

The Place of Radiofrequency Ablation in the Multimodal Treatment of Cervical Cancer. Our Experience

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Rezumat

Locul ablației prin radiofrecvență (RFA) în tratamentul multimodal al cancerului de col uterin. Experiența noastră

Introducere: Cancerul genital beneficiază de tratamente standardizate care includ: chirurgie, radio/chimioterapie. În ultima perioadă se utilizează și tratamente ablativ termice care realizează distrucția tumorilor utilizând diverse surse de energie. Studiul are drept scop stabilirea locului pe care radiofrecvența îl poate ocupa în cadrul protocoalelor actuale de tratament ale cancerului de col uterin.

Material și metodă: Am efectuat un studiu prospectiv, pe 5 ani (2008-2013), în care am analizat utilizarea RFA, pe criterii selective, pentru tumorile de col uterin sângerânde și însoțite de anemie acută secundară (Hb=7-11g/dl). Rezultatele au demonstrat rolul hemostatic al metodei, RFA fiind unica metodă nechirurgicală prin care se obține hemostaza rapid (20 min.), ținând cont că nicio altă terapie cu agenți fizici (hiper/hipotermie) nu o utilizează, iar iradierea (externă/brachyterapie) obține aceleași rezultate cel mai devreme în 12/48 ore. Au fost luate în evidență 61 paciente, cu vârsta între 39 și 73 ani, pentru care s-au realizat 61 proceduri.

Concluzii: Radioablația este utilă în tratamentul cancerelor de col uterin, în toate stadiile bolii, realizând rapid hemostaza. RFA poate fi considerată o tehnică complementară de tratament neoadjuvant în cadrul paletei tumorale. Metoda se poate asocia la chirurgie, radio/chimioterapie. În favoarea sa

pledează rata scăzută a morbidității (1,6%) și a mortalității (0%) specifice. Considerăm că RFA este în curs să câștige un loc important în protocolul terapeutic oncologic.

Cuvinte cheie: radiofrecvență (RF), hemostază, tumoră de col uterin

Abstract

Introduction: Genital cancers benefit from standardized treatment plans which include: surgery and radio/chemotherapy. Lately, treatments involving thermal ablations have entered the clinical use, as they destroy the tumors by the use of different energy sources. Our study aims at establishing a precise role of RFA in current treatment protocols of cancer of the uterine cervix.

Material and method: We performed a 5-year (2008-2013) prospective study in which we analyzed the use of RFA in patients treated for cancer of the uterine cervix at our clinic. RFA was used, on selective criteria, in bleeding tumors of the uterine cervix in patients with acute secondary anaemia (Hb=7-11g/dl). The results revealed the haemostatic role of the method, RFA being the only non surgical method through which one can achieve quick haemostasis (20 min.). 61 patients were clinically observed, with ages between 39 and 73, and the number of procedures performed was 61.

Conclusion: RFA is useful in the treatment of cancers of the uterine cervix, in all stages of the disease, and it achieves quick haemostasis. RFA can be considered an additional treatment option in neoadjuvant tumor palliation. The method can be associated with surgery and radio/chemotherapy. Its assets are low specific morbidity (1,6%) and mortality (0%). We

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consider that RFA is on its way to an important place in oncology treatment protocols.

Key words: radiofrequency (RFA), haemostasis, uterine cervix cancer

Introduction

Treatment for cervical cancer is complex, including surgery and radio/chemotherapy. In advanced cancer stages, radio- and chemotherapy hold the first place in patient treatment, while surgery has a secondary role, in the treatment of complications (intestinal obstructions, invasion of adjacent organs) and of metastases (liver, lungs).

After 1990, radiofrequency ablation (RFA) also appeared among the methods used in advanced tumor treatment. This procedure was accompanied by good results in the thermal ablation of non-resectable tumors and consists in tissue conversion of electromagnetic energy into thermal energy by inserting bipolar needles-electrodes. Coagulation necrosis depends on both the reached temperature level and on the duration of the procedure. Its most frequent use is in liver tumors (metastases, hepatic carcinoma) that are non-resectable or contraindicated for surgery. The effects on tumor destruction can be monitored in real time by ultrasound or controlled by CT-scan /MRI examination (1,2,3,4,5).

The current paper proposes an extension of RFA indications in tumors of the female genital tract, such as: cervical cancer in stages II, III and IV, accompanied by abundant menorrhagia and secondary anaemia or that are refractory to radiotherapy, RFA being used to achieve haemostasis.

