Evaluation of the outcome benefit conferred by intensive surveillance strategies in women with early-stage endometrial cancer

G. Kiran[1], J.P. Kesterson[2], K. Ozerkan[3], M. Kanis[4], A. Groman[5], S. Lele[6]

[1]Department of Obstetrics and Gynecology, Kahramanmaras Sutcu Imam University, Kahramanmaras (Turkey);
[2]Division of Gynecologic Oncology, Penn State Hershey Medical Center, Hershey, PA (USA);
[3]Division of Gynecologic Oncology, Uludag University, Bursa (Turkey);
[4]Mount Sinai Medical Center, Department of Obstetrics and Gynecology, NY (USA);
[5]Department of Biostatistics, Roswell Park Cancer Institute, Buffalo, NY;
[6]Division of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, NY (USA)

Summary

Introduction: The optimum follow-up regimen after treatment for early-stage endometrial cancer with curative intent is unknown. The National Comprehensive Cancer Network recommends a physical exam and vaginal cytology every three to six months for two years then at six to 12 month intervals with annual chest X-rays (CXR). However, there is debate as to whether intensive follow-up results in an improvement in outcomes for those with recurrent endometrial cancer. *Objective*: To determine if intensive surveillance for recurrent cancer in women with early-stage endometrial cancer improves their outcomes. *Materials and Methods*: The Roswell Park Cancer Institute tumor registry was used to identify patients with Stage I and II endometrial cancer initially diagnosed and treated over an 18-year period, who subsequently recurred. Clinico-pathological variables were abstracted. Patients were divided into two groups, depending on their mode of diagnosis of recurrent cancer: 1) routine screening, or 2) symptomatic. The outcomes between the two groups were compared. *Results*: Fifty-two patients met inclusion criteria. Twenty-three patients were diagnosed via routine screening methods and 29 were symptomatic at presentation. Groups were equally represented with respect to age, stage, grade, adjuvant therapy, site of recurrence (local, distant), and time to recurrence ($p > 0.05$). Median survival time was 79 months for those diagnosed during routine screening and 80 months for symptomatic patients ($p > 0.05$). *Conclusion*: Pap smear and CXR appear to be of limited utility as the present study has shown that women diagnosed as a result of intensive surveillance did not have a better outcome than those who presented when symptomatic.

Key words: Endometrial cancer; Surveillance.

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with an estimated 42,160 cases per year [1]. A majority of cases will be Stage I or II at diagnosis. Initial treatment includes hysterectomy with bilateral salpingo-oophorectomy (BSO) ± lymph node dissection. A majority of these patients will be cured with surgery alone. A subset of patients (tumors which are poorly differentiated and/or deeply myoinvasive) will receive adjuvant radiation therapy (RT), with a resultant decrease in the risk of recurrence, however without any improvement in overall survival (OS) [2].

The role of follow-up surveillance in these clinically disease-free patients is uncertain. Currently the National Comprehensive Cancer Network (NCCN) recommends a physical exam and vaginal cytology every three to six months for two years, then at six to 12 month intervals with annual CXR [3]. These recommendations are based primarily on expert opinion and committee consensus, in the absence of prospective, randomized clinical trials. The utility of surveillance for this patient population has been a point of controversy [4] with some studies demonstrating a survival benefit [5-7], while others show no survival benefit [8-11]. The goal of this study was to determine if intensive surveillance for recurrent cancer in women with early-stage endometrial cancer improves their OS when compared to women diagnosed at time of symptomatic recurrence.

Materials and Methods

After obtaining Institutional Review Board (IRB) approval, the Roswell Park Cancer Institute tumor registry was used to identify patients with Stage I and II endometrial cancer initially treated at this institution from January 1, 1990 through December 31, 2007, who subsequently recurred. Data abstracted included: patient age, stage, tumor grade, type of surgery (hysterectomy, BSO ± lymphadenectomy) (LND), lower uterine segment involvement, lymphovascular space involvement (LVSI), tumor volume, adjuvant RT, time to recurrence, site(s) of recurrence, symptoms at recurrence, modality of diagnosis of recurrence, date of last follow-up, and status at last follow-up (alive, dead of disease (DOD), dead of other causes). Patients were excluded if they had non-en-

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dometrioid histology, received radiation prior to surgical staging, had a synchronous or meta-synchronous primary cancer. Stages are reported as per FIGO 2009 staging criteria [12]. Patients were divided into two groups, depending on their mode of diagnosis of recurrence: 1) routine screening, or 2) symptomatic. The outcomes between the two groups were compared.

