



Reconstructive Angioplasty During Secondary Cytoreductive Surgery Performed in Patients with Recurrent Ovarian Cancer

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Abstract: *Background:* Tumor involvement of major vessels, especially the iliac arteries, is used to be the significant limitation for secondary cytoreductive surgery (SCRS) of recurrent ovarian cancer (ROC). *Materials and Methods:* Patients with ROC (n=46) who were treated in the State Establishment «Zaitsev V. T. Institute of General and Emergent Surgery of the Academy of Medical Sciences of Ukraine» during January 2009 – September 2015. All patients received SCRS with restoration and reconstructive angioplasty of the external iliac artery: I group (n=24) – alloprosthesis; II group (n=22) – autoartery angioplasty. *Results:* Duration of surgery was in Group I and Group II 466.3±11.2 min vs 454.8±10.3 min respectively, p>0.05. Postoperative complications occurred in 10 (21.7%) patients (25% in Group I; 18.2% in Group II). The incidence of nonspecific early postoperative complications was 25% in Group I and 19.1% in Group II; p=0.3. The incidence of specific complications was higher in allograft group (12.3% vs 4.5%; p=0.036). There was statistically significant difference between the groups in stage distribution of postoperative complications (p=0.03). There were no cases of late specific and non-specific complications. Postoperative mortality was 0%. Duration of hospital stay in Group I was 21.5±2.3 days vs 12.1±1.7 days; in Group II, p=0.02. SCRS was optimal in all cases. Median follow-up was 42.5 months (range 7-64 months). There was no significant difference among groups in the recurrence rate, medians disease-free and overall survival. *Conclusion:* Usage of the internal iliac artery as autograft during SCRS with restoration and reconstruction angioplasty of external iliac artery leads to reducing risk of specific complications (infection, rejection) and prevents development of destructive processes in the graft wall. There is no negative impact of such surgical approach on the rates of recurrence and overall survival of ROC patients.

Keywords: Ovarian Cancer, Recurrence, Treatment, Secondary Cytoreductive Surgery, Angioplasty

1. Introduction

Despite some advances in modern oncology, treatment of localized recurrent ovarian cancer (ROC) remains difficult problem from medical and social prospective. Its solution requires a multidisciplinary approach. Recurrence is diagnosed in almost 80% of patients with advanced ovarian cancer after primary combined treatment. This rate reaches up to 50% for early stages if unfavorable prognostic factors

are present [15, 22].

According to the results of numerous studies, the optimal management of ROC is combined treatment, including usage of chemotherapy and secondary cytoreductive surgery (SCRS) [18]. The role of platinum-based chemotherapy in the treatment of these patients is undeniable. Such approach can increase the life expectancy by 18-35 month (for platinum-sensitive ROC) [1, 23, 24].

However, the role of SCRS is still debatable because of the limited category of patients with indications for it and the

absence of patient selection criteria. Despite that, some study results have been shown that median survival can achieve 60 months if the optimal SCRS was performed [6].

Until recently, tumor involvement of major vessels, especially the iliac arteries, was the significant limitation for surgical treatment of ROC, so the optimal SCRS was impossible for these patients. That's why the number of publications is small and their results are contradictory. We believe that the implementation of restoration and reconstructive angioplasty during SCRS is important and promising area of oncosurgery that can allow to extend indications for SCRS and to improve long-term outcomes of ROC patients' treatment.

Modern surgical techniques allow carrying out surgery on almost any major vessels, including the iliac arteries, in strict compliance with the principle of en-block removal of the tumor with a fragment of the affected vessels. However, the choice of better plastic material is still questionable. Two basic methods of artery reconstruction are used today: autovenous angioplasty and alloplasty by synthetic vascular prostheses [10, 19, 29].