Pereira recommends the following treatment for advanced genital tumors, accompanied by vaginal bleeding (6):

- Vaginal packing with gauzes soaked in hemostatic solutions (epinephrine, silver nitrate), topical applications of collagen and fibrin gels + external radiotherapy;
- Bilateral embolization of the internal iliac artery (one or two applications);
- Bilateral ligatures of internal iliac artery;
- Systemic haemostatic agents (vitamin-K, anti-fibrinolytic agents - aminocaproic acid, blood products - platelets, fresh frozen plasma, transfusion of red blood cells);
- Radiotherapy (external radiation therapy and/or brachytherapy).

In this way, if bleeding cannot be controlled by packing or hemostatic radiation therapy, then: embolization of uterine artery, ligature of hypogastric arteries or surgical resection are advisable, because they reduce tumor vascular supply. These palliative interventions are regarded as being aggressive for advanced-stage cancer patients and the benefit of using them in these stages is low. That is why a very careful selection of the patients is needed (7,8).

Material and Method

We have conducted a prospective study over 5 years (2008-2013), including patients being hospitalized in the First Clinic of General Surgery and Surgical Oncology of the Bucharest Oncology Institute. 61 female patients with stages IB, II, III, IVA of cervical cancer (FIGO classification), were followed-up; they had vaginal bleeding and secondary acute anaemia (Hemoglobin=7-11 g/dl), and were administered a total of 61 radiofrequency ablation (RF) applications. The age of the female patients varied between 37 and 79 years (mean age of 55 years). The pathology results, done by transvaginal biopsy before the intervention by RFA, were the following: 54 cases of squamous (epidermoid) cell carcinoma (88,5%), 5 cases (9,1%) of endocervical adenocarcinoma and two patients with leiomyosarcoma of the cervix (3,2%). In two patients, due to massive bleeding and severe anaemia (Hemoglobin $\leq$ 7g/dl), the biopsy was taken intraoperatively, before initiating the RFA procedure.

RFA indications were the following:

1. Patients having vaginal bleeding that did not improve with conservative hemostatic treatment or/and radiotherapy;
2. Patients having a histopathological confirmation of the neoplasm; intraoperative biopsy and RFA were performed;
3. Failure in achieving uterine artery embolization;
4. Radiotherapy contraindications in female patients that had previously received maximum admitted radiation doses, with chemotherapy being of low efficacy or even contraindicated in these cases (female patients with anaemia, with high tumor volumes and advanced disease stages);
5. Female patients with comorbidities that did not allow major surgical intervention;
6. Female patients with anaemia (Hemoglobin < 12 g/dl), making impossible an attempt to deliver radio/chemotherapy.

RFA contraindications were the following:

1. Direct-such as pregnancy, due to:
 - The triggering of contractions, bearing a risk of abortion;
 - The increase in amniotic fluid temperature (temperature can be monitored only locally);
 - The electromagnetic radiation with risk of malformations
2. Indirect-such as important alterations in coagulation tests (platelets < 50 000), increased anaesthetic risk.

We should mention that: the biopsy confirming the tumor was mandatory, an interdisciplinary consultation was done (surgeon, oncologist, radiotherapist) and the female patients consented to the new method of treatment.

The tests that were carried on in our clinic on chicken breast muscles and the results that were obtained, as well as the experience that has been gathered using the new procedure, allowed us to extend the application of RFA technique, with hemostatic purpose, in cervical tumors accompanied by vaginal bleeding. Further on, we describe the procedure:

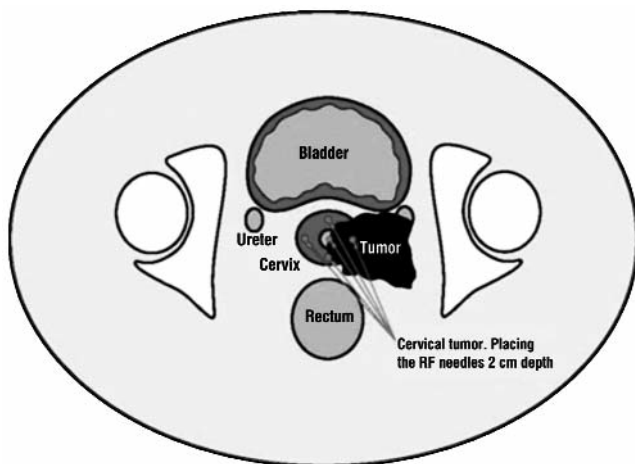


Figure 1. A stage III B cervical tumor with left ureter hydronephrosis; RF needle placement

