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GYNECOLOGIC ONCOLOGY

Transarterial embolisation for the treatment of acute gynecological cancer bleeding

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Abstract

Purpose Acute bleeding in patients with gynecological cancer may result in serious life-threatening complications. In these situations, immediate diagnostic and appropriate treatment is a challenge for attending physicians. Accordingly, transarterial embolisation (TAE) has been described as an increasing and effective treatment alternative to surgery and radiotherapy.

Methods In the present retrospective study, 25 patients were included who underwent a TAE in the period from January 2006 to June 2013 due to acute gynecological cancer bleeding. The objective of this study was to assess the efficiency and outcome of TAE.

Results The primary technical success rate was 92.0% ($n=23$). 21 patients were analyzed in the 30-day follow-up. The clinical success rate was achieved in 90.5% ($n=19$). A clinical failure due to rebleeding was observed in 9.5% ($n=2$). No associations were revealed between rebleeding and technical/clinical factors. Within 30 days after the last TAE, the complication and mortality rates were 0.0% and 5.0% ($n=1$), respectively.

Conclusion TAE was found as an effective and safe treatment in the clinical setting of acute gynecological cancer bleeding. An important component of efficient management is an early and interdisciplinary care. Optimal treatment can be achieved by close cooperation between gynecologists, radiotherapists and interventional radiologists.

Keywords Gynecological cancer · Bleeding · Embolisation · Angiography · Outcome

Abbreviations

TAE	Transarterial embolisation
CT	Computed tomography
DSA	Digital subtraction angiography
PVA	Polyvinyl alcohol
SD	Standard deviation

Introduction

The presence of bleeding is a frequent symptom of gynecological cancer. It emerges in approximately 6–10% of patients with advanced cancer and usually progresses rapidly [1]. Every delay in treatment may result in death either by secondary anemia and its complications or by hemorrhagic shock [2]. Common causes for gynecological cancer bleeding are advanced cervical cancer and endometrial cancer [3]. An acute gynecological bleeding is characterised by a non-cyclical bleeding which usually results from the erosion of tumor vessels. Malignant tissue spreads to healthy neighboring tissue throughout neovascularisation. This results in highly fragile blood vessels with an increased risk for massive bleeding [2].

Conservative treatments include the stabilisation of circulation with intravenous fluids and blood products. Further method to stop the bleeding is vaginal packing. It is a useful temporary measure which provides a tamponade effect [4]. Another non-invasive technique after unsuccessful packing is the temporary compression with a balloon catheter. In a case of cervical cancer, a Foley catheter was inserted into the uterine cavity in heavily bleeding. Patient vital signs became stabilized, and she was transferred to another hospital [5]. Such balloon tamponade technique should be considered as a bridge to next step of treatment. Traditionally, emergency pelvic radiation is one of the inherent therapeutic aspects with more evidence [4]. This treatment is well tolerated in a

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short time, but there is an insecurity about the optimal dose. Furthermore, emergency radiation endangers the subsequent radiotherapy with curative intent [6]. A single fraction is effective in one-third of the patients and the bleeding stops in nearly all the cases after three fractions [7]. Limitations to this technique include infiltrative growth with vascular invasion and inherent tumor radiation resistance [8]. Surgical treatment involves laparoscopic or open surgical ligation of the hypogastric/uterine artery [9]. Success rates of hypogastric artery ligation range from 40.0 to 100.0% [10–13]. A limitation factor of the procedure success is the deformed pelvic anatomy due to radiotherapy, recurrence of tumorous tissue or pelvic tumor infiltration [14]. Moreover, patients with poor general condition will be at high risk for surgical and anesthetic complications, resulting in increased morbidity and prolonged hospital admissions [15, 16].

In recent decades, TAE has become an increasing therapeutic alternative in acute gynecological bleeding. The use of TAE was first reported in patients with gynecologic malignancies in the mid 1970s [17, 18]. Embolisation is a minimally invasive technique to achieve rapid control of hemorrhage combined with low mortality and morbidity rates [19]. Often, these patients are exposed to a high risk for a life-threatening shock, which can lead to complications and the necessity for a large surgical procedure [5].