Autovenous angioplasty has been considered by the majority of surgeons to be the most appropriate method until now. This was due to the biological compatibility of venous transplant, availability and relatively simplicity of its removal, elasticity, resistance to infection and relatively low thrombogenic features. However, there are some negative points of this method along with the advantages described above. These points are: bleeding, formation of haematoma and aneurysm of the vein transplant's wall due to failure of vascular suture, absence of appropriate length and diameter of venous transplant in many patients. In addition, autovenous angioplasty is characterized by prolonged duration of surgery, increased trauma and risk of postoperative complications, which are especially undesirable in oncosurgery. Autovenous angioplasty is mostly used for reconstruction of arteries of small- and medium-caliber during shunt operations on the lower limbs [10, 19, 29].

There is a need for plastic of major vessels of large caliber ("transporting") in most cases. Therefore artery prosthesis with the usage of vascular synthetic prostheses is the method of choice for reconstructive and restoration angioplasty in modern oncovascular surgery. For this purpose textile and corrugated warp-knitted highly porous synthetic prostheses made by double-velour technology are used. The outer velour surface provides adequate implantation; the inner velour surface is a basis of neointima formation. This type of prosthesis does not cause any significant reactions (allergic, immune, local tissue reactions, activation of blood coagulation system) so they are biologically inert. The porosity of prosthesis provides connective tissue growing through their walls and neointima formation on the inner surface. These processes are occurring faster if the porosity is bigger. Thereby, prosthesis is like a frame on which the vascular wall is formed by the own tissues of the recipient. The main drawback of such explants is their excessive

surgical porosity. It can lead to formation of the periprosthetic haematomas and significant blood loss after blood flow restoration. Textile prostheses are impregnated by sealing biological agents in order to provide them with zero surgical porosity and avoid complications mentioned above. In recent years, a data about a possible link of inflammatory reactions and infectious complications in response to biologically impregnated vascular prosthesis was published [10, 14, 19, 29].

Vascular prostheses composed from polytetrafluoroethylene (PTFE) are another popular class. Their advantages are high porosity, strength, elasticity, flexibility, expressed biological inertness and simplicity of sterilization. Despite high porosity, the wall of PTFE-prostheses is characterized by zero surgical porosity. However, this type of material also has some disadvantages: thrombosis, infectious complications, sclerosis, etc. [3, 10, 14, 19, 29].

Thus, none of the existing synthetic vascular prostheses is "perfect". The choice of material for reconstruction should be done individually according to the situation. Autoartery angioplasty is the most optimal method of restoration and reconstructive arterial angioplasty in terms of biocompatibility and biomechanics. But this type of plastic material is not widely used because of limited number of large-caliber arteries that can be used as autograft without significant impairment of blood supply in the donor area [14, 19]. Nevertheless, experience of State Institution «Zaitsev V. T. Institute of General and Emergency Surgery of the Academy of Medical Sciences of Ukraine» is an example of possibility to perform this kind of surgery in patients with ROC with invasion into external iliac artery.

Aim: estimate early and long-term results of restoration and reconstructive angioplasty of the external iliac artery with usage of internal iliac artery as autograft during SCRS in ROC patients.

2. Materials and Methods

Retrospective study "case-control" was performed. Intraoperative data and postoperative treatment results of ROC patients (n=46) were analyzed. All patients received SCRS in State Institution «Zaitsev V. T. Institute of General and Emergency Surgery of the Academy of Medical Sciences of Ukraine» during January 2009 – September 2015.

Selection criteria for SCRS: ROC lesion of external iliac artery (<1/2 and \geq 1/2 of its diameter, circular lesions) in terms of more than 12 months after primary combined treatment, platinum sensitivity, ECOG 0-1. Exclusion criteria for SCRS: ascites, pleural effusion, peritoneal carcinomatosis, distant metastases, acute surgical pathology as a complication of oncological disease, decompensated severe somatic pathology, radiation therapy in anamnesis, atherosclerosis of aorta and iliac arteries.

