 2 mg%; bilirubin = two times normal; SGOT = two times normal; GOG performance status = 2; normal chest X-ray; negative peritoneal cytology; no history of another cancer except skin (excluding melanoma); and no history of radiation therapy or chemotherapy.

A written informed consent fulfilling all institutional, state, and federal regulations was obtained from all patients before study entry. Patients were registered at the GOG Statistical and Data Center (SDC) where therapy was randomly allocated with equal probability within main member institutions between the two treatment arms: (1) no additional treatment (NAT) or (2) external beam whole pelvic radiation (RT). A balanced block randomization scheme was used. The GOG Gynecologic Oncology and Pathology Committees reviewed all operative reports and discharge summaries, representative pathological slides, and pathology and cytology reports to confirm that each case met all eligibility requirements. Radiation treatment plans and port films were reviewed by the GOG Radiation Oncology Committee to assess treatment compliance. Data concerning treatment toxicity (which were graded according to the 1985 GOG Adverse Events Criteria), recurrence, and survival were collected in the GOG SDC and reviewed by the study chair.

The radiation therapy prescribed was 50.40 Gy given more than 28 fractions of 180 cGy. Radiation was initiated no later than 8 weeks after surgery via cobalt^{60} teletherapy or linear accelerator with an energy of 4 meV or greater. The minimum source to skin distance (SSD) or target to skin distance (TSD) was 80 cm. The treatment was delivered either through anterior and posterior treatment fields or with a four-field pelvic treatment technique. The ports were to cover the total pelvis including: the upper half of the vagina, paracervical, parametrial, and uterosacral tissues, as well as the external iliac, hypogastric, and obturator lymph nodes. The superior border was defined as a line drawn through the L4–L5 interspace, while the inferior border was at the mid-portion of the obturator foramen. The lateral borders were set at 1 cm beyond the lateral margins of the bony pelvic wall at the widest plane of the pelvis (at least 7 cm from the midline of the pelvis). Lateral field borders were the posterior border of the S3 vertebral body and the anterior border of the symphysis pubis. No pelvic organs or structures were to be blocked during the radiation treatment. Neither group received vaginal brachytherapy.

The statistical design of this study allowed for an 80% chance of detecting a 58% decrease in the recurrence hazard rate and a 56% decrease in the death hazard rate when a minimum of 39 recurrences and 42 deaths were observed with one-sided significance level set at 0.05 [13]. No formal interim analysis was planned or executed. For the purposes of this paper, all reported significance levels are based on two-sided tests.

The primary outcome, recurrence-free interval (RFI), is defined as the time from study entry to clinical, histologic, or radiographic evidence of disease recurrence. Patients without clinical recurrence are censored at the date of last contact. Additionally, patients who died without clinical recurrence are censored. All-cause survival was analyzed as a secondary endpoint and is defined as the time from study entry to death from any cause. Patients alive at last contact are censored for this analysis. Recurrence-free survival (RFS) is also reported and defined as time from study entry to disease recurrence or death from any cause, whichever occurred first, or the date of last contact for patients remaining alive without recurrent disease. Survival and RFS are estimated using the Kaplan–Meier method [14]. The logrank test is applied using the intent-to-treat analysis of all eligible patients to evaluate differences between regimens with respect to RFI and survival [15]. A Cox proportional hazards model is used to estimate the relative hazards (RH) of recurrence and death associated with treatment [16].

Probabilities of first recurrence, isolated local (vaginal or other pelvic) recurrence, distant recurrence, and death from endometrial cancer are estimated using the cumulative incidence method for competing risks [17]. The competing event for these endpoints is death without evidence of recurrence. Standard errors for these estimates are calculated using the method described by Korn and Dorey [18]. Ninety percent confidence intervals (CIs) are calculated using standard quadratic binomial confidence limits [19]. Relative hazard estimates for these endpoints are calculated using a standard proportional hazards model.

During the course of this study, it became apparent that the patient population targeted for this study was at a lower risk of recurrence than expected so the definition of intermediate risk was reassessed. Factors associated with an increased recurrence rate (25% at 5 years) were identified using proportional hazards regression modeling of historical data from GOG # 33 [9]. These factors are: (1) increasing age, (2) moderate to poorly differentiated tumor grade, (3) presence of lymphovascular invasion, and (4) outer-third myometrial invasion. From the results of that analysis a subgroup of patients with high intermediate risk (HIR) was defined as: (1) at least 70 years of age with only one of the other risk factors, (2) at least 50 years of age with any two of the other risk factors, or (3) any age with all three of the other risk factors. All other patients were considered low intermediate risk (LIR). These definitions were then applied to the current study population. Estimates of relative hazards of recurrence and death with confidence intervals are reported within these subgroups without *P* values, because these analyses were not specified in the original study plan.

