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Original Article

Recurrence risk factors in stage IA grade 1 endometrial cancer

Chika Nwachukwu [1,*] **Mana Baskovic** [2] **Rie Von Eyben** [1] **Dylann Fujimoto** [1] **Stephanie Giaretta** [1] **Diana English** [2,†] **Elizabeth Kidd** [1]

[1]Department of Radiation Oncology, Stanford University School of Medicine, Stanford Cancer Institute, Stanford, CA, USA
[2]Division of Gynecologic Oncology, Department of Gynecology, Stanford University School of Medicine, Stanford, CA, USA

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Correspondence to
Elizabeth Kidd
Department of Radiation Oncology, Stanford University, 875 Blake Wilbur Drive, Stanford, CA 94305-5847, USA.
E-mail: Ekidd@stanford.edu

*Present Address: Department of Radiation Oncology, UT Southwestern Medical Center, 2280 Inwood Rd, Dallas, TX 75219, USA

†Present Address: Department of Gynecology Oncology, University of South Florida, 2 Tampa General Circle, Tampa, FL 33606, USA

ORCID iDs
Chika Nwachukwu
https://orcid.org/0000-0001-9732-9352
Mana Baskovic
https://orcid.org/0000-0001-8540-8723
Rie Von Eyben
https://orcid.org/0000-0003-2355-8667
Dylann Fujimoto
https://orcid.org/0000-0002-6279-4411

ABSTRACT

Objectives: Patients with early-stage endometrial cancers (EC) with disease recurrences have worse survival outcomes. The purpose of this study was to identify clinical and pathologic factors that predict for all recurrences in stage IA grade 1 (IAG1) EC.
Methods: Records from patients diagnosed with EC were retrospectively reviewed. Baseline characteristics of 222 patients with IAG1 EC who underwent surgical resection were analyzed. Cox proportional hazard analysis was used to identify univariate and multivariate risk factors that predict for recurrence.
Results: Seventeen (7.65%) patients had recurrences. The 3-year cumulative incidence of recurrence were significantly higher for patients with time from biopsy to surgery ≥6 months (54% vs. 8%, p=0.003), simple hysterectomy with ovarian preservation vs. total hysterectomy and bilateral salpingo-oophorectomy (31% vs. 9%, p=0.032), any myometrial invasion vs. no invasion (18% vs. 2%, p=0.004), and tumor size ≥2 cm (15% vs. 2%, p=0.021). On, multivariate analysis, any myometrial invasion, increasing time from biopsy to surgery, and larger tumor size were independent predictors of any recurrence. Patients with recurrences had worse outcomes than those without (5-year overall survival [OS]=60%; 95% confidence interval [CI]=16%–86% vs. 5-year OS=95%; 95% CI=87%–99%, respectively, p=0.003).
Conclusion: Time from biopsy to surgery, larger tumors, and myometrial invasion are the most important predictors of recurrence. Though the recurrence rates are generally low in IAG1 EC, the survival rate for the patients with recurrences was worse than those without. Identification of additional recurrence risk factors can help select patients who may benefit from adjuvant treatment.

Keywords: Endometrial Cancer; Recurrence; Risk Factors

INTRODUCTION

Endometrial cancers (ECs) are the most common gynecologic malignancy in developed countries, with incidence and mortality rates increasing over time in United states and worldwide [1,2]. In the US, EC is the fourth most common cancer affecting women and the sixth most common with respect to mortality [3]. Most ECs are diagnosed at an early stage (International Federation of Gynecology and Obstetrics [FIGO] stage I and II), with the 5-year

Stephanie Giaretta
https://orcid.org/0000-0002-8068-9375
Diana English
https://orcid.org/0000-0002-6275-2190
Elizabeth Kidd
https://orcid.org/0000-0003-4749-4098

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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overall survival (OS) for stage 1 EC greater than 90% [3,4]. A number of prognostic factors for recurrence and survival have been identified, including stage, histological subtype, grade, depth of myometrial invasion, and lymphovascular space invasion (LVSI) [5].

