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Is there a place for brachytherapy for patients with ovarian cancer?

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Summary

Ovarian cancer is currently the second cause of death among genitourinary tract neoplasms in developed countries. Surgical treatment combined with chemotherapy is the standard of treatment in ovarian cancer. Disease relapses, cases where standard therapeutic procedures proved unsuccessful and previous radiotherapy significantly limited the possibility of further radiological treatment, constitute the greatest oncological challenge. There are attempts at using radiotherapy and/or brachytherapy. The aim of this retrospective study was to assess the results of brachytherapy among ovarian cancer patients with disease relapse. The study included 24 ovarian cancer patients with disease relapse, treated with brachytherapy at the Department of Brachytherapy of the Oncology Centre in Bydgoszcz from January 2008 to December 2014. Patients in all stages of the disease were subject to analysis. Disease relapse was confirmed in 23 of 24 subjects, the lesion being present beyond the vaginal stump. Twenty-one patients reported symptoms, most often spotting or vaginal bleeding. A trend toward higher survival rate in a group of patients without changes in the vaginal stump ($p = 0.07$) was observed. It was demonstrated that presence of lesions in the stump was associated with more frequent progression and this result was statistically significant ($p = 0.035$). In the entire group of patients, spotting or vaginal bleeding subsided. In summary, brachytherapy may be a useful treatment modality in selected clinical situations involving ovarian cancer. This procedure is particularly useful for women with disease relapse, parametrum infiltration, and/or incomplete tumor resection.

Key word: Brachytherapy; Ovarian cancer; Vaginal stump.

Introduction

Brachytherapy is a form of radiotherapy where the source of ionizing radiation is introduced directly into the neoplastic tissue or in its close proximity [1, 2].

Ovarian cancer is currently the second cause of death among genitourinary tract neoplasms in developed countries. Surgical treatment combined with chemotherapy is the standard of treatment in ovarian cancer [3, 4]. Recurrence is associated with poor prognosis and most common locations of ovarian recurrences involve the pelvis, peritoneum, pleura, liver, lungs, lymph nodes, and central nervous system [5].

Radiotherapy currently plays a minor role and it is mainly used as a next line of treatment or palliative therapy [6]. The role of brachytherapy in ovarian neoplasms is marginal mainly due to the size of the area that needs to be irradiated and proximity of critical organs. Use of brachytherapy in this condition seems like an interesting alternative in selected clinical situations. There are no precise guidelines regarding indications for brachytherapy in ovarian cancer. It is frequently used in cases of residual tumors, relapses and residual lesions after treatment [6].

The aim of this retrospective study was to assess the results of brachytherapy among ovarian cancer patients with disease relapse.

Material and Methods

The study included ovarian cancer patients treated with brachytherapy at the Department of Brachytherapy of the Oncology Centre in Bydgoszcz from January 2008 to December 2014. Primary patients were in all FIGO Stages: two women in Stage 1, four women in Stage 2, and 14 women in Stage 3, and four patients were in Stage 4. According to TNM classification patients: were two patients. were T1, four patient were T2, and 18 women were 18. Among the patients included in the study, tumor grading G was analyzed in 24 women, in the remainder of subjects grading G was not determined. In five (20.8%) patients G2 was diagnosed, in seven (29.2%) patients – G3, 12 (50%) of women the state of G malignancy grade was unknown. Among the group investigated that was subjected to prior brachytherapy, 24 underwent surgical therapy, with seven (29.2%) free from lymph nodes involvement and seven (29.2%) without confirmed metastases to the lymphatic system of pelvis minor, in ten (41.7%) women the state of lymph nodes was unknown. Disease relapse was confirmed in 23 of 24 subjects, the lesion being present beyond vaginal stump. Twenty-one patients reported symptoms, most often spotting or vaginal bleeding. All women underwent repeated surgical and systemic treatment, while 12 patients received radiotherapy at a dose of 20-45 Gy.

All patients were treated with intracavitary HDR brachytherapy at a total dose of 10-30 Gy in 1-4 fractions, 12 subjects had a vaginal applicator, two had a ring-type applicator, and the remaining patients received intratissue radiotherapy using 3-5 needle guides at a depth of 4-6 cm (Table 1). Except for the vaginal applicator, all procedures were conducted in the operating theater and the application was performed under short-term intravenous anesthesia.