The Kruskal–Wallis rank test adjusted for ties is used to test the independence of treatment and the frequency and severity of the toxicities reported [20].

Results

Between June 1987 and July 1995, 448 women were entered into this study. After central evaluation, 392 women (88%) were determined to be eligible. Of the 56 women found to be ineligible (25 assigned to NAT and 31 assigned to RT), the GOG Gynecologic Oncology Committee determined that 38 women (8.5%) had incomplete staging; the majority had unilateral, instead of the required bilateral lymph node sampling. The remaining 18 women (4%) were found to have an ineligible histology or FIGO stage. All exclusions were made without knowledge of outcome data.

Table 1
Demographic, pathologic, and clinical features by treatment arm

Feature	No additional therapy	Radiation therapy
Age at study entry		
<40	13 (6.4%)	4 (2.1%)
41–50	16 (7.9%)	15 (7.9%)
51–60	54 (26.7%)	58 (30.5%)
61–70	75 (37.1%)	69 (36.3%)
71–80	41 (20.3%)	41 (21.6%)
>80	3 (1.5%)	3 (1.6%)
Race		
White	165 (81.7%)	160 (84.2%)
Black	17 (8.4%)	21 (11.1%)
Other	20 (9.9%)	9 (4.7%)
Performance status		
0	122 (60.4%)	109 (57.4%)
1	74 (36.6%)	74 (38.9%)
2	6 (3.0%)	7 (3.7%)
FIGO[a] surgical stage		
IB	119 (58.9%)	110 (57.9%)
IC	64 (31.7%)	62 (32.6%)
II (occult)	19 (9.4%)	18 (9.5%)
Myometrial invasion		
Inner one-third	80 (39.6%)	83 (43.7%)
Middle one-third	88 (43.6%)	72 (37.9%)
	34 (16.8%)	35 (18.4%)
Endocervical involvement	17 (8.5%)	18 (9.5%)
Cell type		
Endometrioid	152 (75.2%)	144 (75.8%)
Adenocarcinoma with squamous differentiation	30 (14.8%)	23 (12.1%)
Adenocarcinoma, unspecified	10 (5.0%)	10 (5.3%)
Other[b]	10 (5.0%)	13 (6.8%)
Tumor grade		
Well differentiated	79 (39.1%)	87 (45.8%)
Moderately differentiated	80 (39.6%)	74 (38.9%)
Poorly differentiated	43 (21.3%)	29 (15.3%)
Lymphovascular space involvement	49 (24.4%)	42 (22.2%)

[a] FIGO = International Federation of Gynaecology and Obstetrics.
[b] Includes mucinous, mixed epithelial, and villoglandular.

Table 2
Outcome by treatment arm and risk group

Endpoint	Group	No. of events[a] in each arm	Relative hazard[b]		48-month observed cumulative incidence[c] % (SE)		
			NAT	RT	90%CI	NAT	RT
First recurrence	All	31	13		0.42 (0.25,0.73)	13 (2.4)	6 (1.7)
	High risk		20	8	0.42 (0.21,0.83)	27 (5.3)	13 (4.4)
	Low risk		11	5	0.46 (0.19,1.11)	6 (2.1)	2 (1.4)
Isolated local initial recurrence	All	18	3		0.17 (0.06,0.48)	7 (1.8)	2 (0.9)
	High risk		9	3	0.37 (0.12,1.11)	13 (4.0)	5 (2.7)
	Low risk		9	0		5 (1.8)	0 (0.0)
Distant recurrence[d]	All		18	11	0.64 (0.34,1.20)	8 (2.0)	5 (1.6)
	High risk		14	6	0.46 (0.21,1.03)	19 (4.6)	10 (3.9)
	Low risk		4	5	1.28 (0.42,3.85)	3 (1.5)	2 (1.4)
Recurrence or death	All		49	32	0.65 (0.44,0.94)	29 (2.9)	9 (2.2)
	High risk	27	18		0.65 (0.39,1.07)	36 (5.8)	17 (4.8)
	Low risk	22	14		0.63 (0.36,1.11)	12 (2.9)	6 (2.1)
Endometrial cancer death[e]	All	17	15		0.93 (0.52,1.67)	8 (1.8)	5 (1.6)
	High risk		14	8	0.60 (0.29,1.24)	17 (4.6)	10 (4.0)
	Low risk		3	7	2.38 (0.77,7.42)	2 (1.3)	2 (1.4)
Death	All		36	30	0.86 (0.57,1.29)	14 (2.5)	8 (2.0)
	High risk		22	16	0.73 (0.43,1.26)	26 (5.3)	12 (4.2)
	Low risk		14	14	1.04 (0.56,1.93)	8 (2.5)	6 (2.2)