According to FIGO staging, stage IA grade 1 (IAG1) EC is defined as tumor confined to the corpus uteri with less than half or no myometrial invasion and less than 5% of a non-squamous or non-morular solid growth pattern. The primary standard treatment includes surgery, without further need for adjuvant therapy [6]. Although stage IAG1 endometrioid EC are characterized as a low recurrence risk group, a subset of women with this early-stage EC do experience recurrence with reported rates between 5% and 10% [7]. However, risk factors associated with recurrence for this group have not been clearly identified in the literature to-date. Therefore, the aim of this study is to identify clinical and pathologic factors that predict for tumor recurrence in stage IAG1 EC.

MATERIALS AND METHODS

1. Patient population

After Institutional Review Board (IRB) approval, patients with primary EC diagnosed by pathologic review between January 1996 and July 2017 were retrospectively reviewed. Based on these criteria, 426 patients were identified from hospital pathology records. These patients were treated with surgical resection in the Department of Gynecologic Oncology, Stanford, CA, USA or had their pathologic specimen reviewed in the Department of Pathology, Stanford, CA, USA.

Excluded patients include those with non-endometrioid histology, grade 2 or higher disease, and/or patients with FIGO stage IB–IV disease. A total of 222 patients diagnosed with IAG1 EC were identified and assigned the appropriate stage based on the FIGO 2009 guidelines.

2. Histologic and pathologic diagnosis

All surgical specimens were examined and interpreted by Stanford's gynecological pathologists. Tumor architectural grades and staging were assigned using standard 2009 FIGO criteria. During the study period, the surgical management of lymph nodes (LNs) varied, from complete pelvic and/or para-aortic lymphadenectomy, no lymphadenectomy (if tumor size less than 2 cm) [8], sentinel LN biopsy, or ovarian preservation in patients with low risk of nodal spread (<2 cm tumor with <50% myometrial invasion on biopsy).

Following surgical staging, patients were followed in clinic with routine surveillance based on the National Comprehensive Cancer Network (NCCN) guideline criteria: 3–6 months for the first 2–3 years, 6 months until 5 years, and then annually [9]. Surveillance included a physical exam with pelvic examination. Imaging studies were performed as indicated based on exam findings and/or concerning symptomology, i.e., vaginal bleeding, abdominal bloating/discomfort.

3. Statistical analysis

Baseline characteristics were compared using a t-test, χ^2 or Fisher's exact as appropriate. Actuarial estimates of OS were calculated using the Kaplan-Meier method and compared using a long-rank test. Cumulative incidence of recurrence (CIR) was estimated using the competing risk methods, with death as a competing risk and compared using the Gray's test. OS was calculated from the date of diagnosis until death from any cause, as determined

by the medical record or Social Security Death Index. Patients with no evidence of recurrence (NED) were censored by the date of last evaluation. Recurrence was defined as date of surgery until the date of first local, regional, and/or distant recurrence. Cox proportional hazards model was used for both univariate and multivariate analysis to identify independent predictors of recurrence. Multivariate analysis was performed with all factors significant in a univariate analysis [10]. In addition to overall recurrences, we evaluated vaginal recurrences as they are the most common recurrences in early stage EC, and can potentially be reduced with adjuvant therapy. Categorical variables were surgery (hysterectomy vs. hysterectomy/bilateral salpingo-oophorectomy [BSO]), tumor size (≥2 cm vs. <2 cm), myometrial invasion (inner half vs. none), MMT protein expression (yes vs. no). Continuous variables were age at diagnosis, body mass index (BMI), time from biopsy to surgery, depth of invasion, LN dissection. Statistical significance was established at a p-value of 0.05, and all tests were 2-sided. Analyses were performed with SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA) and R (version 3.4; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Patient characteristics and recurrence

A total of 222 patients were identified, 74 patients had an open laparotomy, 145 patients had laparoscopic surgery (69 of those were robotic), 2 patients had a vaginal hysterectomy and the surgical technique in one patient was unknown. The majority of the patients with IAG1 EC (208 of the 222) were recommended for observation only after surgical resection. The remainder were either treated with brachytherapy alone, (n=4), combination of external beam and brachytherapy (n=1), hormone therapy or chemotherapy (n=3), or the treatment information was not recorded (n=6).

