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ORIGINAL ARTICLE

Endovascular interventions in advanced cancer of the uterus

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Summary

Purpose: *The primary endpoint of this study was to estimate the efficacy of endovascular interventions -EVI- (occlusion and chemoinfusion of the internal iliac arteries-IIA) in the control of bleeding of patients with advanced cervical and endometrial cancer. Tumor response and survival were also estimated.*

Patients and methods: *EVI were carried out in 95 patients with advanced uterine carcinoma (study group). In 82 (86%) of them EVI preceded primary radiotherapy. Autoclots, Ivalon, and Gelfoam were used for arterial occlusion. In 43 patients intraarterial chemotherapy was followed by occlusion of the internal iliac arteries (IIA). For chemoinfusion, cisplatin (120 mg/m²), and later the combination of cisplatin, doxorubicin and cyclophosphamide (CAP) were administered into the femoral artery using the Seldinger method. These patients were compared with a similar group of 143 patients treated with radiotherapy alone (control group).*

Results: *Bleeding was controlled by embolization in all 95 patients with EVI and in 122 (85.3%) patients of the control group ($p < 0.01$). Repeat angiographic studies in patients undergoing chemoembolization showed complete remission (CR) in 7%, partial remission (PR) in 63% and disease stabilization (SD) in 30% of the patients. The corresponding figures for the control group were 5%, 54% and 23%, while progressive disease (PD) was observed in 18% of the patients of this group. The 3-year overall survival was 47% versus 36% in the study and control groups, respectively ($p < 0.01$).*

Conclusion: *EVI is a method effective in stopping bleeding in patients with advanced uterine carcinoma. Chemoembolization of the IIA increases the efficacy of subsequent radiotherapy in patients with advanced uterine carcinoma.*

Key words: cervical cancer, endometrial cancer, endovascular intervention, intraarterial chemotherapy, occlusion

Introduction

Treatment results in patients with locally advanced cervical and endometrial cancer cannot be seen as satisfactory [1-4]. In 25-30% of such cases death came as a result of primary tumor progression and local spread. In 30-35% of stage III-IV patients the disease progressed within 2 years after diagnosis and of these patients only 10-15% survived during the first year [5-7]. In 55-60% of patients with advanced uterine cancer bleeding is observed, and conservative measures are often ineffective, while the development of anemia limits the application of radiotherapy [8-10]. Sometimes, due to massive bleeding, it is impossible to start intracavitary radiation therapy even for hemostasis. It should be recognized that in cases of advanced tumors radiotherapy is not effective as single therapeutic modality, while possibilities to enhance its efficacy are limited to a considerable extent.

One promising modality to increase the treatment efficacy in these poor prognosis patients is the usage of EVI or the so-called interventional radiological procedures [11-15].

EVI are used in various malignant neoplasms with an aim to stop bleeding, palliate pain and achieve tumor ischemia in an attempt to slow down its growth, as well as for intraarterial drug delivery [16-20].

The value of EVI in patients with locally advanced uterine cancer is not studied sufficiently and this served

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as a stimulus for this study, which was carried out in the radiosurgical department of the Central Research Institute of Roentgenology and Radiology, St. Petersburg.

Patients and methods

Between 1985-1998 EVI were performed in 95 patients with uterine cancer (88 with cervical and 8 with endometrial cancer-study group). All patients presented with uterine bleeding when EVI were performed. Tumors were diagnosed by clinical, laboratory and imaging methods, and were histologically confirmed.

Eighty-two (86%) of the cases were newly diagnosed and EVI were carried out before delivering primary radiotherapy, while in 13 (13.7%) patients EVI were performed because of disease recurrence that occurred within 6-36 months after the completion of primary radiotherapy. Fifty-two patients underwent vascular occlusion alone of the IIA, and in 43 cases (all with squamous-cell cervical cancer) regional intraarterial administration of chemotherapy (chemoembolization) preceded vascular occlusion. Distribution of patients by disease stage is shown in Table 1. Of note is that all 3 stage I patients (squamous-cell carcinoma) presented with severe uterine bleeding because of which they initially underwent urgent embolization of the IIA followed by total hysterectomy and subsequent radiotherapy. All 8 stage II patients suffered from squamous-cell cervical cancer with large bleeding exophytic tumors that prevented intracavitary gamma therapy irradiation. Chemoembolization achieved bleeding control and tumor size was reduced enabling thus the subsequent administration of combined (external beam plus intracavitary) radiation therapy.