We performed this study to evaluate angiographic findings and the efficiency of TAE at our institute over the past 7.5 years. Furthermore, we tried to identify factors that influence the technical and clinical success for acute bleeding in gynecological cancer.

Materials and methods

Patients

This retrospective study included all gynecological cancer patients who underwent (super-)selective TAE to control acute bleeding in the Department of Radiology and Nuclear Medicine of the University of Magdeburg from January 2006 to June 2013. TAE was performed when acute bleeding could not be managed conservatively, surgically, with radiotherapy or in case of rebleeding. The decision to perform TAE was made by taking the patient's clinical presentation, the amount of vaginal bleeding, imaging findings and laboratory parameters into account. The most important findings that effected the decision were computed tomography (CT), digital subtraction angiography (DSA) as well as a drop in hemoglobin and other clinical manifestations (for example, decrease in blood pressure, tachycardia). This study was approved by the Ethics Committee of the Medical Faculty of the University of Magdeburg (reference: RAD243).

TAE

After puncturing the femoral artery as access site, a guided catheter (Cobra, Sidewinder, 5F-Omni-flush or Roberts catheter) was inserted to make plain images of the arterial system. Angiographies were perfromed with mechanical or manual injections of contrast agent (Imeron® 300, Bracco Imaging, Milano, Italy) to localise the source of bleeding. Based on angiographic findings, (super-)selective catheterisation of the guiding bleeding vessel was obtained with a microcatheter (2.4/3.0 F MicroFerret®, Cook Medical, Bloomington, IN, USA). The subsequent embolisation was influenced by material properties, the vascular anatomy and the experience of attending investigators with the embolisation agents. Radiologists with at least 5 years of experience in transarterial therapeutic interventions performed (off-hours) or supervised (regular hours) TAE. There exists a 24-h emergency service even outside of the core working hours. Bleeding arteries were embolised with microcoils (Cook Medical), polyvinyl alcohol (PVA) (Contour, Boston Scientific Corporation, NY, USA) or microspheres (Embozene®, Boston Scientific). They were used as a single agent or in combination. An empirical embolisation was performed in selected cases that did not indicate an active bleeding. This decision was based on the clinical history of the patient or indirect signs of bleeding (in case of a tamponade). After TAE, a final angiography was performed to confirm technical success. In case of persistent bleeding, individual decisions were made regarding the subsequent therapy, for example, surgery (Fig. 1).

Definitions of outcome values

Embolisation outcome parameters were analysed according to the standard practice guidelines published by the Society of Interventional Radiology [20]. In angiography, the positive detection of bleeding was defined as an active extravasation of contrast agent from a vessel. An increased tumor blush or demolition of vessels were defined as indirect signs of bleeding.

Technical success was defined as cessation of extravasation and/or occlusion of the targeted vessel as seen on post-procedure control angiography. A partial technical success was specified as the cessation of a single vessel bleeding out of an amount of several bleeding sites. Clinical success was defined as sustained cessation of bleeding within 30 days after TAE. Rebleeding was characterised as an renewed episode of bleeding with clinical signs, an image-diagnostic detection and/or decrease in hemoglobin level. The decision of following treatment was based on individual and interdisciplinary discussions.