1. Patients in gynecological position, vaginal approach;
2. A 14/16 Foley catheter is inserted into the bladder of the patient, being progressively clipped during the intervention (20 minutes) or a 3-way catheter is used, with 0.9% NaCl at room temperature inserted for lavation. The reason was to prevent complications (such as vesico-vaginal fistulas) due to the necrosis of the urinary bladder wall (heat-sink effect); (9)

3. The position of the 3 RF needles inside the tumor mass at cervical level is controlled by intra-vaginal ultrasound. The depth of RF needle insertion is of approximately 2,5-3 cm. The 3 needles are placed in the following manner: 2 in the lateral incisions of the cervix (right/left) and the median electrode, being inserted, consecutively at each 5 minutes, cranially, at the level of the uterine ostium and at a caudal level (Figs. 1, 2).

Following this procedure we succeeded in destroying the entire cervical tumor (with implicit destruction of the tumor vessels), an aspect that is also confirmed by trans-vaginal ultrasound. Ablation is directed from depth to surface, with 1,5-2,5 diameter spheres of necrosis being constituted. We apply the method of tumor destruction in cylindrical shape-made out of 50% superposed spheres that follow the trajectory of the electrode (10).

RF electrodes used by us have a 15/17 Ga diameter and an internal cooling -cool-tip- (CelonProSurge). They are connected to a radiofrequency generator (CelonLabPower, Olympus) that can produce tumor necrosis in a multipolar fashion, the area of coagulation and hemostasis being increased in this way. Electrode cooling is achieved with saline solution (NaCl) 0,9% at room temperature (22-24°C), the flow perfused by the pump being of 30ml/min. The removal of the electrodes is done while the power generator is active to avoid dislocating tumor cells along the trajectory of electrode insertion and to avoid further bleeding. The procedures took place at a power between 25-75W (mean of 63,63 W). Mean energy consumption was 49,51 kJ (between 15-55,5 kJ), the intervention lasting maximally 20 minutes (15-20 min., mean duration of time=18,4 min.).

4. The positioning of RF needles inside the tumor mass



Figure 2. The positioning of the RF needles - intraoperative image

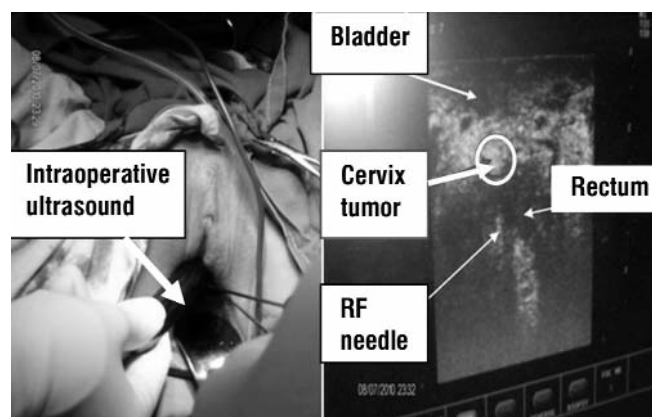


Figure 3. Intraoperative ultrasound-previous to ablation

and the performance of RFA took place under trans-vaginal ultrasound control. We use an Esaote MY LAB 20 ultrasound machine that has a linear transducer, with frequencies varying between 7,5-10 MHz. It also has a color-Doppler function.

In this way we permanently controlled the distance between the electrodes and the urinary bladder and the rectum and also the progression of the coagulation necrosis (Fig. 3 - tumor of hyper-echoic aspect is marked with a red circle, the RF needle is hyper-echoic and urinary bladder and rectum appear as hypo/non-echogenic, in black color on the ultrasound image). The hyper-echoic aspect of the tumor during the RFA is due to gas bubbles resulted from vaporization of the tumor tissue. In this way, we achieve the destruction of the entire cervical tumor and implicitly of the neo-formation blood vessels which bleed, an aspect that is confirmed by trans-vaginal ultrasound (Fig. 4). At this moment the ablation can be stopped as hemostasis has been obtained, thus achieving to avoid carbonization.