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Table 1. — *Brachytherapy characteristics of patients with ovarian carcinoma.*

Number of fractions	Number of patients
1	3 (12.5%)
2	16 (66.7%)
3	1 (4.27%)
4	3 (12.5%)
5	1 (4.17%)
Type of applicator	Number of patients
Vaginal applicator	12 (50%)
Applicator number 2	3 (12.5%)
Applicator number 3	9 (37.5%)
Ring-type applicator	2 (8.33%)
Needle number	10 (41.7%)
4	8 (33.3%)
5	1 (4.17%)
3	3 (12.5%)
Depth of needle (cm)	Number of patients
4	3 (12.5%)
5	5 (20.83%)
6	2 (8.33%)

In the entire group the authors analyzed parameters influencing the probability of overall survival, such as: disease stage (T), FIGO staging, lymph node status, presence of distal metastases, presence of lesions in the vaginal stump, type of applicator, resolution of symptoms after treatment, brachytherapy complications, radiotherapy of the pelvis.

Statistical analysis was conducted using Statistica 10.0 software. Overall survival times were compared between subgroups with a log-rank test and presented as Kaplan-Meier curves. The risk of progression was assessed using the logistic regression model. In all statistical analyses the cut-off value for probability coefficient was set at $p < 0.05$

Results

Patient age ranged from 39 to 82 years, while adenocarcinoma with its subtypes (one patients with clarocellulare, two with papilare, four with serosum, two with mucinosum patients) was the most common histological type of tumor (20/24 patients). Disease relapse was confirmed in 23 of 24 patients, the lesion being present beyond vaginal stump, the patients without relapse was FIGO III Stage with adenocarcinoma serosum.

Disease relapse was confirmed in 23 of 24 patients, including 20 patients who presented with a mass that was visible and palpable in gynecological examination; 15 patients complained of spotting and vaginal bleeding. Symptoms subsided in 13 patients after brachytherapy, while 3 of 24 patients developed a rectovaginal fistula.

In the entire group the authors analyzed parameters influencing the probability of overall survival and the log-rank test showed borderline statistical significance for longer survival time (OS) in a group without lymph node metastases ($p = 0.05$). A trend toward higher survival rate in a group of patients without changes in the vaginal stump

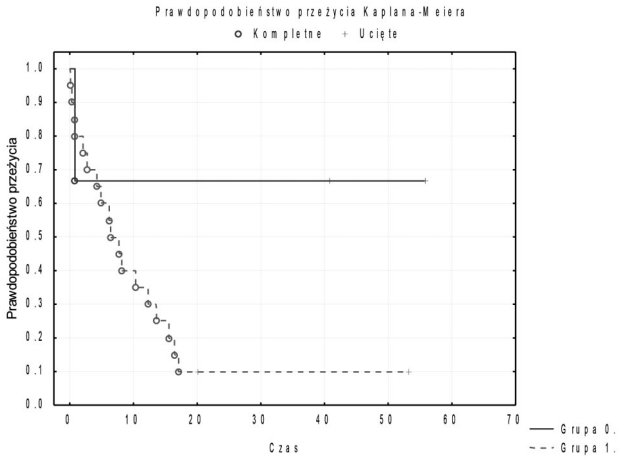

Figure 1. — A trend toward higher survival rate in a group of patients without changes in the vaginal stump ($p = 0.07$)

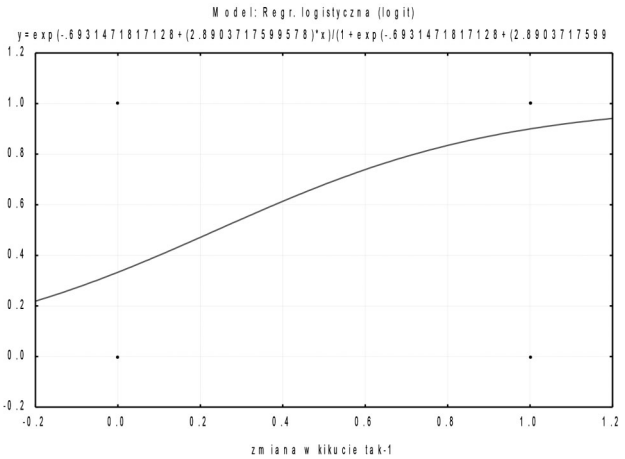

Figure 2. — Lesions in the stump was associated with more frequent progression ($p = 0.035$).