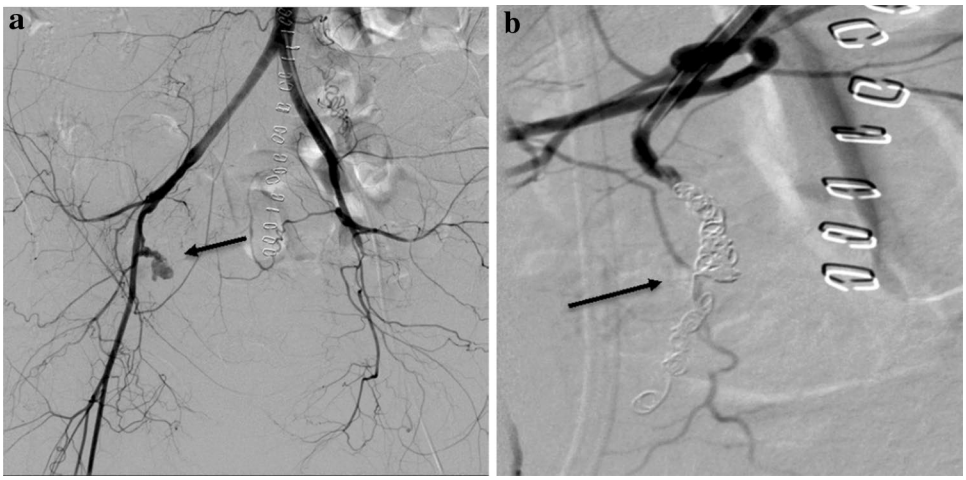

Fig. 1 A 46-year-old patient with advanced cervical carcinoma was admitted to the hospital with acute bleeding into a tumor necrosis cavity. Recently, the patient had explorative laparotomy with the attempt to stop bleeding. **a** Angiography showed active bleeding of the right artery pudenda. **b** Angiography indicated the result of embolisation with multiple coils in front-and-back-door technique

Postinterventional complications were considered as events which were directly linked to the embolisation. Subdivided, minor complications included incidents that could be managed during the intervention (as coil dislocation) and did not require further care. Major complications were events that required an invasive therapy or caused prolonged hospitalization (as intestinal ischemia, sepsis, acute renal failure). The mortality rate was characterized by deaths within 30 days after TAE. Other parameters were defined as contents: concomitant diseases (arterial hypertension, renal failure, diabetes mellitus, cardiac arrhythmia, coronary heart disease, liver cirrhosis, pulmonary embolism, and chronic obstructive pulmonary disease), anticoagulant treatment (phenprocoumon, acetylsalicylic acid, heparin, and clopidogrel), shock ($RR_{syst} < 100$ and heart rate > 100 Hz) and coagulopathy [Quick (analogical to International Normalized Ratio) $\leq 52.0\%$, PTT (partial thromboplastin time) ≥ 45 s, or thrombocyte count ≤ 50 gigaparticles per liter (Gpt/l)]. Regular working hours are from 7:30 a.m. to 3:30 p.m. on weekdays (Monday–Friday), off-hours include the period from 3:30 p.m. to 7:30 a.m. the next day during weekdays and full 24-h periods during weekends and public holidays (Fig. 2).

Statistics

The primary collected data were encoded and anonymised for the statistical analysis with SPSS for Macintosh, version 23.0 (IBM Corp., Armonk, NY, USA). Results for continuous variables were given as means (M) and standard deviations (SD) with ranges. The results of univariate analysis were tested for significance using the Chi-square test, Fisher's exact test or the Mann–Whitney *U* test. For all statistical tests, p value < 0.05 was considered statistically significant. If the follow-up data were not complete, the patient was excluded from the subsequent analysis.

Results

During the study period, the population included 25 consecutive patients. The mean age was 61.3 ± 17.7 years. Nine patients (9/25, 36.0%) were older than 70 years. Cervix cancer was the most common cause of gynecological bleeding (19/25, 76.0%). Also, included were four cases (4/25, 16.0%) of endometrial carcinoma and one case each of ovarian cancer with uterine infiltration (1/25, 4.0%) and vulva cancer (1/25, 4.0%). Vaginal bleeding was the most frequent symptom (17/23, 74.0%). The mean initial hemoglobin level was 9.7 ± 2.6 g/dl. Coagulation disorder was detected in one patient. The amount of packed red blood cells given to all patients ranged from 2 to 6 units (average 1 unit). Four patients (4/23, 17.4%) were transferred for TAE from another clinic. In 12 patients (12/23, 52.2%), the time from bleeding diagnose to embolisation was longer than 24 h. Four patients (4/23, 17.4%) had equal or more than two comorbidities. The most frequent angiographic finding was tumor stain (22/25, 88.0%). In 2 of 25 cases (8.0%), active contrast extravasation was detected. No angiographic bleeding source was observed in one case (1/25, 4.0%). More than 1/3 of all procedures (10/25, 40.0%) were performed after the core working time. The right uterine artery was the most targeted artery in 17 patients. The left uterine artery was embolised in 14 patients. In 20 of 25 cases (80.0%), 2 different arteries in the supply area were embolised in the same procedure. Three different arteries in 1 procedure were embolised in 3 of 25 cases (12.0%). Both, the right and left uterine artery were embolised in the same procedure in 14 of 25 cases (56.0%).

