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Renal Artery Embolization in Treatment of Renal Cancer with Emphasis on Response of Immune System

H. Zielinski, T. Syrylo and S. Szmigielski

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1. Introduction

Role of renal artery embolization (RAE) in strategy of treatment of renal carcinoma (RC) has a multiyear history in scientific literature and in personal experience. In view of personal experience we have a strong feeling that RAE is beneficial both in operable and advanced RC, partially because of longer survival and stimulation of certain immune reactions [1].

RAE was introduced to clinical practice in the 70's of last century. The pioneers who developed the technique of surgery were Lalli et al, in 1973 while Almgard et al. presented their own experience with the application of RAE in renal cancer in humans [2,3]. At that time arteriography was the basic diagnostic methods and identification of renal tumors was made during the embolization. Today, vascular embolization procedures are becoming widely used in the treatment of persistent bleeding, vascular defects and cancer.

In urology RAE is well established in the treatment of bleeding observed after jatrogennie complications of NSS (nephron sparing surgery), PCN (percutaneous nephrostomy), ESWL (extracorporeal shock wave lithotripsy), PCNL (percutaneous nephrolithotrypsy), closing arteriovenous fistulas and the need to rempve kidney in the case of severe nephrotic syndrome or secondary arterial hypertension [4, 7, 22].

Basic form of treatment of locoregional RC is surgical resection of kidney containing the tumor (optionally with adrenal gland and extraperitoneal lymph nodules). Recently it is adviced to introduce new, less invasive surgical techniques (laparoscopy and use of robots), as well as NSS (nephron sparing surgery). These techniques are used mostly in less advanced RC (T1) [25, 28, 29, 30].

In the strategy of treatment of more advanced RC frequently there is adviced application of RAE [2,3]. RAE is a procedure based on introduction, with use of an angiographic catheter,

into blood vessel an obstruction material aimed to interrupt blood supply to an organ or to its particular region. At present different coils, haemostatic spongues, cyanoacrylic glues and alcohols are applied as materials for RAE [2, 11, 19]. This leads to acute necrosis of tissues where blood flow has been amputeed, which in turn results in development of acute phase reaction in the organism.

RAE is applied in treatment of RC for about 40 years [3]. It may be evoked prior to surgery, considered as a technique succouring the surgery, or used as palliative embolization in large, inoperable RC, mostly with intensive bleedings and/or pains. RAE which preceedes nephrectomy provides better conditions for the surgery and allows to shorten time of the intervention [1,4]. There exist informations that RAE may lead to stabilization and/or regression of distal metastases. These effects may be due to immunomodulating effects of RAE suggested by some authors [1,5]. However, knowledge on influence of RAE on immune status and response of immunocompetent cells is still scarce and fragmentaric. Systematic studies of this issue are needed.

In view of multiple limitations in efficacy and safety of RAE the present indications for application of this procedure include mostly [6, 7, 18]:

- Palliative RAE in advanced RC which results in relief of life-treatening haematuria and lumbar pains;

- Embolization of large, highly vascularized neoplasms prior to surgery (effective RAE results in contraction of vascular collaterals, facilitates dissection of the tumour, and allows to change the sequence of affixing renal vascular pedicle, ie first artery and the renal vein later);

- Embolization of highly vascularized RC metastases (e.g. vertebral metastases).

Opinions on the role of preoperative RAE in the management of patients with RC are controversial. Although a significant number of studies on RAE are reported in RC patients, there is no consensus on the benefits and morbidity associated with the procedure [7, 22]. Moreover, many large studies on the use of RAE both prior to nephrectomy and in advanced RC were conducted in the 1980s, before the development of improved techniques and imaging. Most proponents of preoperative RAE report the facilitation of nephrectomy through decreased operative blood loss, ease of dissection secondary to the development of oedema in tissue planes, and decreased operative time [8,9]. For those patients with significant tumour thrombus there might be a beneficial effect of decreasing the size or extent of tumour thrombus before surgery [10]. Interestingly, there might also be an advantage in the form of immunomodulation, whereby RAE-induced tumour necrosis stimulates a tumour-specific response from the immune system of the host [11-13].