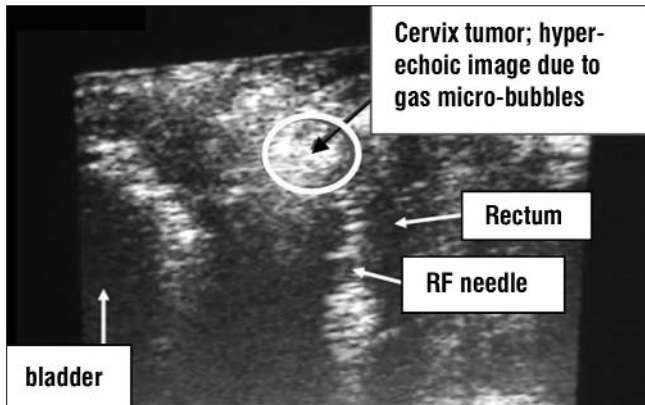


Figure 4. Trans-vaginal ultrasound – the vaporization phenomenon at the level of the malignantly-transformed cervix; hyper-echoic image due to gas micro-bubbles

After 20 minutes, the area of radio-ablated tumor became hypo-echoic (Fig. 5A - the grey circle) due to the inflammation and oedema and the cervical bleeding stopped (Fig. 5B).

5. The procedure was done under general anesthesia with endo-tracheal intubation or spinal anesthesia and administration of injectable antibiotics (third or fourth - generation cephalosporins plus metronidazole) during anesthetic induction.

6. On the first day after the ablation, a control using genital valves is effectuated, the vagina and the cervix being locally disinfected with betadine antiseptic solution

7. During the period of hospitalization the female patients receive intravenous antibiotics (third or fourth generation cephalosporins plus metronidazole) and non-steroidal anti-inflammatory drugs (Ibuprofen) with anti-algic and anti-inflammatory effects

8. Patients were released from the hospital after 3-4 days from the procedure.

Results

In 60 patients tumor bleeding stopped following the first application and the cervical tumor volume, as measured by ultrasound, diminished. The haemostasis was permanent, with no need to repeat the procedure. Only in one patient, under radiotherapy regimen, no permanent haemostasis could be obtained and during the same intervention a decision to perform total hysterectomy for haemostatic reasons was taken. We can state that, up to now, the method had a success rate of 98,3% and a rate of failure of only 1,63%.

The female patients will follow the recommended radio/chemotherapy procedures further on, depending on the stage of the disease according to the interdisciplinary consultation (surgeon, radiotherapist, oncologist) (Fig. 6). Two patients with IB1 and IIA tumor stages refused the treatment that was recommended after ablation, RFA being the only applied procedure.

We mention that no intraop or postoperative complications were recorded (vesico/rectovaginal fistulas, post-procedural bleeding, abscesses, peritoneal perforations). Blood tests revealed a moderate leukocytosis for one week. Anaemia syndrome was corrected in time with iron products by oral or intravenous routes. Two patients required the administration of integral blood to correct acute anaemia (Hemoglobin ≤ 7 g/dl).

The patients included by us in the study were in advanced cancer stages, with important vaginal bleeding that had not ceased after conservative treatments. RF represented only a therapeutic stage in the treatment of these female patients. Only a few patients receiving RF were operated on after administration of radiotherapy. In practice, radical hysterectomy with pelvic lymphadenectomy were done after 4-6 weeks only in 12 patients (19,67%) in IB2, IIA tumor stages. Other two patients that were operated on after RF presented with cervical sarcomas (the percent of operated on female patients was of 23%), the remainder of 47 patients (77%) were in IIB, III, IV