The most preferred embolic agent was PVA, used in 19 of 25 cases (76.0%). PVA was combined with coils in 5 of 25 patients (20.0%). Embolisation with Embozene was performed in 3 of 25 cases (12.0%).

Technical success was achieved in 23 of 25 patients throughout the investigation period. Thus, 92.0% of the

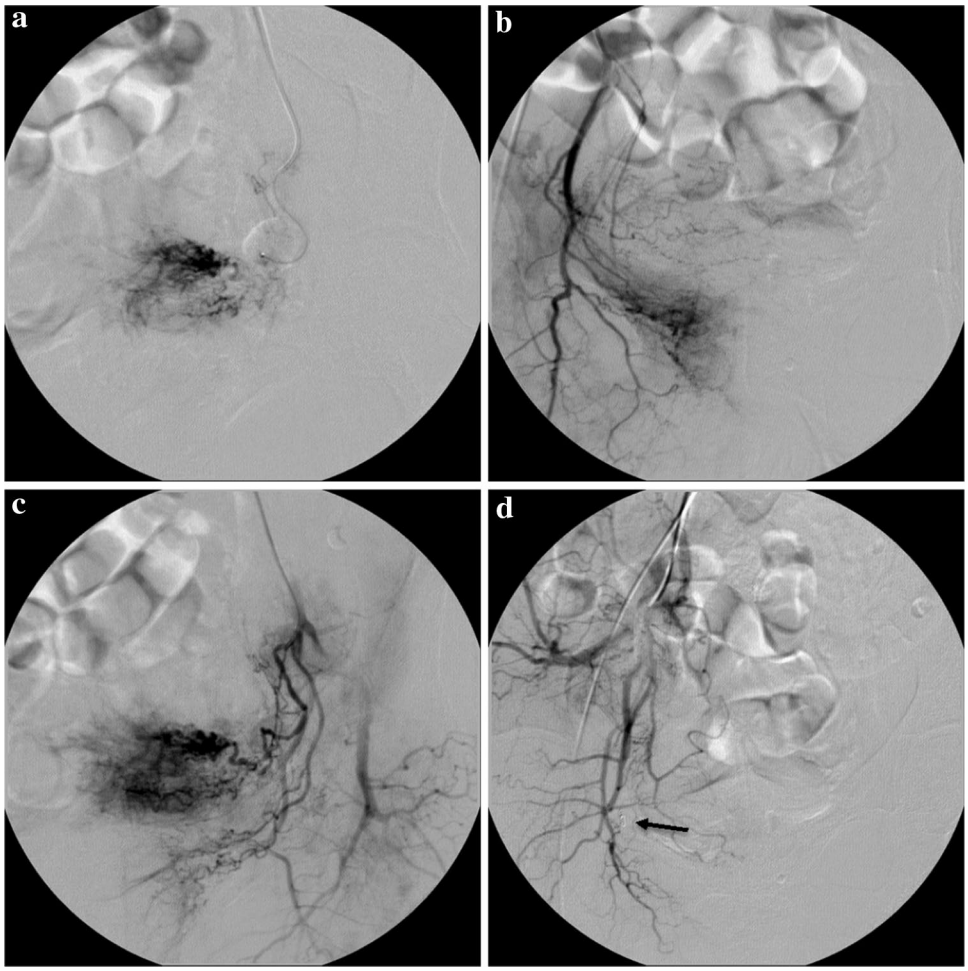

Fig. 2 Case: 64-year-old patient with advanced cervical carcinoma and acute bleeding. In local anesthesia, retrograde puncturing of the Arteria femoralis communis right and introduction of a 5F catheter. Advancing a 5F SOS-Omni and a Robert catheter into the abdominal aorta. Non-complicated contrast agent injection in all series (**a**, **b**, **c** 250 ml Imeron 300 total). Results **d**: embolisation with particle size 350–550 of an acute tumor bleeding from multiple branches of the internal iliac artery. In addition, a single vessel was embolised on the right side of the stroma of the uterine artery by means of two vessels with spirals. At the end of angiography, the hemorrhage ceased

patients demonstrated cessation of bleeding during immediate post-embolisation angiography. The two patients without technical success achieved partial success. In one case, the intubation of all branches was not successful due to an aneurysmatically sacked internal iliac artery and arteriosclerotic changes. Partial embolisation was done in this situation. The tumor blush disappeared mostly without active bleeding in the final series. (Super-)selective embolisation was achieved in 6 of 25 cases (24.0%). Most arteries were occluded with the selective method of embolisation technique. 21 patients (84.0%) were included in the clinical follow-up period. In 19 of 21 cases (90.5%), previous bleeding sites presented still ceased in the follow-up. Recurrent vaginal bleeding occurred in two patients after initial successful technical procedure. The following management based on the individual discussion between gynecologists, radiologists and radiotherapists.

