Intravaginal Brachytherapy in FIGO Stage I Low-Risk Endometrial Cancer

A Controlled Randomized Study

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Abstract: The purpose of the study was to compare postoperative vaginal irradiation with surgery alone in low-risk International Federation of Gynecology and Obstetrics (FIGO) stage IA-IB endometrial carcinoma. The study was a prospective, randomized trial of 645 evaluable low-risk endometrial carcinoma patients from 6 European gynecologic cancer centers. All tumors were in FIGO stage IA-IB, of endometrioid histological type, and FIGO grade 1–2. High-dose-rate afterloading equipments (iridium [Ir] 192 or cobalt [co] 60) were used at 5 centers, and low-dose-rate (LDR) afterloading equipment (cesium [Cs] 137) at 1 center. Perspex vaginal applicators or ovoids were normally used, and the dose was specified at 5 mm from the surface of the applicator. Three to 6 fractions (3.0–8.0 Gy) were given, and the overall treatment time was 4 to 15 days. A total of 319 patients were treated with surgery plus vaginal irradiation (treatment group), and 326 patients with surgery alone (control group).

Twenty-six recurrences (4.0%) were recorded in the complete series. The locoregional recurrence rate was 2.6%, whereas distant metastases occurred in 1.4%. The rate of vaginal recurrences was 1.2% in the treatment group versus 3.1% in the control group. The difference was not statistically significant ($P = 0.114$). Side effects were few and mild (grade 1–2). Dysuria, frequency, and incontinence were slightly more common after vaginal irradiation (2.8% vs 0.6%, respectively). Late intestinal problems were few and similar in the 2 groups. The conclusions were that the impact of postoperative brachytherapy on even the locoregional recurrence rate seems to be limited in patients with low-risk endometrial carcinoma. The overall recurrence rate and survival were similar in the 2 groups.

Key Words: Endometrial carcinoma, Low-risk, Vaginal irradiation, Brachytherapy

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Endometrial carcinoma is the most frequently occurring malignancy of the female genital tract. More than 1200 new cases are diagnosed annually in Sweden.[1] Despite early detection (90% in International Federation of Gynecology and Obstetrics [FIGO] stages I-II) and a rather favorable prognosis in early stages, 15% to 20% of the tumors will recur. The vagina is the site most commonly affected by locoregional failures.[2] To prevent vaginal recurrences, postoperative vaginal irradiation has been part of the therapy for a long time. Many published nonrandomized studies have shown excellent results with intravaginal brachytherapy treatment.[3–15] Because of a lack of randomized studies, this type of adjuvant therapy, as well as other types of radiotherapy in treatment of endometrial carcinoma, is still under debate, and no consensus exists today.[16–20]

During the last 10 years, endometrial carcinomas have generally been sorted into 3 risk groups: high-risk, medium-risk, and low-risk groups. Definitions of these risk groups vary between centers and countries. The main problems to deal with are the distant metastases in the high-risk group, the regional pelvic lymph node metastases in the medium-risk group, and the local vaginal metastases in the low-risk group. The treatment schedules should be tailored with this in mind. The aims of contemporary studies have

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TABLE 1. Radiation technique at the participating centers

Center	Radiation Source	Dose-Rate	Dose/Fraction, Gy	Total Dose, Gy	BED_{10},* Gy	BED_3,† Gy
Stockholm	^{192}Ir	HDR	3.0	18.0‡	23.4	36.0
Örebro	^{192}Ir	HDR	3.0	18.0‡	23.4	36.0
Lausanne	^{192}Ir	HDR	3.0	18.0‡	23.4	36.0
Tampere	^{192}Ir	HDR	5.5	22.0‡	34.1	62.3
Istanbul§	$^{192}Ir/^{60}Co$	HDR	8.0	24.0‡	43.2	88.0
Ljubljana	^{137}Cs	LDR	40.0	40.0‖	46.2	60.7

*BED (α/β = 10)—tumor and early reacting tissue effect.
†BED (α/β = 3)—late reacting tissue effect.
‡The dose was specified at a depth of 5 mm from the surface of the applicator.
§One patient was treated with LDR (30 Gy in 3 days) and vaginal mold.
‖The dose was specified at the surface of the applicator.

been to evaluate the effects of adjuvant chemotherapy in the high-risk group,[21] the effects of external pelvic beam therapy in the medium-risk group,[22–24] and prophylactic vaginal irradiation in the low-risk group. Final guidelines for treatment of these risk groups have awaited the results from these trials. The American Brachytherapy Society has already presented recommendations for high-dose-rate (HDR) brachytherapy for carcinoma of the endometrium.[25,26] The results from a multicenter, randomized, low-risk study are presented in this report.