($p = 0.07$) was also observed (Figure 1). The remaining analyzed parameters did not influence survival time, including the T feature of staging and presence of distant metastases. Using logistic regression model the authors analyzed parameters influencing the risk of progression in the entire group, including disease staging (T feature), FIGO staging, lymph node status, presence of distant metastases, vaginal stump lesions, type of applicator, resolution of symptoms following treatment, brachytherapy complications, and radiotherapy of the pelvis. It was demonstrated that presence of lesions in the stump was associated with more frequent progression and this result was statistically significant ($p = 0.035$) (Figure 2). Complete lack local recurrence was only noted among patients with complete response ($p = 0.053$) (Figure 3). Disease progression was always noted in patients with distant metastases ($p = 0.002$).

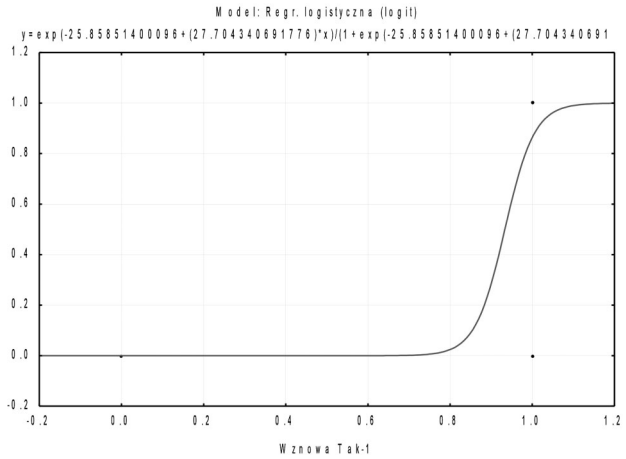

Figure 3. — Complete lack local recurrence was only noted among patients with complete response ($p = 0.053$).

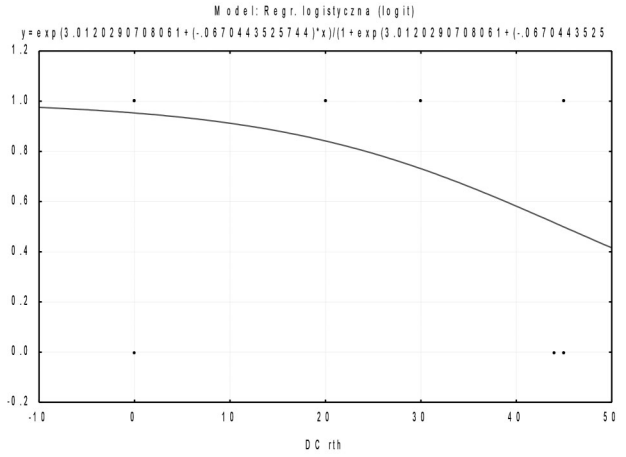

Figure 4. — The risk of progression decreased with increasing total radiotherapy dose ($p = 0.026$).

Brachytherapy dose, number of fractions, type of applicator, number of needles and insertion depth, T and N features of staging as well as age did not influence disease progression. Statistical analysis demonstrated that the risk of progression decreased with increasing total radiotherapy dose ($p = 0.026$) (Figure 4).

Discussion

With current treatment approaches, many patients with epithelial ovarian cancer initially achieve complete clinical remission. Recurrence of chemoresistant ovarian cancer is usually a fatal occurrence because the salvage rate with current treatment modalities is very low. The median disease-free survival is approximately 20–25 months with a median overall survival of 50 months in optimally debulked advanced-stage patients. Survival is poor, but combined modality salvage therapy may be able to palliate symptoms and induce a response that may improve disease-free survival [7]. Vaginal stump recurrence (VSR) after surgery is common in genitourinary tract cancer. The overall incidence of VSR after definitive surgery is reported as being 2.4–15% [8, 9].

The treatment of recurrent cancer is difficult and the factor which determining the prognosis of patients with recurrent cancer is tumor size, what the authors observed also in this study. This is supported by the fact that the five-year survival rates of each tumor size were significantly different: 87% for the small tumor group, 56% for the medium, and 0% for the large [10, 11].

Local resection is rarely indicated for vaginal recurrences due to the risk of microscopic disseminated disease at the time of presentation. For a bulky (> 4 cm) VSR, only surgery is considered as definitive treatment, pelvic exenteration is a consideration, but has pronounced morbidity associated with it. Kasamatsu *et al.* [12] reported that the five-year survival rate after exenteration was 36% and that the procedure-related mortality was 6%. Thus, radiation therapy remains the mainstay of treatment for local recurrent disease [10, 11].