Statistical analysis

Primary interest was in the prognosis of patients' diagnosed with endometrial cancer recurrence, relative to diagnosis method (routine screening vs symmetric visit). The OS endpoint was defined as time (in months) to death. Patients who had not died were censored at the date of last follow-up.

Potential confounding effects of other variables associated with diagnosis method and the outcome were investigated using both univariate and multivariate methods. Univariate associations between potential confounders and diagnosis method were assessed with the Wilcoxon Rank Sum test (for continuous covariates) and the Pearson Chi Square test (for categorical covariates). Associations between potential confounders and OS were evaluated in univariate and multivariate proportional hazards models.

Multivariate proportion hazards modeling methods were used for the primary analyses comparing OS by diagnosis method. Relative prognosis was summarized using estimates and 95% confidence limits for the hazard ratio (HR). The *p* value assesses the probably of observing the estimated HR by random chance, given the null hypothesis of no true survival difference between the two treatment groups. Ninety-five percent confidence limits describe the plausible range of values for the true HR that is supported by the data. In addition to the diagnosis effect, multivariate modeling controlled for effects, adjuvant treatment, grade, recurrence site, and stage.

Multivariate results were supported by univariate analyses of OS. Diagnosis method differences were assessed using the Log Rank test, with time to event distributions based on Kaplan-Meier Product Limit estimation methods. The Log Rank Test assesses the null hypothesis of no diagnosis effect on the time-to-event distribution. Product limit methods was also used to estimate median time-to-event, and the event-free proportion five years after diagnosis. All statistical analyses were done using SAS version 9.2.

Potential confounding effects of other variables associated with diagnosis method and the outcome were investigated using both univariate and multivariate methods. OS associated with routine screening diagnoses and symptomatic diagnoses were compared using multivariate proportional hazards methods controlling for age, adjuvant treatment, grade, recurrence site and stage; *p* values < 0.05 were deemed statistically significant.

Results

Of 850 patients with Stage I and II disease, 52 patients with recurrent endometrial cancer were identified who met inclusion criteria. Their mean age was 64.5 years. A majority of patients had Stage IA disease (58%). The remainder had Stage IB and II disease (19% and 23%, respectively). A majority of tumors were moderately or poorly differentiated (77%). More than half (54%) underwent LND at time of hysterectomy, BSO. A similar percentage of patients received post-operative radiation as those that received no further therapy. Patients were followed for a mean of 75 months. The median progression-free interval (PFI) was 43 months (range, three to 129 months). At time of analysis, 29% of recurrent patients were alive and 71% had died.

Table 1. — *Clinical characteristics of FIGO Stage I/II patients with recurrent disease by means of detection.*

		Routine f/u	Symptomatic	Total	*p* value
N		23 (44%)	29 (56%)	52 (100%)	
Age (mean)		67	62.5	64.5	0.083
Stage	IA	13 (57%)	17(59%)	30 (58%)	0.915
	IB	5 (22%)	5 (17%)	10 (19%)	
	II	5(22%)	7 (24%)	12 (23%)	
Grade	1	7 (30%)	5 (17%)		
	2	8 (35%)	14(48%)		
	3	8 (35%)	10 (35%)		
Surgery	Hyst/BSO	12 (52%)	12 (41%)	24 (46%)	0.438
	Hyst/BSO/LND	11 (48%)	17 (59%)	28 (54%)	
LVSI	Present	8 (80%)	13 (68%)	21 (72%)	0.507
	Absent	2 (20%)	6 (32%)	8 (28%)	
Tumor size (mean)	Volume (cm^3)	17	81	59	0.012
Adjuvant	No	11 (50%)	16 (55%)	27 (53%)	0.070
RT	Yes	11 (50%)	13 (45%)	24 (47%)	

f/u = follow-up; Hyst = hysterectomy; BSO = bilateral salpingo-oophorectomy; LND = lymphadenectomy; LVSI = lymphovascular space involvement; RT = radiation therapy.