METHODS AND MATERIALS

Six European cancer centers (Table 1) recruited patients with low-risk endometrial carcinomas in FIGO stage IA-IB into this prospective, randomized, and controlled study. The period of recruitment was from January 1995 through December 2004. In all, 650 patients were recruited to the study, and 645 patients were evaluable (Stockholm, n = 192; Tampere, n = 162; Örebro, n = 113; Ljubljana, n = 81; Istanbul, n = 55; and Lausanne, n = 42) for analysis in the trial (Table 2). Five patients were excluded because of protocol violation (inclusion criteria were not fulfilled). In 326 patients, surgery alone (control group) was the treatment, and in 319 patients, postoperative vaginal irradiation (treatment group) was added to surgery. Stratification was done per center, and randomization (1:1) by closed envelops at each participating center. The database was closed for follow-up in December 2007. The mean age of the patients was 62.7 years (range, 31–85 years). The definition of low-risk carcinomas was as follows: (1) endometrioid histological type, (2) FIGO grade 1–2, (3) nuclear grade 1–2, (4) infiltration less than half of the myometrial thickness, (5) diploid DNA profile, (6) pathologically negative lymph nodes, and (7) negative abdominal cytology. Points 5 to 7 were optional in this study, and data are not available for all cases. All tumors were in surgical FIGO stage IA or IB. No subgroup analyses were done with regard to stage IA versus IB or FIGO grade 1 versus FIGO grade 2. Lymphovascular space invasion was not regularly included in the pathology reports at the participating centers and was not included in the definition of the low-risk group. The primary surgery was total abdominal or laparoscopic hysterectomy, bilateral salpingo-oophorectomy, appendectomy, node sampling of enlarged lymph nodes, and peritoneal washing with cytology. Lymphadenectomy (iliac or pelvic) was performed at only 1 center (Tampere). The surgery was performed at 6 departments of gynecology and obstetrics (Division of Gynecological Oncology in Tampere), but all patients were then referred to an oncology department for postoperative evaluation and treatment. The time interval between surgery and brachytherapy was 4 to 8 weeks. All patients were then planned for a 10-year follow-up program. The mean follow-up period at the time of analysis (January 2008) was 68 months (range, 2–151 months). During all visits, symptoms and signs related to the therapy were recorded, and the vaginal mucosa was carefully inspected.

For the brachytherapy treatments, MicroSelectron HDR machines with an iridium source (^{192}Ir) was used at 3 centers (Stockholm, Örebro, Tampere), Gammamed at 2 centers (Istanbul, Lausanne), and a Curietron (cobalt 60 [^{60}Co]) at 1 center (Istanbul). At 1 center (Ljubljana), an LDR technique (cesium 137 [^{137}Cs]) was used with a fungal-shaped vaginal applicator. Plastic vaginal cylinders with a diameter of 20, 25, or 30 mm were used as standard at most centers. The diameter of the cylinder was individually chosen to ensure good contact between the surface of the applicator

TABLE 2. Characteristics of the complete series (N = 645) of low-risk endometrial carcinomas

	Control	Treatment	
Tumor stage (FIGO)			
IA-B	326 (50.5)	319 (49.5)	
Tumor grade			
Well or moderately well differentiated (grade 1-2)	326 (50.5)	319 (49.5)	
Type of histology			
Endometrioid	326 (50.5)	319 (49.5)	
Nonendometrioid	0	0	
DNA profile			
Diploid	153 (46.9)	155 (48.6)	
Nondiploid	2 (0.6)	3 (0.9)	
Unknown	171 (52.5)	161 (50.5)	
Survival status			
Alive	310 (95.1)	302 (94.7)	0.815*
Died of endometrial cancer	5 (1.5)	7 (2.2)	
Died of other disease	11 (3.4)	10 (3.1)	
Recurrences			
Vaginal	10 (3.1)	4 (1.2)	0.114*
Pelvic	3 (0.9)	1 (0.3)	0.326*
Distant	2 (0.6)	7 (2.2)	0.087*

Values are presented as n (%).
*Pearson χ^2 test.