All included patients received SCRS with restoration and reconstructive angioplasty of the external iliac artery. Depending on the choice for vascular graft, there were 2

groups of patients: I group (n=24) – alloprosthesis; II group (n=22) – autoartery angioplasty. Preoperative examination was performed in accordance with clinical standards and protocols. In addition to standard examination of patients, ultrasound duplex scanning of iliac and lower limb vessels and contrasted CT with 3D-image reconstruction were performed. Indications for vessel resection were determined based on preoperative examination and intraoperative revision, with the use of algorithm of interventions on vessels in the surgical treatment of retroperitoneal tumors proposed by J. Ghosh (2011) [12]. All patients received anticoagulant therapy (direct anticoagulant in prophylactic doses for 20 days followed by switching to indirect anticoagulant) after operation. Prophylaxis of infectious complications (antibiotics for at least 5 days) was mandatory.

Monitoring of the blood flow adequacy in the area of reconstruction was performed using Doppler ultrasound daily during first 10 days after surgery and on every 7th day during one month later. Patients were examined after SCRS for control every 3 months during the first 2 years and every 6 months during 3 consecutive years. All patients received adjuvant platinum-based chemotherapy.

Evaluation criteria: peculiarities of surgical intervention (duration, blood loss, haemotransfusion), postoperative complications during 30 days after surgery (non-specific and specific, severity of complications), postoperative mortality,

length of hospital stay, type of cytoreduction, recurrence rate, disease-free and overall survival. Duration of surgery was determined starting from the skin incision and until the completion of all surgical procedures. Unrelated to angioplasty surgical complications were considered as nonspecific. Complications associated with the restoration and reconstruction angioplasty were defined as specific. Postoperative complications were staged with the use of Clavien-Dindo classification [9]. Gynecologic Oncology Group (GOG) criteria was used to plan SCRS [31]. Disease-free survival was determined starting from the last adjuvant chemotherapy after SCRS until the diagnosis of recurrence, overall survival – starting from SCRS until the death or date of the last visit.

Statistical analysis was performed using software SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Fisher criteria, χ^2 -test, Mann-Whitney test were used for comparison purposes. Survival of patients was analyzed by Kaplan-Meier and long-rank tests. The results considered statistically significant at $p < 0.05$.

3. Results

SCRS was performed for 46 patients with ROC. Patients characteristics are presented in Table 1. There was no statistically significant difference between the groups in clinical and morphological parameters ($p > 0.05$).

Table 1. Clinical and morphological characteristics of patients.

Characteristic	All patients (n=46)	Group I (n=24)	Group II (n=22)	p
Age, years Mean (SEM)	53.2 (6.4)	52.8 (7.2)	54.5 (6.8)	0.46
Stage (FIGO), n (%)				
I-II	18 (39.1)	10 (41.7)	8 (36.4)	0.15
III	28 (60.9)	14 (58.3)	14 (63.6)	0.21
Histological type of tumor, n (%)				
Serous adenocarcinoma	33 (71.7)	18 (75.0)	15 (68.2)	0.08
Mucinous adenocarcinoma	9 (19.6)	4 (16.7)	5 (22.7)	0.45
Endometrioid adenocarcinoma	4 (8.7)	2 (8.3)	2 (9.1)	0.67
Grade, n (%)				
G2	31 (67.4)	17 (70.8)	14 (63.6)	0.34
G3	15 (32.6)	7 (29.2)	8 (36.4)	0.1
Primary surgical cytoreduction, n (%)				
Complete	8 (17.4)	5 (20.8)	3 (13.6)	0.34
Optimal	15 (32.6)	6 (25.0)	9 (40.9)	0.2
Suboptimal	23 (50.0)	13 (54.2)	10 (45.5)	0.12
Disease free period, months. Mean (SEM)	16, 5 (3.4)	15, 8 (5.4)	17, 3 (4.3)	0.6
Localization of ROC, n (%)				
Vaginal stump and/or uterine cervix + parametrial involvment	19 (41.3)	10 (41.7)	9 (40.9)	0.76
Vaginal stump and/or uterine cervix + parametrial involvment + bladder	3 (6.5)	2 (8.3)	1 (4.5)	0.65
Vaginal stump and/or uterine cervix + parametrial involvment + colon	8 (17.4)	4 (16.7)	4 (18.2)	0.34
Vaginal stump and/or uterine cervix + parametrial involvment + rectum	4 (8.7)	3 (12.5)	1 (4.5)	0.56
Bulky pelvic lymph nodes	8 (17.4)	2 (8.3)	6 (27.3)	0.06
Recurrent tumor of small pelvis + parametrial involvment	4 (16.7)	3 (12.5)	1 (4.5)	0.09
Characteristic of iliac vessels lesions, n (%)				
A. iliaca ext. dex.	21 (45.7)	10 (41.7)	11 (50.0)	0.34
A. iliaca ext. sin.	25 (54.3)	14 (58.3)	11 (50.0)	0.2
< 1/2 diameter	9 (19.6)	5 (20.8)	4 (18.2)	0.32
≥ 1/2 diameter	17 (37.0)	10 (41.7)	7 (31.8)	0.65
Circular	20 (43.4)	9 (37.5)	11 (50.0)	0.1