When recurrence develops after radiotherapy and is unresectable, radiotherapy is to be applied to patients with recurrent cancer, a combination of external irradiation and interstitial irradiation is also recommended.

Patients who have isolated vaginal recurrences of ovarian cancer can be salvaged with brachytherapy, especially patients who have small tumors. Identifying patients at higher risk for a vaginal recurrence or distant metastases may be important in the determination of the treatment [13].

Brachytherapy may be considered as a treatment method in ovarian cancer when changes are located near the vagina or its stump, as well as in cases where neoplastic infiltration involves the parametrium [3]. The choice of the method depends on location of the lesion and size of infiltration. Intracavitary brachytherapy may be implemented when thickness of tissue infiltration is 5 mm or less. If it exceeds this thickness, interstitial brachytherapy is indicated [14].

Randall *et al.* [15] reported that the pathology, tumor volume, implant dose, and site of recurrence were significantly related to the local control rate in his study. While Puthawala *et al.* [16] treated only patients with recurrent tumors measuring < 5 cm in diameter, Brabham *et al.* [17] treated patients with tumors < 1 cm in thickness and median volume of 3.3 cm^3.

Size of the recurrent cancer seems to be a risk factor independent from the location of the recurrence: Ito *et al.* [10, 11] limited the analysis to vaginal stump recurrences of cervical cancer and differentiated between small (no palpable tumor), medium (< 3 cm size) and large recurrent tumors (> 3 cm size) [10, 11]. Three-year local control rates were

about 90%, 50%, and 40% for small, medium, and larger size of the recurrent cancer, respectively. This poor ability to achieve local control for large recurrent tumors combined with high rates of systemic progression was associated with decreased rates of survival. Ten-year survival rates were 72%, 48%, and 0% for small, medium and larger size of the recurrent cancer, respectively [18]

Fujiwara *et al.* [13] in their study irradiated the recurrent or refractory tumors although the patients did not have any symptoms. Since they found that tumors < 5 cm showed better responses to radiation therapy and that nearly 85% of the irradiated disease sites did not progress, the authors suggested that it would be reasonable to irradiate as early as the tumor is found in order to prevent the development of symptoms [13]. In stringently selected patients, however, a few studies have demonstrated some success with re-irradiation using permanent interstitial brachytherapy (ISBT) [17, 19]. Iodine-125, palladium-103, or Au-198 has been used for permanent ISBT, and iridium (Ir)-192 or cesium-137 for temporary ISBT. Badakh *et al.* [19] reported 22 patients with post-radiation recurrent cervical carcinomas treated by HDR-ISBT. The median survival was 9.2 (range, 4.1–56.6) months. Four of the 22 (18%) patients developed Grade IV complications [20]. Moreover, since Au-198 IRI is relatively simple to perform and is well-tolerated by patients, it can be considered even for patients in poor general condition.

In Okazawa *et al.* [20] study 15 patients with post-treatment locally recurrent uterine carcinomas were treated with Au-198 IRI. All of the recurrent tumors were local and located in the central region of the previously irradiated area. All of the patients had received some form of radiation therapy previously, nine of the 15 patients had received definitive radiotherapy EBRT. The median thickness of the tumor was 1 (range, 0.5–2) cm, and the median tumor volume was 1.3 cm^3. The median follow up duration was 18.8 (range, 4.3–146.9) months from the date of implantation of the Au-198 seeds. Of the 15 patients, 13 (87%) showed complete response to the Au-198 IRI, although ten of these 13 (77%) patients developed local recurrence again between 2.5 and 49.7 months after implantation. A poor response was observed in the remaining two patients. The two-year central recurrence free survival rate in the 15 patients was 33%. The overall two-year survival rate of the 15 patients was 64%. A significant relationship was observed between the overall survival rate and the site of recurrence, tumor volume, and local response to Au-198 IRI. Age, primary site, pathology, interval from previous radiation therapy to Au-198 IRI, number of times of recurrence, previous irradiation dose (BED10), Au-198 IRI dose, and M-stage had no significant influence on the overall survival. Rectovaginal fistula (Grade IV) occurred in one patient 14 months after the implantation. None of the other patients developed any late complications that were more severe than Grade III.

In the present study the authors did not observed influence between disease progression and total brachytherapy dose, number of fractions, type of applicator, number of needles, and insertion depth.