The median follow-up for the cohort of 222 patients was 20 months (range, 0–217 months). The median follow-up for the recurrent cohort was 46 months (range, 14–83 months). Of the 222 cases, tumor recurrence was recorded in a total of 17 (7.65%) patients. There were 9 (52.9%) isolated vaginal recurrences, 5 (29.4%) isolated abdominal failures and 3 (17.6%) pelvic co-failures, 1 (5.9%) each in the vagina, pelvis, and distantly. All 9 patients with vaginal recurrences as the only site of first failure were treated with a combination of pelvic radiation therapy (pelvic RT) and brachytherapy, 8 (88.9%) with vaginal brachytherapy (VBT) and 1 (11.1%) with interstitial brachytherapy. The 5 (55.6%) were successfully salvaged with no evidence of disease following treatment of recurrent disease and 44% had progressive disease involving other sites. The 8 patients with first failure outside the vagina were treated with a combination of chemotherapy, surgery, and pelvic radiation. Of these patients, only 1 (12.5%) patient had no evidence of disease, 3 (37.5%) patients were dead of disease and 4 (50.0%) patients had progressive disease.

A comparison of patient characteristics between recurrent and non-recurrent cases is presented in **Table 1**. Pathologic evaluation revealed that 50% of all patients included had inner myometrial invasion and the median depth of invasion was 14%. There were more recurrences in patients with any myometrium invasion compared to those without (13% vs. 3%, p=0.009). Eight (3.6%) patients had a hysterectomy with ovarian preservation (simple hysterectomy) and the remainder received a total hysterectomy/BSO. Of the 8 patients treated with ovarian preservation only, 2 (25.0%) had a recurrence (1 in the vagina, and 1 co-failure in the pelvis and abdomen).

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Table 1. Clinical and pathologic characteristics of FIGO stage IA grade 1 endometrioid endometrial cancer

Baseline characteristics	Total (n=222)	Recurrence (n=17)	No recurrence (n=205)	p-value
Age at diagnosis (yr)	59.7±10.6	61.5±10.3	59.5±10.7	0.453
BMI	33.6±9.9	32.3±8.8	33.7±10.0	0.658
Time from biopsy to surgery (mo)	2.0±3.3	3.9±6.5	1.9±2.9	0.245
Surgery				0.117
Hysterectomy	8 (3.6)	2 (25.0)	6 (75.0)	
Hysterectomy + BSO	214 (96.4)	15 (7.0)	199 (93.0)	
Tumor size (cm)				0.007
<2	79 (35.6)	1 (1.3)	78 (98.7)	
≥2	143 (64.4)	16 (11.2)	127 (88.8)	
Myometrial invasion				0.009
None	111 (50.0)	3 (2.7)	108 (97.3)	
Inner half	111 (50.0)	14 (12.6)	97 (87.4)	
Time from biopsy to surgery (mo)				0.032
<6	212 (95.5)	14 (6.6)	198 (93.4)	
≥6	10 (4.5)	3 (30.0)	7 (70.0)	
LVSI*				0.608
Absent	204 (91.9)	17 (8.3)	187 (91.7)	
Present	14 (6.3)	0 (0.0)	14 (100.0)	
LN dissection				1.000
No dissection	76 (34.2)	6 (7.9)	70 (92.1)	
Pelvic LNs only	145 (65.3)	11 (7.6)	134 (92.4)	
Para-aortic LNs only	31 (14.0)	1 (3.2)	30 (96.8)	
Pelvic and paraaortic LNs	146 (65.8)	11 (7.5)	135 (92.5)	
MMR protein expression†				0.691
Absent	101 (45.5)	10 (9.9)	91 (90.1)	
Present	25 (11.3)	1 (4.0)	24 (96.0)	

Values are presented as mean±standard deviation or number (%).
FIGO, International Federation of Gynecology and Obstetrics; BMI, body mass index; BSO, bilateral salpingo-oophorectomy; LVSI, lymphovascular space invasion; LN, lymph node; MMR, mismatch repair.
*Missing data: LVSI (4 patients without LVSI data), †MMR (96 patients without MMR status).