No minor- or major-complications occurred during the 30 day-follow-up. In the period of 30 days after embolisation, one patient died. She died 14 days after the intervention of her the underlying cancer disease with multiorgan dysfunction. No predictive factor was evaluated as significant value for the technical or clinical outcome. A summary of angiographic findings, embolisation and outcome is shown in Table 1. The analysis of predictive factors is presented in Table 2.

Discussion

In the current study, embolisation demonstrated a high level of efficacy to control acute bleeding in patients with gynecologic cancer.

Angiography does not always identify active bleedings, because of intermitted bleeding characteristics [4]. The most common angiographic finding in this study was tumor stain or blush (23/25, 92.0%). The study of Mihmanli et al. had similar results that showed tumor blush in 100.0% [14]. Despite the absence of angiographic extravasation, an empiric embolisation can still be reasonable. Good clinical experience can reduce the likelihood of subsequent bleeding after empiric embolisation.

An immediate cessation of acute bleeding by TAE was achieved in 23 of 25 patients (92.0%). Pisco et al. performed TAE of the internal iliac arteries in 108 patients with

Table 1 Technical features and outcome

Patient	Angiographic finding	Embolic agent	Target artery	Technical success	Clinical success
1	Blush	PVA	AUR + AUL	√	√
2	Blush	Coils + PVA	AUR + AUL	√	√
3	Blush	PVA	AUR + AUL	√	√
4	Active	Coils	A. pudendus right	√	√
5	Blush	Embozene	AUR + AUL	√	√
6	no sign	PVA	AUR	√	√
7	Blush	PVA	AUR + AUL	√	√
8	Blush	PVA	APIIL	√	√
9	Blush	PVA	AUR + AUL	√	x
10	Blush	PVA	AUR + AUL	√	√
11	Blush	PVA	AUR + AUL	√	√
12	Blush	Embozene	AUR + AIIL + AIIR	√	√
13	Blush	Coils	Tumor related vessel	√	
14	Blush	PVA	AUR + AU	√	√
15	Blush	PVA	APIR + APIL	√	x
16	Blush	Coils + embozene	AIIL + AIER	√	√
17	Blush	Coils + PVA	AIIL + AOR	√/x	
18	Blush	Embozene	AIIL + AOR	√	√
19	Active	PVA	AUR + AUL	√/x	
20	Blush	Coils + PVA	AIIL + AIER	√	
21	Blush	PVA	AUR + AUL	√	√
22	Blush	Coils + PVA	AUR + AIIR + AIER	√	√
23	Blush	PVA	AUR + AUL	√	√
24	Blush	PVA	AUR + AUL	√	√
25	Blush	Coils + PVA	AUR + AUL	√	√