For analysis purposes, patients were divided into two groups, those that were diagnosed with recurrent disease at a routine surveillance visit and those that presented secondary to symptoms. Twenty-three (44%) patients had their recurrence diagnosed at time of routine follow-up. Their median time to recurrence was 24 months (range, six months, 129 months). Recurrence diagnosis modalities included clinical exam (22%), vaginal cytology/biopsy (39%), CXR (30%), and advanced imaging technique (9%). Upon review of symptoms, 74% of patients were asymptomatic, while others admitted to vaginal bleeding or pelvic pressure (22% and 4%, respectively). Recurrence sites were equally distributed between local and distant (52% and 48%, respectively). At time of analysis, 15 patients had died (65%), with a majority of those deaths cancer-related (12/15, 80%). Median survival time was 79 months, with 55% of patients diagnosed with recurrence at routine screening alive five years after diagnosis.

Twenty-nine (56%) patients were diagnosed with recurrence at time of interval visit, scheduled secondary to symptoms. Their median time to recurrence was 50 months (range, three to 125 months). Symptoms at time of recurrence included: pain (55%), pelvic pressure (10%), and bleeding (31%). Recurrence diagnosis modalities were as follows: advanced imaging technique (72%), vaginal smear/biopsy (21%), and clinical exam (7%). A majority of recurrences were distal (72%). At time of analysis, a majority of patients were dead (76%), with a majority of those deaths being cancer-related (19/22, 86%). Median survival time was 80 months for symptomatic patients with 59% of symptomatic patients alive five years after initial diagnosis.

The two groups were similar with regards to demographic and clinic-pathologic factors (Table 1). There was no statistically significant difference between groups with regards to patient age, stage distribution, grade distribution, LVSI, and adjuvant RT. Patterns of

Table 2. — *Patterns of recurrence.*

		Routine f/u	Symptomatic	Total	*p* value
N		23 (44%)	29 (56%)	52 (100%)	
Time to recurrence	< 1 year	5 (22%)	6 (21%)	11 (21%)	
	> 1 year	18 (78%)	23 (79%)	41 (79%)	0.927
Time to recurrence (mean)		33 months	51 months	43 months	0.077
Site of recurrence	Local	12 (52%)	8 (28%)	20 (39%)	
	Distant	10 (44%)	18 (62%)	28 (54%)	0.179
	Both	1 (4%)	3 (10%)	4 (8%)	
Symptoms at recurrence	None	17 (74%)	1 (3%)	18 (35%)	
	Pain	0	16 (55%)	16 (31%)	
	Bleeding	5 (22%)	9 (31%)	14 (27%)	
	Pelvic pressure	1 (4%)	3 (10%)	4 (8%)	<.001
Detection of recurrence	Clinical exam	5 (22%)	2 (7%)	7 (14%)	
	Pap smear	9 (39%)	6 (21%)	15 (29%)	
	CXR	7 (30%)		7 (14%)	
	Adv imaging	2 (9%)	21 (72%)	23 (44%)	<.001
Status	Alive	5 (22%)	6 (21%)	31 (60%)	
	DOD	12 (52%)	19 (66%)	11 (21%)	
	Dead (NED)	3 (13%)	3 (10%)	6 (12%)	
	Lost to f/u	3 (13%)	1 (3%)	4 (8%)	0.571

f/u = follow-up; CXR = chest X-ray; Adv = advanced imaging technique; DOD = dead of disease; NED = no evidence of disease.

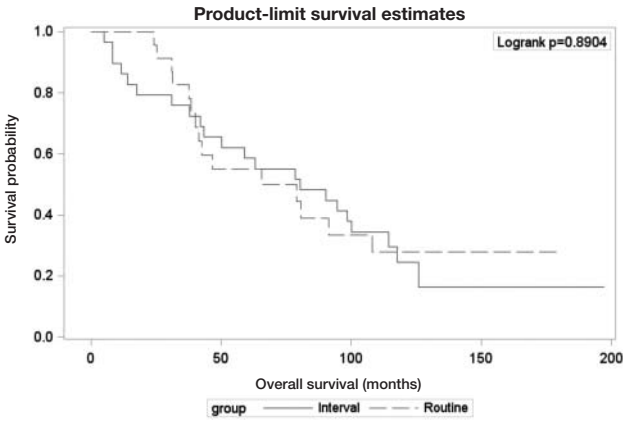

Figure 1. — Kaplan-Meier plot of OS.

recurrence were similar between the two groups (Table 2). There was a trend towards a greater number of distant recurrences in the symptomatic group (*p* value 0.070). There was also a trend towards a shorter PFI in those diagnosed with recurrence as a result of routine surveillance (mean 33 months vs 51 months, *p* value 0.077). Multivariate proportion hazard modeling showed no statistically significant OS disadvantage for patients diagnosed during a symptomatic visit vs patients diagnosed as a result of routine screening [HR = 1.45 (0.64,3.29), *p* value < 0.373] (Figure 1).