Tumor size was ≥2 cm in 64.4% of cases. There were more recurrences in patients with tumor size ≥2 cm compared to those with <2 cm (11.2% vs. 1.3%, p=0.007). Median number of pelvic nodes removed in patients with lymphadenectomy was 8. However, there was no difference between the two groups with regards to LN dissection or other historic risk factors such as age, BMI, LVSI, and mismatch repair mutation status (**Table 1**).

2. OS and factors associated with any recurrence

The median survival for the entire cohort was 217 months and 5-year OS was 92% (95% confidence interval [CI]=82%–96%). Analysis of OS showed that patients with tumor recurrence had much worse survival compared to those without (5-year OS=60%; 95% CI=16%–86% vs. 5-year OS=95%; 95% CI=87%–99%, respectively, p=0.003) (**Fig. 1**). The median time between surgery and recurrence was 15 months and the CIR at 3 years was 10% (95% CI=6–17). Univariate cox regression analysis of clinical and pathological risk factors associated with recurrence revealed that four factors were predictive of recurrence; time from biopsy to surgery (hazard ratio [HR]=1.15; 95% CI=1.06–1.25; p=0.003), surgery type (HR=4.91; 95% CI=1.06–22.6; p=0.041), tumor size (HR=1.15; 95% CI=1.03–1.29; p=0.010), and myometrial invasion (HR=5.26; 95% CI=1.50–20.0; p=0.010) (**Table 2**). There was no relationship between the risk of recurrence and conventional adverse risk factors such as age, number of LNs removed, and LVSI. Multivariate analysis confirmed that any myometrial invasion, increasing tumor size, and time from biopsy to surgery were independent predictors of recurrence (**Table 3**). The 14 patients who received adjuvant treatment had no recurrences; we ran all the data excluding those 14 patients and noted no differences in the results.

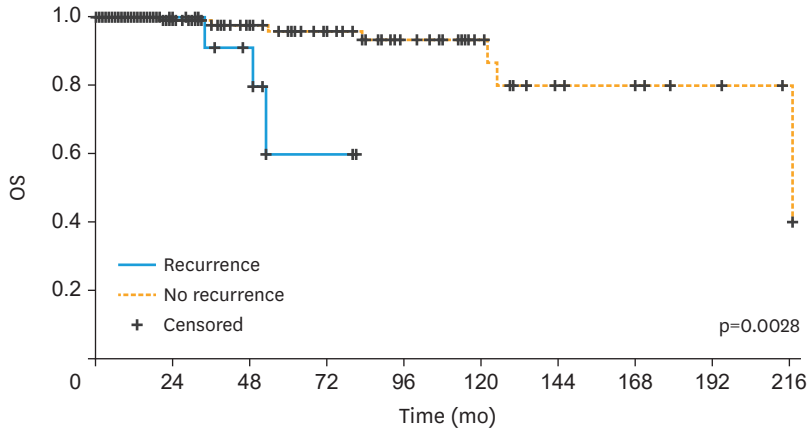

Fig. 1. OS of patients with stage IA grade 1 endometrial cancers based on recurrence status.
OS, overall survival.

Table 2. Univariate analysis of factors associated with recurrence of FIGO stage IA grade 1 endometrioid endometrial cancer

Predictive factors	Recurrence		
	HR	95% CI	p-value
Age at diagnosis	1.01	0.96–1.06	0.554
BMI	1.00	0.94–1.06	0.902
Time from biopsy to surgery	1.15	1.06–1.25	<0.001
Surgery (Hyst vs. Hyst/BSO)	4.91	1.06–22.6	0.041
Tumor size (≥2 cm vs. <2 cm)	1.15	1.03–1.29	0.010
Myometrial Invasion (inner half vs. none)	5.26	1.50–20.0	0.010
Depth of invasion	2.15	0.30–15.1	0.440
LN dissection	-	-	-
Pelvic	0.99	0.98–1.03	0.761
Paraaortic dissection	0.90	0.71–1.13	0.377
MMR protein expression (no vs. yes)	1.68	0.21–13.2	0.621

FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; CI, confidence interval; BMI, body mass index; Hyst, hysterectomy; BSO, bilateral salpingo-oophorectomy; LN, lymph node; MMR, mismatch repair.