√ success, √/*x* partial success, *x* no success, *A* arteria, *AUR* right uterine arteria, *AUL* left uterine arteria, *AIIL* arteria iliac interna left, *AIIR* arteria iliac internal right, *APIL* arteria pudendus interna left, *APIR* arteria pudendus interna right, *AIER* arteria iliac external right, *AOR* arteria obturatoria right

bleeding from pelvic malignancies (uterus, $n = 39$; ovary, $n = 16$; urinary bladder $n = 50$ and prostate gland, $n = 3$). They showed complete cessation of the bleeding in 69.0% of the patients and partial control in 21.0% [21]. Yamashita et al. reported 100.0% temporary control of bleeding in 17 patients with gynecological cancers. However, reembolisation was required in three patients. These patients underwent subsequent cancer treatment with radiation or surgery [10]. Likewise, two recent studies reported a successful selective embolisation in 100.0% (11 patients) and 80.0% (10 patients), respectively [4, 22].

Different embolic agents were applied to embolisate. The choice depended on the experience and skills of each interventional radiologist. The embolic agents can be used as single agent or in combination. Common agents include PVA, microcoils, glue and gelatin sponge [23, 24]. PVA is effective, especially in cancer bleeding, because of distal vascular bed occlusion and being independent of patients' coagulation. Furthermore it blocks the collateral vessels by forming a cast [25]. However, the use of PVA requires adequate training and experience. Permanent microspheres, ranging in size from 40 to 1300 microns, are used as an alternative to PVA. Microcoils, as permanent embolic agents, are also effective in occlusion of the internal iliac arteries [23]. They are used selectively to occlude larger vessels which are more proximal.

The clinical success of 90.5% was almost as high as the technical success. The procedure showed low incidence of rebleeding because of the effective technique procedure. One of the crucial reasons is a more distal embolisation in small vessels compared to surgical ligation. The most frequent reasons for bleeding persistence are an unilateral or incomplete embolisation, coagulation disorders or change in pelvic anatomy due to radiation [21]. It has to be emphasized at this point that the pelvic vascular anatomy can be challenging. In most cases, the collaterals of pelvic vessels require bilateral embolisation. In this study, both opposite uterine vessels were embolised in 14 cases (56.0%).

Massive bleeding of primary cervical cancer can delay the initiation of cancer treatment. If radiotherapy has already been started, interruption due to massive bleeding is undesirable. It may prolong the overall treatment

Table 2 Predictive factors for the outcome of gynecological bleeding

Variable	Technical success		*p* value	Clinical success		*p* value
	Success	No success		Success	No success	
Age (in years)	59.1 ± 16.7	86.9 ± 5	0.497	54.4 ± 14.2	82.0 ± 6.3	0.057
≥ 2 comorbidities	20.0% (4/20)	0.0% (0/3)	0.614	21% (4/19)	0.0% (0/2)	0.000
Hb-value in g/dl	9.4 ± 2.1	8.3 ± 1	0.143	9.4 ± 2.2	10.0	0,130
FFP	0.2 ± 1	0.0	0.898	0.2 ± 0.9	0.0	0.000
EK	5 ± 8	0.0	0.196	5 ± 9	0 ± 2.4	0.857
≥ 6 EK	5.0% (1/20)	0.0% (0/3)	0.000	5.3% (1/19)	0.0% (0/2)	0.000
No bleeding detection (CT)	83.3% (5/6)	0.0% (0/2)	0.107	83.3% (5/6)	0.0% (0/2)	0.286
No active bleeding (DSA)	4.5% (1/22)	0.0% (0/3)	0.000	5.3% (1/19)	0.0% (0/2)	0.000
TAE in night service	40.9% (9/22)	33.3% (1/3)	0.000	42.1% (8/19)	50.0% (1/2)	0.000
Only selective probing	77.3% (17/22)	66.7% (2/3)	0.000	73.7% (14/19)	100.0% (2/2)	0.000
> 1 vessel embolised	77.3% (17/22)	66.7% (2/3)	0.000	84.2% (16/19)	50.0% (1/2)	0.352
Anticoagulation	5.0% (1/20)	0.0% (0/3)	0.000	5.3% (1/19)	0.0% (0/2)	0.000
Corticosteroids	10.0% (2/20)	0.0% (0/3)	0.000	10.5% (2/19)	0.0% (0/2)	0.000
Shock state before DSA	0.0% (0/20)	0.0% (0/3)	–	0.0% (0/19)	0.0% (0/2)	–
Time from bleeding to TAE > 2 days	5.0% (1/20)	0.0% (0/3)	0.000	5.3% (1/19)	0.0% (0/2)	0.000
Coagulopathy	7.1% (1/14)	0.0% (0/3)	0.000	7.1% (1/14)	0.0% (0/1)	0.000
Out-patients	15.0% (3/20)	33.3% (1/3)	0.000	15.8% (3/19)	50.0% (1/2)	0.352
ICU before	0.0% (0/20)	0.0% (0/3)	–	0.0% (0/19)	0.0% (0/2)	–