CI = Confidence interval; SE = Standard error.
[a] Cause specific.
[b] Estimated assuming proportional hazards.
[c] For recurrence-free survival and all cause survival one minus the Kaplan–Meier estimate is reported, for all other, but comes the estimate of cumulative incidence accounting for competing risks is reported.
[d] May be preceded by an isolated local recurrence.
[e] Includes treatment-related deaths and deaths from unknown cause.

Demographic characteristics and pathologic data of eligible patients (Table 1) suggest that the randomization process was successful in producing two similar groups. In addition, high risk factors such as outer one-third myometrial invasion (17%), grade 3 histology (18%), lymphovascular space involvement (23%), more than 70 years of age (22%), and occult cervical involvement (9%) are all well represented in this study population with similar distribution between the two study arms.

Thirteen patients in the RT arm refused all radiotherapy and in another five patients, less than 90% of the prescribed dose was delivered. Two patients assigned to NAT received full-dose pelvic irradiation.

The median follow-up of surviving patients is 68 months. Fifteen patients remain alive following recurrence at the last follow-up, with a median of 80 months. Twenty-four patients are lost to follow-up after a median of 50 months of follow-up.

Analysis of recurrence-free interval (Table 2) reveals a decrease in hazard among those women treated with RT when compared to those treated with NAT (relative hazard [RH] = 0.42, 90% confidence interval [CI] = 0.25–0.73, P = 0.007). The estimated hazard of recurrence among those randomized to RT is 58% less than those randomized to NAT. Data from this study, as well as GOG # 33, suggest that most recurrences occur within 18 months of initial therapy. The 24-month estimated cumulative incidence of recurrence (CIR) is 3% (90% Cl = 0.02–0.06) for the RT group and 12% (90% Cl = 0.09–0.17) for the NAT group (Fig. 1). A review of the sites of recurrence (Table 3) suggests that the major difference between these two groups is the number of vaginal vault recurrences observed (13 in the NAT arm versus 2 in the RT arm). The estimated 24-month cumulative incidence of isolated local (vaginal or other pelvic) recurrence is 1.6% (90% CI = 0.6–3.9%) for RT and 7.4% (90% CI = 4.9–11.0%) for NAT.

The analysis of survival (Table 2) demonstrates a slight difference between the two treatment arms favoring those who received RT. The estimated risk of death from any cause among those randomized to RT is 14% less than among those randomized to NAT (RH = 0.86, 90% CI = 0.57–1.29). This difference is not statistically significant

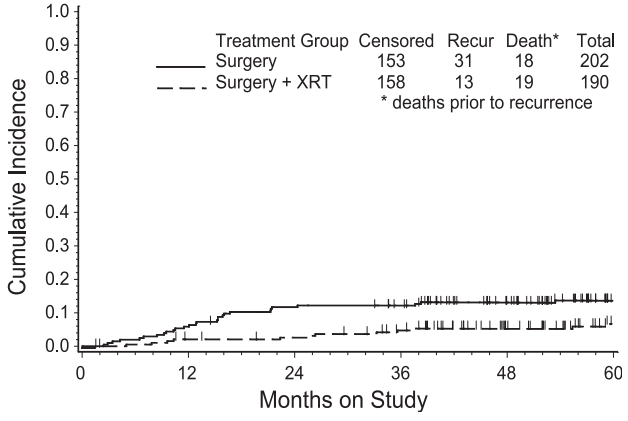

Fig. 1. Cumulative incidence of recurrence by treatment group.

Table 3
Sites of initial recurrence by treatment arm

Site	No additional therapy (n = 202)	Radiation therapy (n = 190)
No evidence of disease	171 (84.7%)	177 (93.2%)
Recurrence	31 (15.3%)	13 (6.8%)
Local recurrence	18 (8.9%)	3 (1.6%)
Vagina	13	2[a]
Pelvis	4	0
Vagina and pelvic	1	1
Distant recurrence	13 (6.4%)	10 (5.3%)
Retroperitoneal	1	1
Abdomen	4	4
Abdomen and pelvis	2	0
Lung	1	2
Lung and vagina	1	0
Lung and other sites	0	2
Bone and vagina	1	0
Inguinal	2	0
Brain	0	1
Spine	1	0

[a] These two patients refused radiation therapy.