Discussion

The role of routine surveillance for recurrent disease in patients treated for endometrial cancer has not been fully established. Currently, the National Comprehensive Cancer Network recommends surveillance in the form of physical exam every three to six months for two years, then every six months or annually, vaginal cytology every six months for two years, then annually, annual CXR, and patient education regarding symptoms [3]. However, recent attention has focused on the efficacy of currently implemented screening modalities and schedules [4].

The goal of the present study was to determine if intensive surveillance of women with early-stage endometrial cancer improves outcomes for those with recurrent disease. In the present study with prolonged follow-up and detailed clinic-pathologic data, the authors have demonstrated that, in patients with Stage I and II endometrial cancer, those diagnosed with recurrence as a result of currently implemented screening strategies did not fare better than those diagnosed when symptomatic. This lack of survival benefit despite rigorous and scheduled screening warrants a critical analysis of currently implemented screening tests and schedules in order to rationalize their continued use.

To justify screening in a particular population, including that the condition be an important health problem for the individual and the community, that there is a useful intervention, that there be a latent or early symptomatic stage, acceptable screening tests, and that treatment started at early-stage should be of more benefit that treatment started later [13]. Screening for recurrent endometrial cancer is done so on the premise that early detection will afford an opportunity for a therapeutic intervention with a subsequent decrease in morbidity and mortality which would not be possible for the patient who presents later, when symptomatic. This currently implemented screening approach presumes several things necessary to justify screening this particular population, specifically, that recurrence affects a significant proportion of those treated with endometrial cancer, that currently implemented screening strategies (vaginal cytology and CXR) are effective in detecting pre-symptomatic disease, and that current treatments for recurrent disease are potentially curable, with those treatments more efficacious in the pre-symptomatic or latent phase in the natural history of the disease process.

Recurrent endometrial cancer is a clinically significant problem, with those even with early-stage disease at risk. Morrow *et al*. defined risk factors for recurrence in early-stage disease, including deep myometrial invasion and moderate to poor cellular differentiation [14]. More recently, in GOG 99, patients with early-stage disease with high-risk features (i.e., increased age, moderate to poorly differentiated tumors, LVSI, and deep myometrial invasion) were randomized to adjuvant pelvic RT vs no further treatment [2]. The addition of pelvic radiation decreased the risk of localized recurrence (1.6% vs 8.9%), without any decrease in distal recurrence or in OS. These findings were consistent with those from another large randomized study evaluating post-operative RT in early-stage endometrial cancer [15]. Considering

these large, prospective trials one can appreciate the real risk of recurrence, even in early-stage disease and the efficacy of RT in achieving local control while failing to positively impact survival. Considering the lack of adjuvant treatment-induced improvement in survival, we must search for another modality by which to improve survival in these patients. One intriguing possibility is to screen for asymptomatic patients with early-stage disease treated with curative intent for recurrent disease before they present with symptoms to allow for an earlier therapeutic intervention.

In patients who do recur, a majority do so within three years of initial surgery and treatment [4]. Most studies report greater than 80% of all recurrences occur within the first three years following surgery [8, 11, 16-18]. The site-specific risk of recurrence in patients varies depending on the use of adjuvant RT. Patients who received adjuvant RT are less likely to recur locally, without any difference in risk of distant recurrence when compared to patients who did not receive adjuvant radiation [15]. Common sites of recurrence include vaginal vault, pelvis, abdomen, and lungs. A majority of patients will be symptomatic at recurrence, with reports of symptomatic recurrences ranging from 41% to 100% [4]. Symptoms most often include bleeding and/or pain.