All patients were performed combined operations with restoration and reconstruction angioplasty of external iliac arteries. External iliac vein was preserved in all cases. General characteristics of surgical interventions are presented in Table 2. There was no statistically significant difference between the groups in surgery ($p > 0.05$).

Table 2. Characteristics of combined surgical interventions (without restoration and reconstruction angioplasty).

Surgery, n (%)	All patients (n=46)	Group I (n=24)	Group II (n=22)	p
Removal of recurrent tumor of vaginal stump and/or uterine cervix + pelvic lymphadenectomy	19 (41.3)	10 (41.7)	9 (40.9)	0.32
Removal of recurrent tumor of vaginal stump and/or uterine cervix + pelvic lymphadenectomy + resection of the bladder	2 (4.3)	1 (4.2)	1 (4.5)	0.98
Removal of recurrent tumor of vaginal stump and/or uterine cervix + right-sided hemicolectomy	3 (6.5)	1 (4.2)	2 (9.1)	0.53
Removal of recurrent tumor of vaginal stump and/or uterine cervix + left-sided hemicolectomy	3 (6.5)	2 (8.3)	1 (4.5)	0.65
Removal of recurrent tumor of vaginal stump and/or uterine cervix + resection of the sigmoid colon	2 (4.3)	1 (4.2)	1 (4.5)	0.34
Removal of recurrent pelvic tumor + pelvic lymphadenectomy	4 (8.7)	3 (12.5)	1 (4.5)	0.33
Anterior pelvic exenteration	1 (2.2)	1 (4.2)	0	0.8
Posterior pelvic exenteration	4 (8.7)	3 (12.5)	1 (4.5)	0.56
Pelvic lymphadenectomy	8 (17.4)	2 (8.3)	6 (27.3)	0.78

PTFE allotransplants MAXIFLO™ (VASCUTEK, Scotland, UK) and Gelsoft™ (GORE-TEX®, USA) 8-10 mm in diameter were used. We have developed a method of prosthesis of external iliac artery in order to improve results of restoration and reconstruction angioplasty of external iliac arteries during SCRS performed for patients with ROC. It is based on the usage of internal iliac artery as an autograft for replacement of involved in tumor process external iliac artery. Restoration and reconstruction angioplasty was performed only after a thorough mobilization of tumor conglomerate, exposure of the aortic bifurcation, skeletonization of iliac vessels distal and proximal to the tumor involved area. Tumor mobilization was performed in accordance to oncosurgery principles (en-bloc removal with surrounding tissue and adjacent structures that are involved in tumor process). Vessel resection was performed after imposition of atraumatic instruments on intact areas (visually) in at least 1 cm from tumor margin on both sides. Polypropylene 4/0 was used as a suture material. Reconstruction was performed according to the generally accepted technical principles of angiosurgery.

There were no cases of circulatory disorders in the donor area in Group II. Data evaluation was performed using dopplerography. Duration of surgery was not statistically different in Group I and Group II (466.3±11.2 min vs 454.8±10.3 respectively, $p>0.05$). There was no statistical difference in blood loss (367.4±24.5 ml in Group I and 402.1±20.3 ml in Group II, $p>0.05$). Intraoperative haemotransfusion was not performed in any case. Postoperative complications occurred in 10 (21.7%) patients ($n=6$, 25% in Group I; $n=4$, 18.2% in Group II). More than one complication was diagnosed in 5 (10.9%) patients.