Randall M *et al.*[15] present 13 patients with recurrent or new primary gynecologic malignancies after previous radiation therapy (RT) underwent interstitial reirradiation (IRI). Overall, 9/13 (69%) patients had complete responses to IRI and six (46%) continue to have no evidence of disease (NED) 24-71 months later (median follow-up, 59 months). Trends toward improved outcomes were observed in squamous *vs.* adenocarcinoma, smaller tumor volumes, higher implant doses, and vaginal wall/suburethra *vs.* vaginal cuff location. One possible complication, a rectovaginal fistula, developed in the presence of recurrent cervical cancer 22 months after IRI. Authors conclude that interstitial re-irradiation is an effective treatment for selected patients with recurrent gynecologic malignancies after previous RT. Advantages of IRI over radical surgery include its potential to preserve organ structure and function and its applicability to patients with medical contraindications to salvage surgery.

Petignat *et al.* [21] were reviewed patients diagnosed with endometrial cancer who had presented an isolated vaginal recurrence. Twenty-two patients were identified; 18 (82%) received both EBRT and HDRB, and four (18%) received HDRB only. The median EBRT dose prescribed was 45 (range: 44–50.4) Gy, and median HDRB was 26 (range: 8–48) Gy. Complications were assessed in terms of early and late Radiation Therapy Oncology Group toxicity. No Grade 3 or worse early toxicity was observed, but significant, late gastrointestinal toxicity, defined as Grade 3, occurred in four (4/22;, 18%) patients. Two patients developed (Grade 3) persistent rectorragia, one was then treated with argon laser. Among Grade 4 toxicity cases, one patient developed refractory rectorragia with deep ulcer, and another patient had complete colon obstruction two years after treatment for recurrence. Both required surgical intervention and definitive colostomy. Eleven patients developed Grade 3 vaginal complications, corresponding to < 1/3 normal length (11/22; 50%). No Grades 3–4 urinary toxicity was noted [21].

Ogino *et al.* [22] assessed the long-term survival, disease control, and complication rates of high dose rate intracavitary brachytherapy (HDR-ICR) alone or combined with external beam irradiation (HDR-ICR + EBRT) in patients with recurrent lesions in the vaginal cuff following hysterectomy for cervical carcinoma. Patients received HDR-ICR only, and 11 patients received HDR-ICR + EBRT with or without paravaginal shielding. The five-year AS was lower when tumors were larger than 3 cm or infiltrated, and authors recommend a treatment regimen of 25-30 Gy of HDR-ICR alone for patients with superficial recurrent lesions, and a treatment regime of 50 Gy whole pelvis EBRT combined with 10-15 Gy HDR-ICR for patients with infil-

trated recurrent lesions [22].

Ito *et al.* [10, 11] in their study in patients with small size tumors were treated with intracavitary irradiation alone. In this group, there was no difference in survival rates between patients with brachytherapy alone and those who received a combination of external irradiation and brachytherapy. On the other hand, a combination of external irradiation and brachytherapy increased the incidence of late sequelae. These results suggest that intracavitary irradiation alone may be adequate treatment for patients with recurrence but without palpable tumor masses of the vaginal stump. The prognosis of patients with palpable tumor masses was very poor. However, it is impossible to draw a definitive conclusion about a lack of difference in outcome for those treated with external versus those treated with intracavitary irradiation only in any of the groups, because of the small numbers in the patient sets.

In the present group the authors analyzed parameters influencing the probability of survival, such as: T feature of staging, FIGO Stage, lymph node status, presence of distant metastases, presence of vaginal stump lesions, type of applicator, resolution of symptoms after treatment, brachytherapy complications, pelvic radiotherapy. A log-rank test demonstrated borderline statistical significance for longer survival (OS) among patients without lymph node metastases confirming, as in case of the T feature of staging, imprecise disease staging and/or presence of micrometastases among N0 patients. The role of lymphadenectomy is unclear in patients with advanced ovarian cancer. There are authors who recommend removal of pelvic and periaortic lymph nodes during surgery. They emphasize the fact that lymph node metastases are present in 50% to 70% of women with ovarian cancer. Researchers stress the notion that it is the only approach towards proper disease staging and removing bulky lymph nodes, which significantly affects progression-free time, although studies demonstrate that it does not influence total survival. One should remember that aside from lymph node metastases accompanying disease dissemination, there may be isolated lymph node metastases, where various forms of therapy, including radiotherapy, are worth considering [23, 24].