Table 3. Multivariate analysis of factors associated with recurrence of FIGO stage IA grade 1endometrioid endometrial cancer

Predictive factors	Recurrence		
	HR	95% CI	p-value
Time from biopsy to surgery	1.15	1.07–1.24	<0.001
Myometrial invasion (inner half vs. none)	5.53	1.44–21.2	0.013
Tumor size	1.14	1.01–1.29	0.033
Surgery (Hyst vs. Hyst/BSO)	4.16	0.69–33.3	0.121

FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; CI, confidence interval; BMI, body mass index; Hyst, hysterectomy; BSO, bilateral salpingo-oophorectomy.

3. Factors associated with vaginal recurrence

Univariate and multivariate cox regression analysis of clinical and pathological risk factors associated with vaginal recurrence revealed that only time from biopsy to surgery ≥6 months (HR=1.16; 95% CI=1.07–1.26; p≤0.001) and any myometrial invasion (HR=10.1; 95% CI=1.11–93; p = 0.051) were independently predictive of recurrence (**Table 4**).

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Table 4. Multivariate analysis of factors associated with vaginal recurrence of FIGO stage IA grade 1 endometrioid endometrial cancer

Predictive factors	Recurrence		
	HR	95% CI	p-value
Time from biopsy to surgery	1.16	1.07–1.25	<0.001
Myometrial invasion (inner half vs. none)	9.54	0.98–92.1	0.051
Tumor size	1.10	0.91–1.32	0.319
Surgery (Hyst vs. Hyst/BSO)	3.48	0.34–25.7	0.293

FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; CI, confidence interval; BMI, body mass index; Hyst, hysterectomy; BSO, bilateral salpingo-oophorectomy.

DISCUSSION

The factors associated with increased risk of recurrence for patients with early stage EC include histologic factors like outer half myometrial invasion, LVSI, high histologic grade, lower uterine segment involvement [5,11-13], and molecular factors such mutations in TP53 or beta catenin [14]. Currently in clinically practice, mostly the histologic factors drive the decision making for adjuvant management [15,16]. Patients with IAG1 EC lack the above conventional risks factors and therefore the recommendation for these patients following surgery is generally observation. Despite being categorized as low-risk, recurrence rates for IAG1 ECs range from 5%–10% as observed in this study and others [7,17-19]. However, the factors associated with recurrence in this cohort are not clearly defined.

Although the number of recurrences in this study is small, and our results are hypothesis generating, we identified additional risk factors associated with recurrence in patients with IAG1 tumors including tumor size (≥2 cm), time between biopsy and surgery (≥6 months), surgical extent, and any myometrial invasion. We observed that only time between biopsy and surgery (≥6 months), any myometrial invasion, and increasing tumor size, were predictive of isolated vaginal recurrences. Our data shows worse OS in patients with recurrence, therefore identification of additional risk factors that are associated with increased risk of recurrence in stage IAG1 patients is of clinical value. Patients with isolated vagina recurrences had much better outcome than those with occurrences outside of the vagina, confirming existing evidence that vagina as first site of failure may be more salvageable than other sites [20].

The risk factors we identified in this study have been associated with poor prognosis in other studies on early-stage ECs [5,11]. One study examined the prognostic factors for tumor recurrence of stage I EC, and observed that tumor size and myometrial invasion were significant prognostic factor for tumor recurrence [17], similar to our findings, which suggest that subsets of IAG1 EC patients with any myometrial invasion and tumors >2 cm are at an increased risk of vaginal and any recurrence. Notably, we did not find age as a factor associated with increased risk of recurrence, likely because our study compromised of a homogenous population (mean age, 60 years), with few patients older than 70 or younger than 50.

Though IAG1 EC patients are considered low risk, and recurrence rates are overall uncommon, perhaps a more frequent surveillance plan for patients with the risk factors identified in our study may be warranted. The current guidelines recommend a thorough history and physical exam including speculum exam every 3–6 month within the first year [21], but perhaps patients with recurrence risk factors, as identified in our study, should follow a similar schedule to patients with high risk ECs. This would include follow-up and pelvic exam every 3 months for the first 1–2 years, to permit identification of patients prior to the development of symptoms, as

asymptomatic patients at disease recurrence had a better prognosis than symptomatic patients [22]. Although clinical vaginal exams can detect asymptomatic recurrences, identification of a "high recurrence risk" group in IAG1 may allow for the selection of patients that may benefit from adjuvant radiation given the well-established role of brachytherapy to decrease rate of vaginal recurrences with minimal side effects [23,24].