The incidence of nonspecific early postoperative complications was non-significant (25.0% in Group I and 19.1% in Group II; $p=0.3$). Wound infection (8.3% in Group I and 4.5% in Group II), dynamic ileus (4.2% in Group I), hypostatic pneumonia (3.3% in Group I and 1.3% in Group II) were among nonspecific complications. All the mentioned above was successfully treated with appropriate strategy.

The incidence of specific complications was significantly higher in allograft group (12.3% vs 4.5%; $p=0.036$). Specific complications in the Group I were: partial graft thrombosis –

4.5%, periprosthetic haematoma – 2.3%, infection of synthetic prosthesis with arrosive bleeding – 1.4%. The last case needed relaparotomy with appropriate surgical tactics. According to the microbiological study, *Escherichia coli* was detected from infected area. Partial graft thrombosis was diagnosed in 4.5% cases in Group II and was treated conservatively. There was no single case of specific complications. Partial graft thrombosis was not complicated by ischemia of lower limb or embolism in all patients.

There was statistically significant difference between the groups in stage distribution of postoperative complications ($p=0.03$). Grade I-II was diagnosed in 15.9% cases and grade III-IVa – in 8.3% cases in the Group I. Only cases of grade I-II were in the Group II (5.6%). There were no cases of late specific and non-specific complications. Resected segment was passable without hemodynamic disorders. There were no cases of postoperative mortality.

Duration of hospital stay in Group I was significantly higher (21.5±2.3 days vs 12.1±1.7 days; $p=0.02$). That may be associated with higher incidence and grade of specific complications. Tumor invasion of external iliac artery was diagnosed in all cases preoperatively and intraoperatively. Invasion was confirmed by pathology in 8 cases (17.4%). That points the importance of improvement in preoperative diagnostic of invasive component.

SCRS was optimal in all cases. Median follow-up was 42.5 months (range 7-64 months). The difference in recurrence rate was not statistically significant (14.5% in Group I and 10.3% in Group II; $p=0.12$). Locoregional recurrence was diagnosed in 8.5% of patients in Group I and in 6.8% of patients in Group II, distant – in 3.4% and 4.1% respectively. Median disease-free survival was 21.3 months in Group I and 20.8 months in Group II ($p=0.46$). Overall survival does not differ significantly among groups (38.2 months vs 37.5 months; $p=0.68$).

4. Discussion

Current study was designed to analyze immediate and long-term results of reconstructive and restoration angioplasty during SCRS performed on localized ROC with involvement of external iliac artery. The role of SCRS in

treatment of ROC remains one of the most actual and debatable problems of modern oncogynecology. Nowadays, SCRS is performed for limited category of patients. Effectiveness of SCS is controversial according to the research results [1, 17, 18, 22-25].

Residual disease after SCRS is one of the main prognostic factors that can affect long-term results of treatment of platinum sensitive ROC [2, 6, 17, 22, 25]. Median survival is 38-61 months after complete or optimal SCRS and 4.5-27 months after suboptimal SCRS [25, 32]. Model of SCRS technic proposed by Chen L. M. et al. (2000) is still not approved [8]. According to Eisenkop S. M. et al. (2000) and Bae J. et al. (2009) more aggressive surgical approach (for example pelvic exenteration, combined surgery with intestinal, liver, bone resections etc.) should be used to achieve optimal cytoreduction [2, 11].

Optimal SCRS was performed in all cases in our study. It was possible thanks to carrying combined surgery with en-bloc removal of all structures involved in tumor process (including a fragment of the affected vessel). Morbidity rate was acceptable; there were no cases of postoperative mortality. Median of overall survival was 38.2 months in group I and 37.5 months in group II.

Oncovascular surgery started to be more popular during last decades. Reconstructive and restoration angioplasty became an important component of surgical treatment of patients with malignant tumors of the abdominal cavity, retroperitoneal space and extremities. Resection of vessels affected by tumor and their further reconstruction leads to increase of resectability rates and improvement of treatment results [30]. Current experience of the angioplasty in oncosurgery of soft tissues and abdomen resulted in establishment of selection patient criteria which may help to determine the most eligible cases for this kind of surgery [7, 12, 20, 27].