(P = 0.55). The 48-month Kaplan–Meier estimates for overall survival are 86% for NAT and 92% for RT (Fig. 2). Approximately half of the deaths were due to causes other than endometrial cancer or treatment (NAT: 19 of 36; RT: 15 of 30). With this number of intercurrent deaths in both arms, even if RT reduces the risk of endometrial cancer-related deaths, the size of this trial is not adequate to reliably detect an overall survival difference.

Subgroup analysis identified one-third (132) of the women entered into this protocol as part of the HIR subgroup. This group accounted for nearly two-thirds (28) of the recurrences and two-thirds (22) of the cancer-related deaths. Treatment differences in RFI are assessed separately for the HIR subgroup and all remaining patients (LIR subgroup) (Fig. 3). The relative treatment hazard estimates (90% CI) for LIR and HIR subgroups, respectively, are 0.46 (0.19–1.11) and 0.42 (0.21–0.83) (Table 2). In terms of absolute differences, the HIR subgroup has an estimated decrease in the cumulative incidence of recurrence at 24 months of 4% (5% versus 2%). Survival is similar between

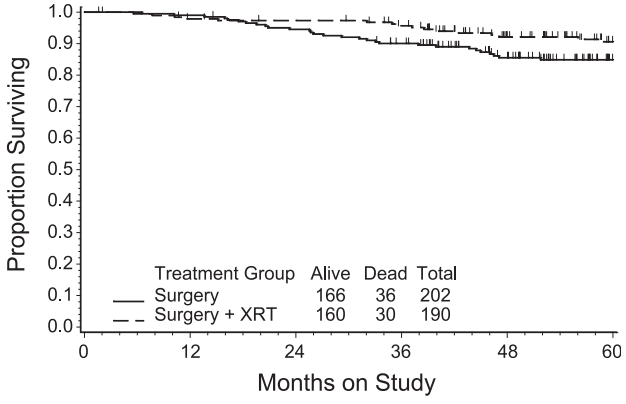

Fig. 2. Survival by randomized treatment group.

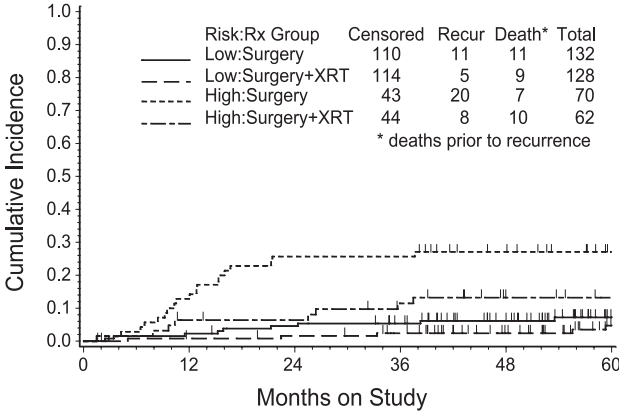

Fig. 3. Cumulative incidence of recurrence by randomized treatment group and risk group.

treatment arms for those in the LIR subgroup (RH = 1.04, 90% CI = 0.56–1.93). On the other hand, in the HIR subgroup, those on the RT arm demonstrate a somewhat lower overall death rate when compared to those on the NAT arm (RH = 0.73, 90% CI = 0.43–1.26, Table 2, Fig. 4). However, these estimates within subsets are imprecise.

Treatment-related adverse events were graded for all women enrolled into this study (Table 4). The group treated with RT experienced more frequent and more severe toxicities than those in the NAT group. Two women in the RT arm died from complications involving intestinal injury believed to be radiation-related. Statistically significant (P < 0.001) differences in frequency and severity of hematologic, gastrointestinal, genitourinary, and cutaneous toxicities are seen between the two treatment arms. There is no statistically significant difference between the treatment arms with respect to bowel obstructions; however, six women in the RT arm experience grade 3 or 4 obstruction versus only one in the NAT arm. The reported lymphatic toxicities were mostly cases of chronic lower extremity lymphedema. It must be pointed out that the mechanism for reporting toxicity is slightly different for the two arms. A form used to report acute effects during radiation was collected for patients assigned to receive pelvic radiation therapy, while standard