Patient outcomes after recurrence are dependent on several factors, including site(s) of recurrence, prior RT, and time from diagnosis to recurrence [9]. Ackerman *et al.* reported that 14 of 21 patients (67%) who received RT for isolated pelvic relapse achieved pelvic control until death or last follow-up[19]. In the Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial, the three-year survival after isolated vaginal recurrence was 69% compared to 13% after pelvic or distant relapse [15]. The poor outcomes for patients with recurrence of their early-stage disease have been consistently born out. In their follow-up of patients with Stage I and II endometrial cancer, Morice *et al.* noted 27 patients who recurred [20]. Nineteen of those patients died at a median of 12 months, six were alive with progressive disease, with only one patient, with an isolated vaginal recurrence, alive without disease. Similarly, Reddoch *et al.* reported on 39 patients with recurrent Stage I disease [18]. Thirty patients had died, six were alive with disease, and only three were alive without disease. Those long-term survivors had isolated, localized recurrences (two patients with a vaginal vault recurrence and one patient with an isolated cutaneous lesion).

Individual studies are conflicting in terms of survival benefit, if any, of screening for recurrent endometrial cancer. In an excellent review of the literature Fung-Kee-Fung *et al.* synthesized data from 16 published retrospective studies evaluating the benefit of long-term surveillance in patients treated for endometrial cancer [4]. Based on their synthesis of the available literature, they concluded that "there is no evidence to support that intensive follow-up schedules with multiple routine diagnostic interventions result in survival benefits any more or less than non-intensive follow-up schedules without multiple diagnostic interventions".

More recently, investigators from Japan reported a better prognosis for asymptomatic recurrences found by routine follow-up than for symptomatic recurrences [7]. Upon further review, in their study which consisted of only ten patients with Stage I or II disease, the median time to recurrence was the same in the symptom and symptom-free groups. However, the PFS after recurrence was six months longer in the asymptomatic patients than in the symptomatic patients (nine months vs three months, respectively, $p = 0.017$). There was no statistically significant difference between the groups in median OS. The reported improvement in PFS in the patients without symptoms may be a result of lead time bias, which plagues these retrospective studies, whereby the screening only serves to diagnose the recurrence earlier, adding that lead time to the interval from symptoms until death. The reported improvement really only being an earlier detection of the same disease process is supported in the present study by the lack of statistically significant difference in OS between symptomatic and asymptomatic patients.

The lack of beneficial early detection despite frequent visits with oft implemented screening tests, forces us to examine the sensitivity of commonly used tests to detect recurrent endometrial cancer, specifically vaginal vault cytology and CXR. In a systematic review of the means by which recurrent endometrial cancer was detected, vaginal vault cytology detected only 0%-4% of asymptomatic recurrences [4]. The lack of sensitivity of vaginal cytology in this setting is highlighted in a report by Morice *et al.* [20]. In their follow-up of analysis of women with recurrent Stage I and II endometrial cancer, none of the recurrences were detected with routine Pap smear. Furthermore, all asymptomatic patients with biopsy-confirmed vaginal recurrence had a normal Pap smear. Ng *et al*. reported similar findings with vault cytology being negative in all patients with recurrences, including local recurrences [21]. While the Pap smear is highly-effective at detecting dysplastic lesions of the cervix, it does not appear to be very beneficial in detection of asymptomatic endometrial cancer recurrences. The inability of vaginal cytology to detect asymptomatic recurrences may be secondary to a need for the recurrent tumor to invade through the vaginal mucosa before cells will be present for capture during cytologic evaluation, at which point the patient would most likely have symptoms and/or a pelvic exam would detect the tumor [10]. Routine CXR have a similarly low yield for detecting asymptomatic recurrence, the utility of which is called in to question further considering the historically poor outcomes for those with distal recurrences.

In conclusion, in the present study of the role of screening for recurrence for patients with a history of early-stage endometrial cancer, the authors have shown that intensive surveillance does not benefit those with recurrent disease when compared to those diagnosed secondary to symptoms. Considering, the relative low-

risk of recurrence in early-stage endometrial cancer, the primarily symptomatic nature of recurrences, the low yield of currently used screening tests (e.g., vaginal cytology and CXR), and the limited effective treatment modalities for recurrence, the use of routine surveillance in asymptomatic patients does not appear to be justifiable for the purpose of improving survival. Resources should instead be re-directed to further research on development of newer screening tests and on improved treatment options for those with distant and more extensive recurrences.

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Address reprint requests to:
J.P. KESTERSON, M.D.
Division of Gynecologic Oncology
Penn State Hershey Medical Center
500 University Drive
Hershey, PA 17033 (USA)
e-mail: jkesterson@hmc.psu.edu