Literature review was performed, no publications devoted to researches of reconstructive and restoration angioplasty during SCRS for ROC with involvement of external iliac artery has been found neither in domestic, nor in foreign sources. Few available articles were designed as a description of clinical cases [13, 16].

Resection of major arteries followed by implantation of a synthetic vascular prosthesis may be accompanied by specific postoperative complications such as bleeding, thrombosis and infection of vascular prostheses, embolic complications, anastomotic false aneurysm, entero-prosthetic fistula. Rate of complications associated with vascular prostheses implantation is between 1.5-9.4% [4]. In current study specific complications were diagnosed in 12.3% cases.

Some authors report postoperative bleeding rate is about 2%; bleeding as a result of anastomotic defect occurs in 1.3% cases [4, 26, 29]. In our study postoperative bleeding rate was 1.4%. The reason of that case was infection of vascular prostheses with arrosive bleeding development.

Thrombosis of vascular prostheses is the most common complication of angioplasty. It can occur either in early or late postoperative period. The incidence of acute thrombosis is 1-3%. Technical flaws of anastomoses (especially distal),

torsion or bending of prosthesis are among the main causes [4, 26, 29]. Early partial thrombosis was diagnosed in 4.5% cases among the operated patients for whom synthetic vascular prostheses were used. However, this complication did not need a surgical correction.

Early thrombosis can lead to the development of embolic complications and associated acute ischemia of the extremities. These complications are diagnosed in 0.5-1.2% of cases [4]. There were no such complications in our study. Late thrombosis is diagnosed in 30-50% patients after reconstructive and restoration operations. The main reasons of its development are formation of false aneurysms and development of stenosis due to neointimal hyperplasia in vascular anastomosis [5].

Anastomotic false aneurysms are among the most frequent (rate between 1-29%) and severe postoperative complications of reconstructive and restoration angioplasty with synthetic vascular prostheses. False aneurysms are more common for distal anastomosis (3.2-13.3%) than for proximal anastomosis (0.1-10%). This complication develops because of the vessel wall degeneration, the disparity of elastoplastic properties of prosthesis and the arterial wall that lead to increased tension in the area of mechanical anastomosis, infection, hypertension, degradation of the suture material and drawbacks in technique of anastomosis [4, 5, 21, 26, 29].

There were no cases of late stenosis, thrombosis, false aneurysms in current study. The passability of resected segment was maintained in all cases without hemodynamic disorders.

According to the literature data, vascular prosthesis infection rates between 0.8-6.0%, meanwhile infection of aortoiliac prosthesis occurs in less than 1%. Early (within 4 months after surgery) infection of prosthesis is more common. Development of infectious and inflammatory processes in the area of vascular implants leads to the destruction of the vessel wall and anastomosis impairment which, consequently, result in the arrosive bleeding. *Staphylococcus aureus*, *Escherichia coc*, *Proteus*, *Pseudomonas aeruginosa* are the main bacterial agents of early infection. *Staphylococcus epidermidis* is present in 60% of late infection cases [4, 29]. Synthetic prosthesis infection may happen at any stage of the operation, but most often it occurs during implantation [4, 19, 29]. In our study early infection of synthetic prosthesis occurred in 1.4% cases and has led to arrosive bleeding. This complication required relaparotomy with appropriate surgical tactics.

Entero-prosthetic fistulas formation is not so common and occurs predominantly after reconstruction of the aorta (0.3-2.0%) [4, 19, 29]. There were no cases of entero-prosthetic fistulas among patients enrolled in our current study.

5. Conclusions

The results of our study indicate that usage of the internal iliac artery as autograft during SCRS with restoration and reconstruction angioplasty of external iliac artery leads to reducing risk of specific complications (infection, rejection) and prevents development of destructive processes in the

graft wall. There is no negative impact of such surgical approach on the rates of recurrence and overall survival of ROC patients.

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