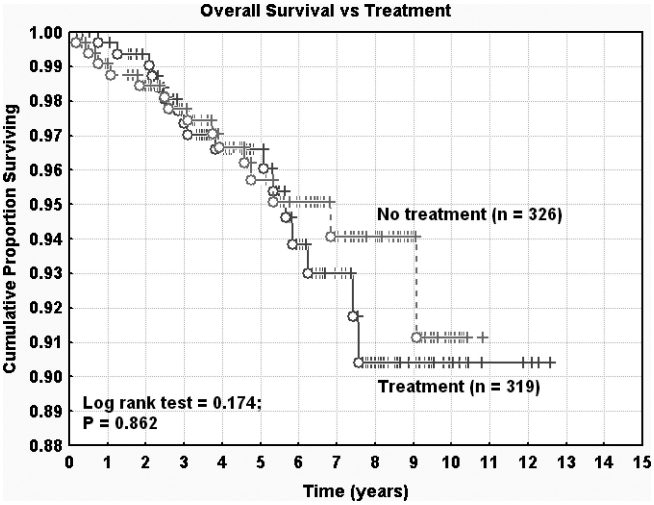

FIGURE 1. Overall survival rate of patients treated with surgery alone (control) and patients treated with surgery and postoperative vaginal irradiation (treatment). There was no significant difference between the 2 groups.

and the vaginal mucosa. In most cases, 30-mm cylinders were used. The length of the vagina was measured from the vault to the level of introitus. The proximal two thirds of the vaginal length was defined as the target volume when cylinders were used. The dose per fraction was specified at a depth of 5 mm from the surface of the vaginal cylinder (including the vault region) with the HDR technique and at the surface of the applicator with the LDR technique (Ljubljana). Library dose plans that covered different vaginal lengths in steps of 10 mm and the different diameters of the cylinders were used. The dose calculations were made on the Nucletron Planning System (NPS v. 10) and the PLATO Brachytherapy Planning System (BPS v. 14) at centers using this equipment. At the surface of the cylinder, the mean dose was approximately 150% of the specified reference dose at 5 mm. There was a slight variation of the surface dose (143%–157%) along the surface of the cylinder. No optimization was used. At 1 center (Istanbul), 2 vaginal ovoids were used instead of the cylinder, and 1 patient at that center was treated with a vaginal mold. Six fractions were given during an 8-day period at 3 centers (Stockholm, Örebro, and Lausanne). Three fractions during 15 days were used in Istanbul, and 4 fractions during 4 days in Tampere (Table 1). The overall treatment time in Ljubljana was 36 hours (LDR technique). The dose per fraction was assigned to 3.0, 5.5, or 8.0 Gy, depending on the number of fractions given. Thus, the total doses delivered were 18.0 to 24.0 Gy. Recalculated to 2-Gy-equivalent doses, the total doses were 19.5 to 36.0 Gy at a depth of 5 mm and 29.3 to 54.0 Gy at the surface of the vaginal applicator (α/β = 10.0). The biologic effective doses (BEDs) were also calculated using the linear-quadratic dose-effect equation. All treatments were given on an outpatient basis. No external beam therapy was given to these patients. The details of the radiation techniques at the participating centers are presented in Table 1.

The first follow-up visit was scheduled at 1 month, then every 3 months during the first year, every 4 months during the second and third years, and every 6 months to 5 years and then annually up to 10 years. All data were collected in a computerized database at the Department of Gynecological Oncology, Örebro, Sweden. The study was approved by the Committee of Ethics at the Karolinska Institute (KI dnr 94:79, 1994), Stockholm, and at the local committees of ethics of the participating hospitals. Informed consent was achieved from each participating patient according to the routines at the 6 individual centers.

In the statistical analyses, survival curves were generated using the Kaplan-Meier technique, and differences were tested with the log-rank test. The χ^2 test was used for comparison of proportions, and the independent t test for comparing means of the 2 randomized groups. A sample size of 645 patients allowed a detection of a 4% difference (1% vs 5%) in the vaginal recurrence rate in the 2 groups (α = 0.05, β = 0.80, 2-sided test). $P < 0.05$ was regarded as statistically significant. The Statistica software package (version 8, 2007; StatSoft Inc, Tulsa, Okla) was used for the statistical analyses.