Own experience [1] includes 474 patients with RC of which 118 had RAE before nephrectomy. It was reported that RAE significantly prolonged survival time in T2 and T3 RC. Additionally, it was found preliminarily that RAE exerted immunotropic effects and enhanced immune status of the patients. This diminished risks of the surgery. Recently we-continued these investigations and performed series of studies on response of immune

system in patients with RC undergoing RAE [14]. We analyzed 50 patients with RC exceeding diameter of 7 cm (T≥2) and tested immune status of persons with less and more advanced RC. 30 patients underwent palliative RAE and assessment of immune status at different times after embolization. The complex assessment of immune status included large battery of microculture tests of peripheral blood mononuclear cells (PBMC), estimation of levels of certain cytokines and cytometric measurement of lymphocyte subpopulations in peripheral blood. It was found that RAE lowers the suppressive action of neoplastic cells on the immune system, results in normalization of disordered proportion of lymphocyte subpopulations (CD4, CD8) and enhances the antiinflamatory response (increases levels of certain cytokines- IL-10 and IL-1ra). All together, the result reveal stimulation of certain functions of immunocompetent cells isolated from blood of RAE-treated RC patients. Clinical relevance of these findings and concluding whether or not RAE improved immune status of patients needs further studies.

2. Techniques of renal artery embolization

The initial indications developed in the 1970s for RAE were limited to symptomatic haematuria and palliation for metastatic renal cancer [2,3]. With technical advances and growing experience the indications have broadened to include conditions such as vascular malformations, medical renal disease, angiomyolipomas (AMLs), and preoperative infarction. The introduction of smaller delivery catheters and more precise embolic agents has drastically improved the morbidity associated with this technique [4]. RAE has continued to gain popularity as a minimally invasive approach for various urological conditions.

The technique of embolising hypervascular renal carcinomas dates back to 1969 when first reported by Lalli et al [2]. Since then, various techniques and embolic materials have been described. RAE has been used pre-operatively to facilitate nephrectomy [8], or to stimulate a possible systemic response in patients with metastases [5]. Renal embolisation has been established as a palliative treatment for unresectable renal carcinoma and in patients with less advanced disease (stage I–III) who, for whatever reason, are unsuitable or unwilling to undergo surgery [18, 22, 24]. In this group of patients the technique reduces tumour bulk and relieves local symptoms such as pain or intractable haematuria.

However, opinions on the role of preoperative RAE in the management of patients with RC are controversial. Although a significant number of studies on RAE are reported in these patients, there is no consensus on the benefits and morbidity associated with the procedure [7-9].

Effective embolization induces acute ischemic necrosis zone to form infarct of the organ tissues, which results in the onset of symptoms called postembolization syndrome, which usually occurs within the first few days after RAE [8]. Greater risk of developing the postembolization syndrome occurs in patients with small tumors, developing peripherally, when still remains a large part of the normal, not embolized part of the kidney [9]. The side effects which occur after RAE include: pain in the lumbar region, nausea and vomiting, hy-

perthermia, and fluctuations of blood pressure. These symptoms are usually temporary and transient, and their severity depends on the extent of ischemia in the kidney area. In a small percentage RAE may also lead to serious complications that are associated primarily with the movement (migration) or embolic material backflow [12, 22]. The consequence of this may be embolization of contralateral artery, mesenteric arteries, arteries of the lower limbs, and ischemic spinal cord injury. The risk of serious complications is low, if RAE is performed well and professionally. In our clinic material including hundreds of treatments was observed and serious complications developed, except of various symptoms of postembolization syndrome [1].

If there is a real benefit to be gained, most proponents of preoperative RAE cite the facilitation of nephrectomy through decreased operative blood loss, ease of dissection secondary to the development of oedema in tissue planes, and decreased operative time [10, 11, 26]. For those patients with significant tumour thrombus there might be a beneficial effect of decreasing the size or extent of tumour thrombus before surgery [12]. Interestingly, there might also be an advantage in the form of immunomodulation, whereby RAE-induced tumour necrosis stimulates a tumour-specific response [1,5,13]. It is likely that RAE is underutilized, perhaps because of a lack of prospective randomized studies demonstrating these potential benefits.

In our Departament of Clinical Urology the treatment of REA is performed under local anesthesia wit 1% xylocaine after puncturing the femoral artery under fluoroscopic control [1,14]. Vascular catheter is inserted into the abdominal aorta (Seldinger method). Aorto-nephrography is performed as the first step of the procedure (Fig.1 - A). This is followed by selective catheterisation of renal arteries and contrast agent (usually Omnipac) is applied using an automatic syringe (Fig. 1 - B). Image of arterial and venous intermediate is obtained with angiographic confirmation of following RC characteristics:

- Increased flow through the renal artery and the resulting expansion of the arteries,

- Presence of pathological vascularization in arterial phase (numerous, tortuous vessels with impaired angioarchitectonics)

- Nephrograms with the image of tumorous discoloration occuring due to retention of contrast in blood vessels,

- Loss of saturable renal parenchyma.

This is followed by injecting the embolizing material through a vascular catheter. Most frequently used is Spongostan which is fragmented and placed at the end of a syringe filled with 0.9% NaCl, and then injected into renal artery. Spongostan embolization often supplemented with different coils. In case of confirmation in renal arteriography of tumor vascularization by more than one artery, respectively all the supplying vessels are embolized, as above.