Sixty-nine out of 71 stage III patients had squamous-cell cervical cancer. Ten out of 13 relapsing patients had squamous-cell cervical cancer and 3 suffered from endometrial cancer.

EVI were performed in the following situations:

1. Locally advanced cervical and endometrial cancer complicated by bleeding.
2. Incomplete tumor regression at the end of the primary radiation therapy accompanied by bleeding.
3. Disease recurrence complicated by bleeding.

Table 1. Stage distribution of patients with and without EVI as primary treatment or for recurrent disease

Stage	*Study group patients, n (%)*	*Control group patients, n (%)*
I	3 (3.2)	3 (2.1)
II	8 (8.4)	10 (7.3)
III	71 (74.7)	105 (73.3)
Recurrence	13 (13.7)	25 (17.3)

Diagnostic and therapeutic angiographic studies were performed in the X-ray operational room using the "Gigantas-Multistar" unit (Siemens). Puncture and catheterization of the femoral arteries were carried out by the Seldinger method [21]. Initially, the pigtail catheter was placed below the bifurcation of the abdominal aorta, and a series of X-ray images was taken with the administration of 30-40% urografin solution, making it possible to estimate the topographic-anatomical features of the iliac arteries and the tumor blood supply. Then the catheter was replaced by one of the "hook" type, and selective catheterization of the IIA was carried out. Depending on the technical possibilities, features of tumor blood supply and size, embolization of the anterior portions and/or trunks of the IIA were carried out from both sides. Particles of polyvinylalcohol (ivalon), thinly cut hemostatic sponge and autoclots were used as embolizing material in order to obtain full occlusion of tumor blood supplying vessels.

Hemoglobin and erythrocytes indices in the peripheral blood before and after the procedure were estimated.

In 43 out of 95 patients the IIA occlusion was preceded by intraarterial chemotherapy and in 11 of these patients 2 courses of chemotherapy every 3 weeks were administered. Chemotherapy consisted of cisplatin 100 mg/m^2, and later the combination of cisplatin (100 mg/m^2), doxorubicin (60 mg/m^2) and cyclophosphamide (1000 mg/m^2) (CAP) was administered. For drug administration, various methods of infusion were used. During the initial period we used prolonged (4-7 hours) regional infusion (22 patients). The total dose of the drugs per course was administered in equal or fractionated doses during 2-3 days. Since 1990, chemotherapy was administered during one day as 4-6 hour infusion, and since 1993 chemotherapy was given as a bolus directly in the x-ray operational room.

The antitumor efficacy and tolerance of the regional chemotherapy were estimated by objective and subjective criteria. Tumor response was evaluated by ultrasound imaging (USI), magnetic resonance imaging (MRI) and computed tomography (CT). Complications induced by the angiographic studies, vessels' catheterization, IIA occlusion and side effects of intraarterial chemotherapy were registered.

Results

Bleeding was controlled in all 95 (100%) patients with EVI (Table 2). In 52 patients with advanced can-

cer and IIA occlusion only (without intraarterial chemotherapy) the hemostatic effect was observed during the first day. In 2 of them recurrence of the bleeding took place, requiring repeat embolization. In the control group bleeding control was achieved in 122 (85.3%) patients ($p < 0.01$, Table 2).

After IIA occlusion in patients with anemia, there was a significant improvement of the hematological indices in the peripheral blood up to complete normalization. Intraarterial chemotherapy resulted in PR in 27 (63.0%) out of 43 patients, lasting from 20 to 36 months (median 28 months), and CR lasting from 30 to 35 months in 3 patients (7.0%, Table 3). The corresponding numbers for the control group were 5%, 54% and 23%, while PD was observed in 26 (18%) of the patients of this group (Table 3). Forty-nine out of 52 patients with arterial occlusion only showed PR lasting from 16 to 32 months (median 24 months).

A statistically significant increase in the 3-year overall survival in patients of the study group was observed, compared with patients in the control group (47% *versus* 36% in the control group; $p < 0.01$; Figure 1).

Complications related with the infusion of x-ray contrast material were infrequent (2.1%). Rigor, skin hyperaemia and tachycardia observed in patients disappeared after infusion of antihistaminic drugs (Table 4).