RESULTS

Tumor stage (FIGO), tumor grade, type of histology, and DNA ploidy were similar and well balanced between the 2 randomized groups (Table 2). The cancer-specific and overall survival rates at 5 years of the complete series were 98.4% and 96.1%, respectively. There were no differences between the 2 randomized groups (Fig. 1). Twenty-six recurrences (4.0%) were recorded in the complete series (Table 2). In the control group, 14 recurrences (4.3%) were noted versus 12 recurrences (3.8%) in the treated group (Pearson χ^2, P = 0.731). The 5-year overall survival rate for patients with recurrent disease was 59%, and for patients with no recurrence(s), 98% (Fig. 2). The long-term survival rate among patients with recurrent tumors was similar (log-rank test, P = 0.889) in the control group and in the treated group. Seventeen locoregional recurrences (2.6%) and 9 distant metastases (1.4%) were recorded in the complete series. The 5-year overall survival rate for patients with locoregional recurrences was 55%, and for patients with distant recurrences, 63%. For patients with isolated vaginal recurrences, the survival rate was 77%. In the group treated with surgery alone, the survival rate was 60% after vaginal recurrences. No significant differences were recorded between the 2 randomized groups with regard to sites of recurrences. Primary surgery with (n = 162) or without (n = 483) lymphadenectomy did not influence the overall or vaginal recurrence rate. However, the rate of vaginal recurrences was lower in the treatment group (1.2%) compared with the control group (3.1%), but probably because of the small absolute number of vaginal recurrences (n = 14), this difference was not statistically significant (Pearson χ^2, P = 0.114) (Table 2). All vaginal recurrences, both in the treated and the untreated groups, were located in the upper two thirds of the vagina. Patients with vaginal recurrences were significantly (t test, P = 0.018) older (mean age,

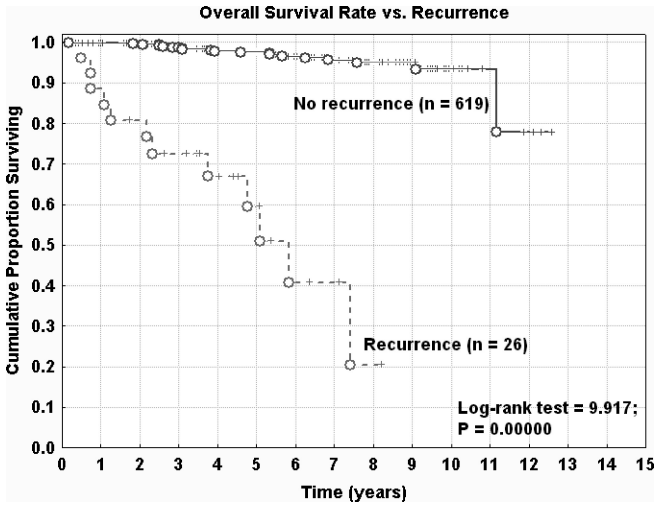

FIGURE 2. Overall survival rate of patients with and without tumor recurrence. There was a highly significant difference between the 2 groups.

TABLE 3. Late side effects (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer toxicity criteria) versus control or treatment

Side Effect	Control	Treatment	*P**
Vaginal	5 (1.5)	28 (8.8)	0.00004
Grade 1	2 (0.6)	24 (7.5)	
Grade 2	3 (0.9)	4 (1.3)	
Grade 3	0	0	
Urogenital	2 (0.6)	9 (2.8)	0.063
Grade 1	2 (0.6)	5 (1.6)	
Grade 2	0	4 (1.3)	
Grade 3	0	0	
Intestinal	2 (0.6)	3 (0.9)	0.599
Grade 1	2 (0.6)	2 (0.6)	
Grade 2	0	1 (0.3)	
Grade 3	0	0	

Values are presented as n (%).
*Pearson χ^2 test.

68.6 years) than patients without vaginal relapses (mean age, 62.6 years). At centers using a BED_{10} greater than 30 Gy, no vaginal recurrences were recorded compared with 4 recurrences (2.2%) at centers using a BED_{10} less than 30 Gy (Pearson χ^2, $P = 0.047$). Twelve (46.2%) of the 26 patients with recurrent disease died of their disease. Twenty-one patients (3.3%) died of other diseases during the period of observation (Table 2). Among 14 patients with vaginal recurrences, 5 (36%) died of their disease. In the control group, 30% died of their disease, and 2 (50%) of 4 patients in the irradiated group.