The whole procedure of RAE (Fig. 1 A – D) lasts about 30 – 60 minutes and its effectiveness (lack of blood flow in renal vessels) is confirmed in angiography after re-injection of contrast medium through the catheter withdrawn to the aorta.
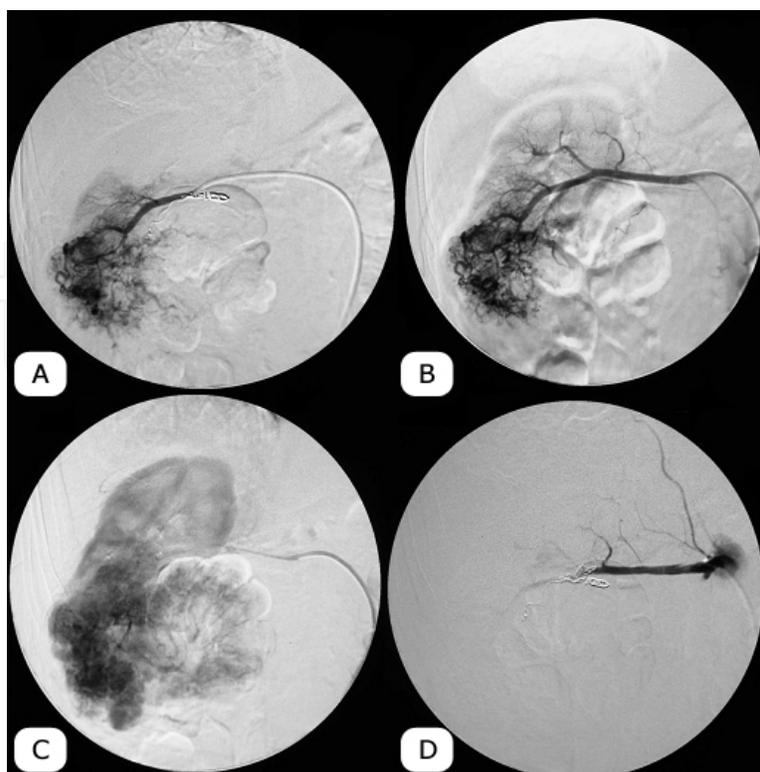
Figure 1. Stages of vascular embolization of renal artery. A. arteriography; B. vascularization of renal tumour; C. material for embolization injected to renal artery; D. closed renal artery.

After completing the RAE procedure the femoral artery puncture site is deemed temporary with pressure dressing. Few hours after RAE standard blood tests, monitoring of urine output and assessment of severity of postembolization symptoms (lumbar pain - a symptom that occurs in nearly all patients after effective RAE, nausea, vomiting, fever, transient renal failure and symptoms of gastrointestinal paralytic ileus). Medication (analgesic, antispasmodic, prokinetic agents, anticoagulants drugs and antibiotics) are prescribed appropriately to symptoms and depending on the clinical situation. In the study group of 474 patients there were no clinically significant complications (death, femoral hematoma, migration of embolizing material or ischemic spinal cord injury) [1,14].

Time schedules of RAE and nephrectomy are not established precisely, usually RAE is made few – several days before nephrectomy. In some cases RAE is made one only day before surgery to avoid acute postembolization syndrome.

3. Survival of renal cancer patients treated with renal artery embolization

Up to 30% of patients diagnosed with RC have metastatic disease at presentation [27]. Despite its sometimes favourable course, patients with metastatic RC generally die within 2 years of diagnosis. DeKernion et al [20] found that cumulative survival in 86 patients with metastatic RCC was 53% at 6 months, 43% at 1 year, 26% at 2 years and 13% at 5 years. The

treatment of patients with metastatic RC has not improved over the years and continues to pose a problem for clinicians. Surgery is not curative in this group; however, recent advances in immunotherapy have rekindled interest in cytoreductive nephrectomy. A combined analysis [21] of two prospective randomized trials, [15, 16], found a small survival advantage (5.8 months) in patients who underwent nephrectomy followed by interferon-alpha based immunotherapy compared with immunotherapy alone. This survival benefit relates to patients with a good performance status whose primary tumour has been assessed to be surgically operable and who are good candidates for subsequent immunotherapy. Unfortunately, many elderly patients with disseminated RC do not fit these criteria and have significant comorbidity. Radical nephrectomy may cause significant morbidity post-surgery, particularly in elderly patients, and in some cases precludes the use of systemic therapy. It is in this situation that renal artery embolisation appears to have a role.