Side effects caused by ischemia in the occlusion zone were noted in 68.6% of the patients (Table 4). The so-called "postembolization syndrome" included pain in the lower part of the abdomen, lumbar and gluteal areas, and rise of the body temperature. None of these complications required special therapy and lasted for 2-10 days. Systemic side effects related to the chemotherapeutic agents were mild and are shown in Table 5. No life-threatening complications or death were observed after EVI.

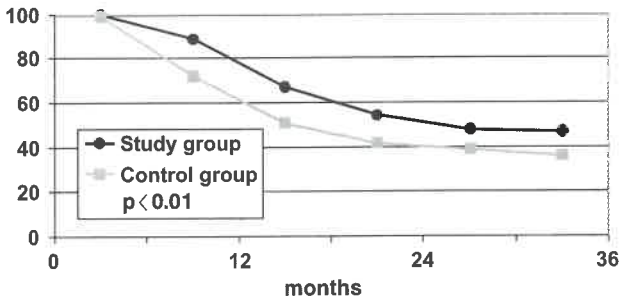


Figure 1. 3-year overall survival in the study and control groups.

Discussion

EVI, and in particular occlusion and embolization of the internal iliac arteries, can be recommended in locally advanced cervical and endometrial cancer complicated by bleeding because it results in hemostasis in all patients and in tumor regression or stabilization in a considerable number of them. So, it can be stated that IIA bilateral embolization possesses cytoreductive effects.

Regional chemotherapy with the use of IIA embolization is suggested in cases of partial tumor regression following completion of combined (external beam plus intracavitary) radiotherapy and disease recurrence.

Objective responses to regional intraarterial chemotherapy are observed in 15-60% of the patients, while complete remission is rarely seen [22,23]. This

Table 2. Bleeding control in the study and control groups

	Study group (n=95) patients, n (%)	*Control group (n=143) patients, n (%)*	*p-value*
Bleeding control	95 (100)	122 (85.3)	< 0.01
Failure	–	21 (14.7)	

Table 3. Objective tumor response in the study and control groups

	Study group (n=43) patients, n (%)	*Control group (n=143) patients, n (%)*	*p-value*
Complete remission	3 (7.0)	7 (5.0)	< 0.01
Partial remission	27 (63.0)	77 (54.0)	< 0.05
Disease stabilization	13 (30.0)	33 (23.0)	< 0.01
Disease progression	–	26 (18.0)	–

Table 4. Complications due to EVI

Complication	*n (%)*
Catheterization-technical (bleeding from the puncture, hematoma, arterial thrombosis)	6 (6.3)
Reaction due to the X-ray contrast material	2 (2.1)
Occlusive-ischaemic complications	65 (68.6)

Table 5. Side-effects in patients with chemoembolization (study group) and with radiotherapy alone (control group)

Side-effect	*WHO grade*	*Study group (n=43) n (%)*	*Control group (n=143) n (%)*
Nausea/vomiting	I-II	17 (40)	—
Leucopenia	II	15 (35)	46 (32)
Thrombocytopenia	I-II	12 (28)	37 (26)

wide range of responses can be attributed to a number of reasons: most relevant studies have included small number of patients (around 15-20); intraarterial chemotherapy was administered at different stages of treatment; different antitumor agents were used, either as monotherapy or as combination chemotherapy.

In contrast to the relative uncertainty of the frequency of objective responses, subjective improvement with decrease or disapearance of pain and bleeding is seen in 60-80% of the patients. Of note is also the remarkable decrease of systemic toxicity of the intraarterially administered drugs [24-26].

EVI is a relatively safe method, and complications in most cases do not require special therapy and do not threaten the patient's life.

A comparative estimation of the infusional methods used has shown that the use of bolus administration has some advantages: it is less traumatic; it excludes extravasation of drugs into IIA anterior branches; it is shorter by 2-3 times; toxicity is not increased; and objective responses are similar compared with the other infusional methods.

It should be noted that all complications of technical character took place mainly between 1985 and 1990; complications of such type were not observed thereafter.

It should also be noted that since 1998 we began to use EVI in patients with local recurrences of ovarian cancer in the pelvis, and encouraging results have already been obtained.

We believe that it is advisable to introduce this method into clinical practice more widely for hemostatic purposes, and as a component of the multimodal treatment of patients with cervical, endometrial and ovarian cancer.

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