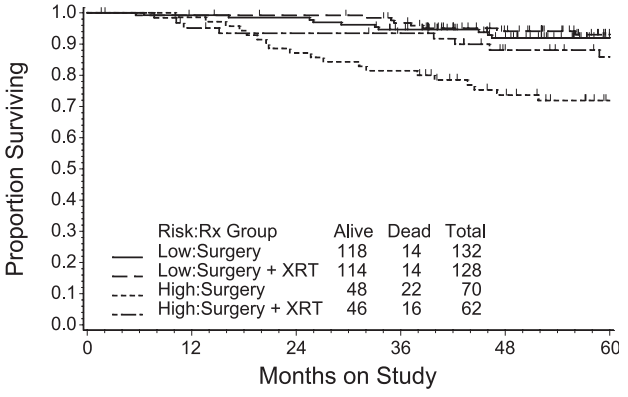

Fig. 4. Survival by randomized treatment group and risk group.

Table 4
Reported adverse effects by treatment arm

Adverse effect	No additional therapy (n = 202)					Radiation therapy (n = 190)				
	Frequency of grade of severity									
	0	1	2	3	4	0	1	2	3	4
Hematologic*	182	15	3	2	0	123	53	13	1	0
Gastrointestinal[a,*]	188	9	4	0	1	61	64	55	7	2
Gastrointestinal obstruction	186	12	3	1	0	168	9	7	1	5
Genitourinary*	186	9	7	0	0	133	49	8	0	0
Cutaneous*	187	6	7	2	0	129	46	9	5	1
Pulmonary	186	15	0	1	0	172	14	3	0	1
Cardiovascular	191	3	4	4	0	180	3	5	2	0
Neurologic	198	2	1	1	0	185	2	3	0	0
Lymphatic	197	3	2	0	0	180	3	7	0	0
Fever	173	28	1	0	0	157	26	5	2	0

No hepatic adverse effects were reported.
[a] Other than obstruction.
* $P < 0.001$.

follow-up forms were used to capture any other adverse events for all patients.

Discussion

The role of adjuvant postoperative irradiation has been studied previously in two large randomized trials, neither of which required detailed surgical staging evaluation. A Norwegian from the 1970s followed 540 stage I endometrial cancer patients who were randomly assigned to receive either vaginal irradiation alone (control group) or vaginal plus external pelvic radiation therapy [23]. The latter group had fewer vaginal and pelvic recurrences (1.9 versus 6.9% $P < 0.01$) than the control group, but suffered more distant metastases (9.9 versus 5.4%) [8]. The 5-year survival was not improved by the addition of external pelvic irradiation.

A more recent Dutch trial (the PORTEC trial—Post-Operative Radiation Therapy in Endometrial Carcinoma) had more restrictive eligibility requirements. Patients with grade I lesions with 50% or deeper myometrial invasion, grade II lesions with any amount of myometrial invasion, grade II lesions with any amount of myometrial invasion, and grade III lesions with less than 50% invasion were randomized postoperatively to receive either external pelvic irradiation or observation. All histologies of endometrial carcinomas were eligible, including papillary serous and clear cell types. Peritoneal cytology evaluation was recommended, but not required, and lymph node sampling was not required either. There were 714 patients available for follow-up evaluation. Locoregional recurrences were less frequent in the radiation therapy group (4 versus 14%, $P < 0.001$) than in the controls. Survival at 5 years was similar in the two groups (81 RT versus 85% for the controls, $P = 0.37$).

This study represents the first prospective randomized investigation of the therapeutic effect of pelvic radiotherapy on recurrence-free interval in women with surgically staged node-negative intermediate risk (FIGO stages IB, IC, II occult) endometrial adenocarcinoma. The results of this study are clinically important because the majority of patients with endometrial carcinoma in this country fall into this subset, and therapy, to date, has largely been based upon either single institution retrospective studies or individual physician bias.

At the time this study was undertaken, surgical staging was considered to be the standard of care by the GOG. This study does not address the clinical importance of surgical staging and the results neither argue for or against the routine performance of surgical staging. Only patients without evidence of extra-uterine cancer spread were eligible for this trial, so any patient found by surgical staging to have more extensive disease was excluded from entry into this study. Completeness of surgical staging was judged by the operating surgeon and entry based on that evaluation.