Our data shows that patients treated with a simple hysterectomy with ovarian preservation had a higher risk of recurrence. These patients were incompletely staged and whether this small group of patients truly had stage IA disease is unknown. Therefore, patients may benefit from a surgical staging consisting of BSO and with LN assessment based on tumor size, if frank invasion is identified on the pathological specimen.

Much has been reported on time to recurrence after surgery [6,25,26], and the time to relapse after surgery is an independent prognostic factor for survival [27], but there is limited data about the risk associated with time between biopsy and surgery. In our study, 10 patients had greater than six months elapse between their biopsy and surgery and their risk of recurrence begins to increase at 5 months. The delays were due to comorbid medical conditions that prevented immediate surgery in two patients, complex social factors/patient related delays in five patients, and Megace/hormonal therapy failure in three patients. It is unclear whether the increased risk of recurrence associated with the time between biopsy and surgery is secondary to the time elapsed or related to inherent disease aggressiveness that may be identified by molecular profiling features.

Stelloo et al. (2016) [28] confirmed the prognostic impact of the four molecular subgroups originally proposed by The Cancer Genome Atlas (TCGA) [28,29]. In their study, *L1CAM* and *p53* were noted as consistent independent predictors for worse outcome whereas patients with *POLE* mutations, or microsatellite stable (MSS) and *CTNNB1* wild type had a more favorable prognosis [28]. Recently, a secondary analysis of PORTEC-3 study, showed that molecular classification of EC has a strong prognostic value in patients with high risk features compared to clinico-pathologic factors, and this may identify those who will derive a benefit from adjuvant treatment [30]. Therefore, combining these molecular factors with the clinico-pathologic factors from our study may define a cohort that is truly at "higher risk" and may benefit from adjuvant treatment, however larger studies with larger numbers of recurrences would be needed to confirm this. We recognize that adjuvant treatment is not associated with an improvement in OS in patients with early-stage disease and treatment in this group will likely not impact survival, but if our results are confirmed, then adjuvant radiation would impact local recurrence similar to other early stage ECs

There are several limitations inherent to our study due to the retrospective nature of the study. Unmeasured confounders could have influenced the survival and recurrence outcome estimates. Additionally, the small number of recurrent cases limits our ability to make definitive statement regarding predictive values of the covariates, nonetheless, we identified certain factors that predict for a significantly higher risk of recurrence, suggesting that certain subpopulations of the IAG1 may benefit from closer attention in follow up. We anticipate that in a larger sample size with more recurrences we may observe similar trends, and validating our findings with a separate cohort will be important.

In addition, only 8 patients had simple hysterectomies with ovarian preservation making it difficult to draw a conclusion from the small subgroup. The next steps include pooling

of data from multiple institutions/larger databases that could provide results that are more robust, validate our data and allow definitive conclusions/recommendations about IAG1 risk factors. Nevertheless, this study had similar recurrence rates comparable to those reported in the literature and identified risk factors associated with recurrence that can perhaps, in a larger data set, be used to create nomograms that allows risk stratification [31].

In conclusion, patients with IAG1 EC are at a low risk for recurrent disease and do not meet the standard criteria for adjuvant therapy. The recurrence rate in our study is 8% and the survival rate for the patients with recurrence is significantly worse than for those without recurrences. Although these patients are considered low risk, identification of additional risk factors for recurrence could help identify patients who are likely to benefit from more frequent surveillance or adjuvant treatment as opposed to salvage treatment, which has variable efficacy and can be morbid for some patients. Adjuvant therapy with brachytherapy is quick and relatively well tolerated by patients and may be of value in IAG1 patients with identified risk factors. Combining clinico-pathologic and molecular factors associated with an increased risk of recurrence may best define the group of patients that would benefit from a heightened surveillance strategy or adjuvant radiotherapy.

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