The side effects (Table 3) were few, and for most of them, no significant differences were noted between the 2 randomized groups. However, vaginal grade 1 reactions were significantly (Pearson χ^2, $P = 0.00004$) more common in the treatment group (7.5%) than in the control group (0.6%). Slight atrophy, vaginal dryness, and sporadic mucosal bleedings were most frequent. Shortening of the vagina and more extensive mucosal changes and subjective problems were rare (approximately 1%) in this series. Recordings of sexual activity and of sexual function were not performed in this study. Urogenital problems were not frequently recorded in either group. Dysuria, frequency, and incontinence were the most common symptoms and slightly more frequent in the group after vaginal irradiation (2.8%) than in the untreated control group (0.6%). This difference did not reach statistical significance, however (Pearson χ^2, $P = 0.063$). Late intestinal symptoms were few (<1%) and of similar frequency in the 2 groups. No significant differences with regard to side effects from vagina, bladder, or intestine were recorded between centers using a BED_3 ($\alpha/\beta = 3.0$) greater than 40 Gy compared with centers using a total dose less than 40 Gy.

DISCUSSION

Even if endometrial carcinoma is the most frequent gynecologic cancer with an increasing incidence,[1] there is a shortage of randomized clinical studies and no universally accepted guidelines for treatment of the various risk groups.[16–20] Both external beam therapy and vaginal brachytherapy are disputed matters in the literature.[12–19] Local vaginal recurrences are the most common type among the locoregional metastases.[23] Prophylactic postoperative vaginal irradiation seems to be an effective method to prevent vaginal recurrences or to reduce the frequency to less than 1%.[4,10,14,15] In the low-risk group, vaginal irradiation is probably the only adjuvant treatment to discuss. The rationale for its use is obvious, but the cost-effectiveness is disputed. In the medium-risk group, the importance of additional external beam therapy has been investigated in a number of randomized studies.[22–24,27–29] For the high-risk group, systemic chemotherapy added to radiotherapy seems to improve recurrence-free and overall survival in a newly presented multicenter study.[21]

Even if the value of vaginal irradiation is reasonably proven, alternative treatment strategies are still discussed, for example, to wait and see and treat recurrences when they develop. The results from such a strategy are presented in a number of studies with varying outcomes.[16,17,19]

In the study presented in this report, randomized data from vaginal irradiation compared with surgery alone are presented for the first time. The overall recurrences rate was low (4.0%) in this series of low-risk endometrial cancer, and the vaginal recurrence rate in the complete series was only 2.2%. The criteria used to allot the patients into this study seem to be efficient, and a true low-risk group was selected for the trial. On the other hand, the possibility to find a statistically significant treatment effect of vaginal irradiation was difficult because of the small number of recurrences in both arms. In fact, the rate of vaginal recurrences was reduced by 60%[30] in the treated group, but from a very low rate (3.1%) in the group treated with surgery alone. The expected recurrence rate in the group treated with surgery alone was 4% to 5% when the study was designed. However, the recurrence rate in the treatment group (1.2%) was in agreement with the results (0.7%) of our prior studies.[4,10] Despite the fact that 645 patients were included in the study, the power was still too low to detect such a small absolute difference (1.9%) in the rate of vaginal recurrences. The study was powered to detect a difference of at least 4%. For medium-risk endometrial carcinomas with a higher expected rate of vaginal recurrences, for example, data presented in the PORTEC-1 study,[23,24] the situation may be different. In a number of studies published during the last years, vaginal brachytherapy alone has been proposed for patients with cancers belonging to this risk group and also other risk groups.[29,31,32]

The side effects associated with vaginal irradiation are sometimes mentioned as a great problem. In the present study, this was not the case, and few and only low-grade reactions from the vagina and the bladder were recorded. Intestinal problems were a concern in neither of the groups.