Hb hemoglobin, *FFP* fresh frozen plasma, *EK* erythrocyte concentrate, *CT* computed tomography, *DSA* digital subtraction angiography, *TAE* transarterial embolisation, *ICU* intensive care unit

time by tumor cell repopulation. Because of its minimal invasive technique, embolisation is an efficient way to stop bleeding rapidly so that cancer treatment can be continued without long interruption [4].

Although it is difficult to assess, there is a theoretical concern that embolisation of vessels feeding the tumor might later reduce the efficacy of chemotherapy and reduce the amount of oxygen in the tumor that is crucial for the response to radiotherapy. In case of cervical bleeding, the strategy is the use of PVA particles that do not completely stop the circulation of the tumor. The aim is to reduce the pressure of the pathological capillaries. Hereby, necroses are prevented. Particle sizes between 700 and 350 microns still allow capillary oxygenation. The oxygen in the tumor was not measured before and after embolisation. However, no necroses were observed.

Another part of this study was to evaluate predictive factors to determine the outcome. Poorly, there was no predictive factor with significant effect on the outcome.

Known complications of TAE are skin necrosis, necrosis of urinary bladder, neurological dysfunction, thrombosis, non-target embolisation of vessels and pain [26, 27]. The present study had no complications that could be associated with the embolisation. The absence of procedure related pain and ischemic complications can be attributed to the embolisation technique and the experience of radiologists. Due to (super-)selective procedures, vessels were embolisated precisely while protecting the surrounding tissue [28].

The study had limitations including its retrospective design, being a single-center study and the small number of enrolled patients. Nevertheless, it is the largest population in this subject compared with current published literature. In general, there were no restrictive criterias for an embolisation in the situation of acute bleeding. The decision was made interdisciplinary between gynecologist and radiologist, which might be a cause of selection bias. Otherwise, this patients' recruitment represents the daily routine in the embolisation unit.

Conclusion

In summary, TAE is an increasingly provided procedure for the treatment of acute gynecological cancer bleeding. Thus, transarterial embolisation should be considered as a highly effective and safe procedure to control acute bleeding even in instable patients with high surgical risk. This treatment not only improves the patient's quality of life, but also enables them to be prepared for the next step of treatment which could be radiotherapy or surgery.

Author contributions All persons who meet authorship criteria are listed as authors, and all authors have participated sufficiently in the work to take public responsibility for the content. PM-W and MP: project development, data analysis, manuscript writing and manuscript reviewing. MP, FF, JO, RD: manuscript reviewing.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

Ethical approval This study was approved by the Ethics Committee of the Medical Faculty of the University of Magdeburg. Reference number to the ethics approval statement: RAD243. The ethical committee decided that no consent for participation was necessary, because the study was retrospective. The ethic approval is attached herewith.

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