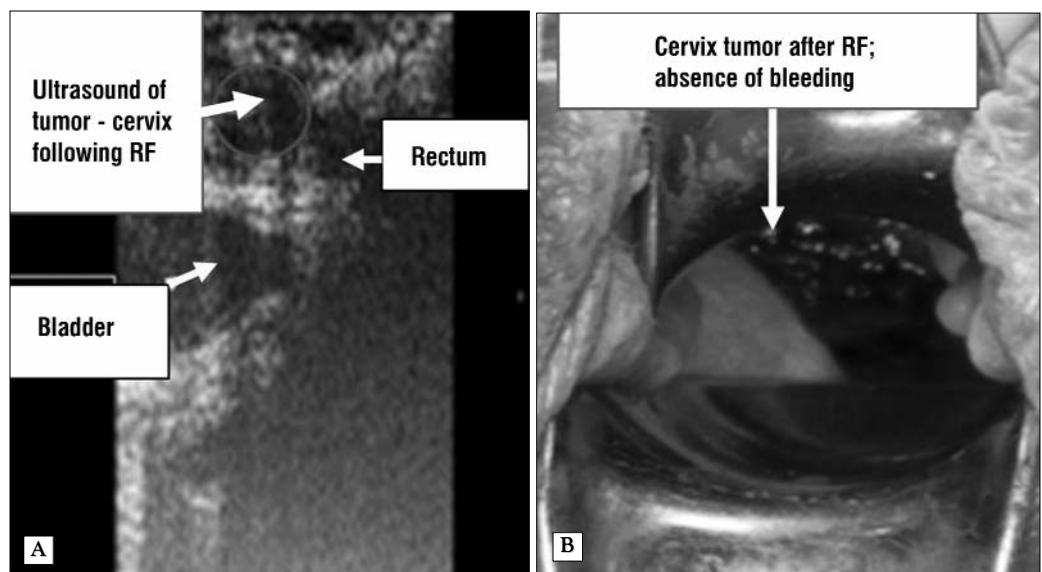


Figure 5. (A) Ultrasound of tumor-cervix following RF (B) intraoperative aspect after RFA

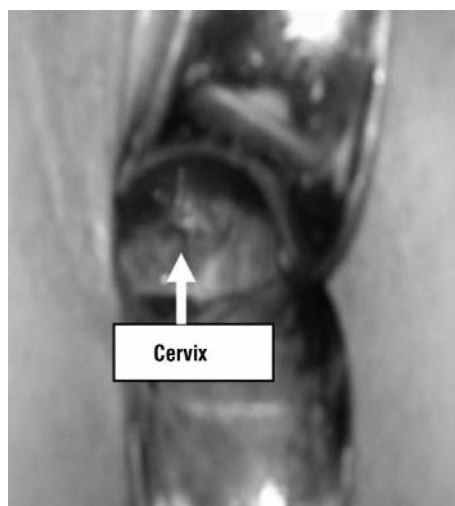


Figure 6. Vaginal control at 2 months post-RF and post-radiotherapy; no tumor mass and bleeding at the cervix

tumor stages and were treated only by radio/chemotherapy. The follow-up of the female patients was done for 2-4 years by clinical examination, biological tests (Hb, CA-125) and medical imaging examination (trans-vaginal ultrasound, CT-scan /MRI/PET-CT of thorax, abdomen and pelvis).

Discussions

Cervical tumors at advanced stages can determine the occurrence of cervical haemorrhage accompanied by severe anaemia, sometimes carrying a fatal risk. Performing a biopsy is indicated to confirm the presence of the neoplasm and vaginal swabbing is done with haemostatic solutions (gels) at cervical level. Systemic haemostatic drugs can also be administered (vitamin-K, aminocaproic acid, blood products). After appropriate staging, external radiotherapy can be initiated, which will control bleeding after 8-10 days of treatment. Broad-spectrum antibiotics are given to the patients to control infections. This conservative type of treatment is preferred to vascular ligation in previously untreated female

patients. Severe cases could require embolization of the uterine artery, a procedure that may exclude laparotomy (11).

From the results that were obtained and presented in this paper, it becomes clear that RFA has a good efficacy (98%), providing haemostasis in maximally 20 minutes. Data from literature show that the application of vaginal brachytherapy or external radiation therapy has the same effect, that of haemostasis, in 24-48 hours for female patients in IIB, IIIB, IVA stages. The patients that were followed-up after the RFA did not present tumor recurrence at the place where RFA was administered. We mention that RFA does not produce the same complications as pelvic irradiation: enteritis, proctitis or/and radiation cystitis, vesico/rectovaginal fistulas, perforation of the uterus following brachytherapy probe insertion, ureteral strictures, etc (12,13).