Recurrence confirms that good local control rates can be achieved with RT and suggests that the best results are obtained when high doses of radiation are given via a combination of EBRT and brachytherapy [22], but Krauss *et al.* [25] investigated whether the recurrence rate concerning the vaginal cuff and pelvis in ovarian cancer patients can be reduced by postoperative irradiation with after loading technique. In retrospective analysis 20 patients with ovarian cancer, Stage I-IV, received radiological contact therapy with 192-Iridium 2×7.5 Gy in 0.5 cm tissue depth after surgical and chemotherapeutic treatment. A control group of 20 patients with similar oncological parameters was formed. In both groups a local recurrence occurred in six women, which was confirmed clinically, histologically and by diagnostic devices. After two years, six of the irradiated patients survived and 11 of the control group. The results show, that the irradiation of the vaginal cuff, as applied in endometrial carcinoma, will not reduce local recurrence rate of ovarian cancer.

Many authors recommend use of radiotherapy and/or brachytherapy in palliative care, i.e. in cases of brain metastases, which influences time of clinical remission and/or prolongs survival in ovarian cancer patients [23, 24]. Clinical studies indicate the importance of brachytherapy in ovarian cancer, particularly its advanced forms with infiltration of uterine trunk, cervix, and/or vaginal wall, as well as its usefulness in local control of the disease, and/or antithrombotic effect [19]. The present results demonstrate the effect of adjuvant treatment, such as brachytherapy, on remission of clinical symptoms, but fail to show its influence on survival time among ovarian cancer patients. The present results, including the lower risk of progression with increasing total external beam radiotherapy dose, should be analyzed on larger patient groups. The frequency of follow-up examinations and their value in detecting asymptomatic recurrences have been subject of discussion [19]. It was argued that the majority (50–75%) of women with relapse were symptomatic and that regular follow-up is not cost effective as patients with relapse can only occasionally be salvaged.

In the present study, statistical analysis demonstrated that the risk of progression decreased with increasing total radiotherapy dose, several studies reported improved outcome for patients treated with combined EBRT and brachytherapy compared to patients treated with EBRT alone. Haasbeek *et al.* analyzed 35 patients treated with EBRT ± brachytherapy for recurrent cervical cancer [26]: only a brachytherapy boost and a long interval between surgery and recurrence were predictors for improved overall survival on multivariate analysis. Hille *et al.* reported pelvic control rates of 83% and 0% after combined EBRT and brachytherapy and EBRT only, respectively, for radiotherapy treatment of central recurrences of cervical cancer [27]. This difference in pelvic control significantly influenced survival of these patients: all patients treated with EBRT and brachytherapy were alive at the last follow-up compared to a 100% death rate within 32 months after EBRT only [18].

Complete lack local recurrence was only noted among patients with complete response, and disease progression was always noted in patients with distant metastases. Similar results presented Ito *et al.* [10, 11] in the small size tumor group, one of 43 (2%) patients had residual disease; however, 30% in the medium size group and 40% in large size group had residual disease. The overall ten-year survival rate for all patients with CR was 63%, compared to 10% for patients with residual disease ($p = 0.0001$). Furthermore, 68% of patients with CR survived more than ten years, but all patients with residual disease died within five

years in the medium size group. When the incidence of distant metastases was compared between patients with and without local failure, the former patients had significantly higher incidence of metastases (55% *vs.* 13%, $p = 0.0001$).

Conclusions

It is certainly true, that not only EBRT but also brachytherapy made tremendous technological progress in recent time, which resulted in improved local control and survival. Kishi *et al.* [28] described a minimally invasive gel injection procedure performed in the outpatient clinic, in which the patient was safely treated with an eradicative dose by HDRBT, with bowel preservation. They consider that the gel injection procedure enables improvement of the HDRBT therapeutic ratio in eradicative dose treatment of stump relapse of gynecologic cancers. Temporary separation by percutaneous hyaluronate gel injection provided a safe distance for the critical organs during (HDRBT). The gel was injected into the pararectal space between the target, the rectum, and the peritoneum that includes the bowel. The injected gel pushes the rectum, the peritoneum, and the bowel away from the target while the rectosacral ligament anchors the rectum to the sacrum [28].

In summary, brachytherapy may be a useful treatment modality in selected clinical situations involving ovarian cancer. This procedure is particularly useful for women with disease relapse, parametrum infiltration, and/or incomplete tumor resection. Unfortunately, there are still no therapeutic standards for this kind of treatment. They should be developed and introduced in every oncological treatment facility as soon as possible.

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