The benefit of radiation therapy in patients with intermediate risk endometrial cancer has been very difficult to assess. In this 12-year study, few recurrences (44) were observed among these patients. Furthermore, an overall survival benefit is difficult to detect because this disease occurs in an older population with age-related attendant comorbidity. In fact, more than 50% of the deaths reported in this study do not appear to be cancer related. Nevertheless, this study clearly indicates that whole pelvic radiation reduces the risk of recurrence by 58%. While survival was better in the RT arm (92% versus 86%), it did not reach statistical significance. Similar RFI and survival results are obtained when ineligible patients are included in the analysis (RFI RH: 0.42, survival RH: 0.86). Local recurrences were significantly altered by the use of radiotherapy. In particular, recurrences in the vaginal apex were significantly reduced by the use of radiotherapy from 13 (CIR: 8.7%) to 2 (CIR: 1.1%). It must be noted that the two women developing vaginal recurrences in the RT group, in fact, did not receive the prescribed radiation, but they are kept in the RT group as a result of the intent-to-treat analysis employed in the study. Prevention of this vaginal recurrence alone accounts for a large part of the benefit of radiotherapy seen in this study.

It became apparent during this study that our original definition of intermediate risk needed further refinement. This definition (myometrial invasion without lymph node metastasis) could be challenged, as the cumulative incidence of recurrence at 24 months for those assigned to NAT was only 12%. Therefore, previously published data were used to formulate a HIR subgroup (i.e., those with high grade, advanced age, deep myometrial invasion, or lymphovascular space involvement) [9]. Applying the definition of HIR described above, it is found that approximately one-third of the patients and two-thirds of the recurrences fall into this

new intermediate risk group. Furthermore, the cumulative incidence of recurrence at 48 months on the NAT arm for this group is 27%. These data are more consistent with what is generally considered to be an intermediate risk of recurrence than with the definition originally devised for this study.

Comparison of treatment effect within the LIR and HIR subgroups indicates consistent reduction in proportional risk but dramatic difference in absolute reductions. The overall 58% reduction in the recurrence hazard estimate in this trial is consistent with the treatment effect found within the HIR subgroup as well as the LIR subgroup. In absolute terms, the data indicate that the RT patients within the HIR subgroup showed a 19% improvement in cumulative incidence of recurrence at 24 months when compared to the NAT group. This result is in contrast to the 4% improvement among the remaining LIR patients. This finding in terms of absolute benefit draws a clearer boundary between low and intermediate-risk disease. It also highlights the fact that the majority of women on this study (66%) are at a very low risk of recurrence regardless of treatment, and allows a clearer decision regarding the need for adjuvant radiotherapy.

Furthermore, a consistent reduction in the hazard of isolated local (RH: 0.37) and distant metastatic recurrence related to RT (RH: 0.46) was observed within the HIR subgroup. A consistent improvement in RFS was observed in the entire cohort (RH: 0.65) and within subgroups (RH: high 0.65, low 0.63). The magnitude of the RFS hazard reduction is slightly less dramatic than for RFI. In view of all the evidence observed, the consistency of a treatment effect across outcomes is only seen within the HIR subgroup (Table 2).

In large part, the difference in RFI appeared to be attributable to the reduction in the rate of vaginal recurrences. It is conceivable that a similar reduction in risk might be obtained by substituting vaginal vault radiation for whole pelvic radiation. This has been suggested by other authors who have reported near complete prevention of potential vaginal vault recurrences with the use of brachytherapy [21,22]. In contrast, the report of Aalders et al. [23] has found that vaginal brachytherapy does not provide the same level of pelvic control as external radiotherapy (6.9% versus 1.9%, $P < 0.01$). Unfortunately, in that study, surgical staging was not employed, and all women were treated with brachytherapy, thus a true comparison between these two forms of radiotherapy is not present in that study. A randomized trial to determine whether a clinically significant increase in recurrence risk exists for vaginal brachytherapy compared to whole pelvic radiation would require a very large number of patients. Given that the present trial took 8 years to accrue 392 eligible patients, such a trial may not be feasible. An alternative treatment approach would be to give no adjuvant radiotherapy following the initial staging surgery and provide radiation only to those women who develop vaginal recurrence. This is, in fact, how 12 of the 13 women in this study with an isolated vaginal recurrence on the NAT arm were treated. Crude observations of those so treated are that 5 of 13 thus far have died as a result of endometrial cancer.

In summary, this first prospective randomized evaluation of whole pelvic radiotherapy versus no additional therapy for surgically staged patients with intermediate risk endometrial adenocarcinoma provides strong evidence for the use of adjuvant RT in the subgroup defined herein as high intermediate risk. In view of the potential toxicity of such adjuvant therapy, it is not recommended for those patients at lower risk of recurrence.

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