Of all the 54 female patients with squamous carcinoma, 35 presented infiltrative forms that required high levels of energy to achieve haemostasis (40-56 kJ). Other 7 patients, of which 5 had adenocarcinoma and 2 had sarcoma, consumed high amounts of energy for ablation (50-55.5 kJ). Using RF for cervical tumors with infiltrative characteristics (IIB, IIIB, IVA tumor stages) show that these neoplasms are high energy consumers and are ablated after a prolonged application time (20 minutes) (Table 1). We cannot achieve the destruction of the tumors at the levels of the parameters or that are extended to the uterine body. The risks of increasing the volume to be ablated (lesion of urinary bladder, rectum, ureter, occurrence of complex vaginal fistulas, ureteral stenosis or perforations in the peritoneal cavity) would overpass the benefits: mainly-that of achieving hemostasis and secondly-that of decreasing tumor volume.

Tumor destruction achieved by RF can be monitored in real-time by ultrasound. Doppler ultrasound can be useful to estimate the remaining areas of tumor, with presence of vessels. The procedure will allow its repeat with no adverse effects and patient recovery is fast after RF (3-4 days). RF is efficient, being an available possible solution and sometimes representing the only solution, for advanced cervical neoplasms that had been irradiated with maximum admitted dose.

The standard for treating vaginal bleeding, having a cervical neoplasia as a cause is represented by internal iliac

Table 1. The amount of consumed energy depending on the histo-pathological cervical tumor type and the period of time required to obtain haemostasis

Histopathologic type of the cervical tumor	The interval of amount of energy consumed (kJ)	Number of cases	Duration of time of RF application (minutes)
Squamous carcinoma	35-39	19	15
	40-49	13	20
	50-56	22	20
	Average value of the energy that was consumed = 46,7	54	Mean duration of time = 18,24
Adenocarcinoma	50-55	5	20
	Average value of the energy that was consumed = 52,78	5	20
Sarcoma	52-55,5	2	20
	Average value of the energy that was consumed = 53,7	2	20
Mean value of the total energy consumed = 63,63 W (25-75 W)		61	Mean duration of time = 18,44

artery ligation that has a success rate of 40-100% (14). But these interventions are considered aggressive for female patients in precarious states of health and the benefit is low. That is why female patients will be selected very carefully (7,8). Some physicians recommend the embolization of uterine artery in severe cases, in emergency. The procedure is accomplished in approximately 1 hour and the bleeding completely stops in 24 hours. After embolization, complications such as: pelvic pain, fever, pelvic abscesses, rebleeding, vesicovaginal fistulas, etc., may be recorded (6,15,16,17,18,19). We have not encountered such complications after RFA. Vascular occlusion can finally lead to a decrease in blood flow, but also in the oxygenation of the tumor. However, the effect of radiotherapy is dependent on tissue oxygen content and therefore its efficacy will be compromised (8). Radiotherapists would agree with the application of RFA as its action is strictly local.

Radiofrequency ablation can be an important adjuvant procedure for radiotherapy:

1. obtaining a fast haemostasis (correction of anaemia);
2. tumor sterilization due to the high temperatures that are achieved (66-105°Celsius);
3. decrease of tumor volume-it helps decreasing target radiation volume and RFA association to brachytherapy has favorable cumulative effects;
4. preservation of uterine and vagina blood supply.

The female patients (12 in number) having a Wertheim operation performed after radioablation and radiotherapy, had a favorable postoperative evolution, with no sign of local recurrence or distant metastases. We mention that RF was used as a palliative procedure, in advanced tumor stages, sometimes after the failure of other palliative treatments, permitting a longer survival, with a better quality of life and favoring recommended adjuvant radio/chemotherapy.

Conclusions

Following the performed study, we have extended the indication mainly to haemostasis and secondarily to cytoreduction. The use of radiofrequency as a haemostatic method its a new indication. The use of RF to achieve haemostasis in cervical cancer has a maximum effect at a power of 75W applied for 20 minutes. The studies that were done allowed the elaboration of a treatment protocol and the confirmation of the method was obtained in all the 61 cases and by follow-up of these cases in time.

Radiofrequency ablation can be accepted as a neo-adjuvant treatment technique as part of tumor palliation, to obtain haemostasis in case of bleeding from tumors. This method finds therapeutic applications in the primary, advanced and haemorrhagic tumor forms. RF must be regarded as an additional method, that could possibly be associated with surgery and radio/chemotherapy. Recorded morbidity (re-bleeding) was of 1,63% and specific mortality due to the procedure was null. Radiofrequency ablation does not pretend to substitute the classic methods in the complex cervical tumor treatment. It is not an alternative method, but it is already on its way to a place in the sequentiality of oncotherapy.

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