In fact, the risk of late tissue reactions in the vagina is related to the treatment schedule, for example, total dose, treatment time, dose-rate, dose per fraction, type of applicator, and the target volume.[4,10,33–37] In a randomized study of 2 different doses per fraction (2.5 vs 5.0 Gy), presented earlier, the number of fractions, overall treatment time, and target volumes were the same in both groups.[10] The patients were followed up for more than 5 years, and vaginal shortening as a measure of late tissue reactions in the vaginal walls was assessed at regular intervals. The analyses of these measurements showed convincingly that 2.5 Gy per fraction had little or no effect on the length of the vagina, whereas 5.0 Gy per fraction significantly shortened the vagina by 25% in mean after 5 years. Macroscopic inspection of the vaginal mucosa (atrophy, telangiectasia, and adhesions) could also verify this difference between the 2 doses per fraction. Subjective side effects reported by the patients themselves also revealed marked differences between the 2 groups. For the 2.5-Gy group, these signs and symptoms were probably not different from what could be expected in a group of healthy women of similar age not treated with vaginal brachytherapy.[38] The differences in toxicity were probably due to the fraction size, but maybe also due to different total doses.[33] From our earlier experience with HDR irradiation in treatment of endometrial carcinoma (intrauterine and vaginal), the fraction size seems to be more important than the total dose for the risk of late tissue

reactions.[4,10] Two-gray-equivalent doses calculations support the assumption that the dose schedules recommended for HDR vaginal brachytherapy by the American Brachytherapy Society (7.0 Gy × 3, 5.5 Gy × 4, and 4.7 Gy × 5) probably are associated with more late tissue toxicity than the 2.5 Gy × 6 schedule.[25,26,39]

From these experiences of earlier studies, the size of the fraction dose was set to 3.0 Gy in the present study and the number of fractions to 6 at 3 participating centers. The other 3 centers used higher doses per fraction or an LDR technique. The 3.0-Gy-dose level instead of 2.5 Gy (commonly used at the Örebro center) was chosen to be in line with the treatment schedules used by other participating centers in this trial. However, it was not the aim of the present study to compare different doses per fraction, and it was not designed or sized for this purpose. The treatment schedules in the brachytherapy arm varied quite strongly between the centers, and this was a weakness in the study design, but it was necessary to accept this variation in the radiotherapy technique to recruit the participating centers and to be able to perform a randomized study in true low-risk endometrial carcinoma. This is the first randomized study published for this group of patients.

In our earlier published randomized study, treatment efficacy was similar for the 2 different dose schedules (2.5 vs 5.0 Gy per fraction), and the rate of vaginal recurrences was 0.7% in both groups, and overall, 1.4%.[10] This was also in agreement with the results of a study that we published in 1990,[4] as well as with other published studies.[3,6] The conclusions from that study were that the fractionation dose of 2.5 Gy and a total dose of 15 Gy seemed adequate to prevent vaginal recurrences in a low-risk group of endometrial carcinoma treated with primary surgery.[10] However, in the present study, no vaginal recurrences were recorded at centers using a total BED_{10} greater than 30 Gy compared with 2.2% (4 vaginal recurrences) at centers using a total BED_{10} less than 30 Gy. This difference was statistically significant ($P = 0.047$) and might indicate a dose-response effect[30] not reported before for adjuvant vaginal irradiation. The rate of vaginal recurrences in our series was rather similar in the low-dose group (2.2%) and the untreated control group (3.1%). Thus, dose-finding studies are needed in the future to find the minimum dose level for an effective prophylactic vaginal irradiation. The figures for untreated groups (surgery alone) of endometrial cancer are reported to be 5% to 15%, depending on the selection of the patients studied.[9] These figures seem to be less reliable and more variable and explain the problem we had to dimension this study correctly with regard to the statistical power.

The method of postoperative HDR vaginal brachytherapy is simple to use, suitable for outpatient praxis, and is associated with few and well-tolerable side effects.[10] However, the cost-effectiveness of this treatment as a routine when compared with treatment of recurrent disease is not obvious for a true low-risk group defined as the one studied in this randomized trial.[40,41] Our future recommendation for treatment of this group of patients will be surgery alone and close follow-up. Still, it is entirely possible that certain other subgroups of low- or medium-risk patients (only stage IB, grade 2 or tumors with lymphovascular space invasion, or only patients of higher age) may benefit from vaginal brachytherapy.

Probably, for the future, medium- and high-risk endometrial cancer patients are the target populations for postoperative vaginal brachytherapy[12,14,15,24,29] and for further studies of this treatment modality as the only treatment or in combination with external pelvic irradiation[42,43] and/or chemotherapy[21,44] or other types of targeted therapies.

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