Previous studies had reported that delayed nephrectomy following embolisation of RC may be of clinical benefit to high risk patients with reduction in the size and vascularity of the primary tumour prior to surgery [9]. Subsequent studies have, however, found no survival benefit for patients with metastatic disease undergoing embolisation and nephrectomy [23]. The survey also indicated that a significant proportion of respondents (35%) still believed that the technique had a role in palliation of haematuria or pain in unfit or inoperable cases, or as the sole treatment modality in patients with metastatic disease.

Park et al [19] investigated the effectiveness of RAE with a mixture of ethanol and lipiodol in 27 patients with unresectable RC. 10 of the patients had stage III disease with 15 of the 27 patients having stage IV disease. Overall the median survival of the 27 patients was 8.5 months. The median survival was 23 months in the 10 patients with stage III disease and 7 months in 15 patients with stage IV disease. A similar study by Onishi et al [24] compared two groups of patients with unresectable RC with stage IV disease. 24 patients underwent renal embolisation with ethanol while 30 patients did not have any intervention. The median survival for the renal embolisation group was 229 days and for the control group 116 days. Those undergoing renal embolisation had a significantly better prognosis than those who did not (p=0.019). Other authors [18, 25, 26] have reported median survival times for patients treated with renal embolisation ranging from 4 months to 8.4 months. This equates to a 1 year survival rate of 36.8% and a 2 year survival rate of 15.8%. Ridley et al. [28] support the view that embolisation is not a curative treatment and probably only minimally alters the natural course of the disease, but it gives palliation of local symptoms related to advanced renal malignancy and is a safe alternative to radical nephrectomy, with low morbidity and complication rate and shorter hospital stay.

In own studies [1] a series of 474 patients with RC, who had radical nephrectomy during a period of 15 years, was studied to assess the prognostic significance of various pathologic parameters (tumor stage [pT], lymph node status, metastasis, tumor grade, venous involvement) and value of preoperative RAE. There were: 20 (4%) pT1, 204 (43%) pT2, 245 (52%) pT3, and 5 (1%) pT4 patients. All 474 patients underwent nephrectomy including a group of 118 (25%) patients (24 pT2, 90 pT3, and 4 pT4) who underwent preoperative embolization of the renal artery. To compare treatment outcomes in embolized patients with RC, a group of 116 (24%) nonembol-

ized patients with RC was selected. This group was matched for sex, age, stage, tumor size, and tumor grade, with the embolized patients ($p < 0.01$). All important prognostic factors were studied as to their influence on survival by the treatment group. The overall 5- and 10-year survival was 62% and 47%, respectively (Figure 2). The 5- and 10-year survival rates were significantly better ($p < 0.01$) for patients with pT2 than for those with pT3 tumors (79% vs. 50% and 59% vs. 35%, respectively) (Figure 2). Involvement of regional lymph nodes (N+) was an important prognostic factor for survival in patients with pT3 tumors. The 5-year survival for pT3 N+ was 39%, compared with 66% in those with pT3N0 ($p < 0.01$). Preoperative embolization was also an important factor influencing survival (Figure 3).
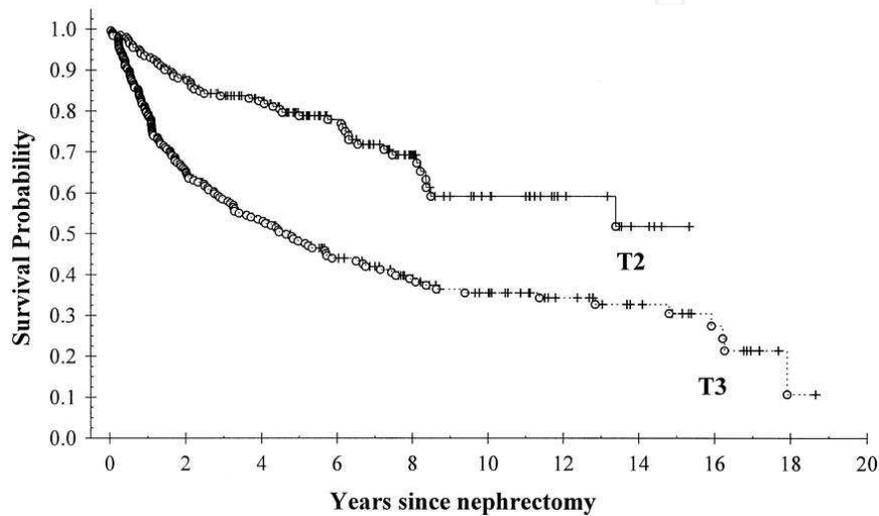

Figure 2. Estimated probability of survival from all causes of death by pathologic stage, pT2 vs. pT3. Open circles represent death of a patient. Tick marks represent a patient who was alive at last follow-up.
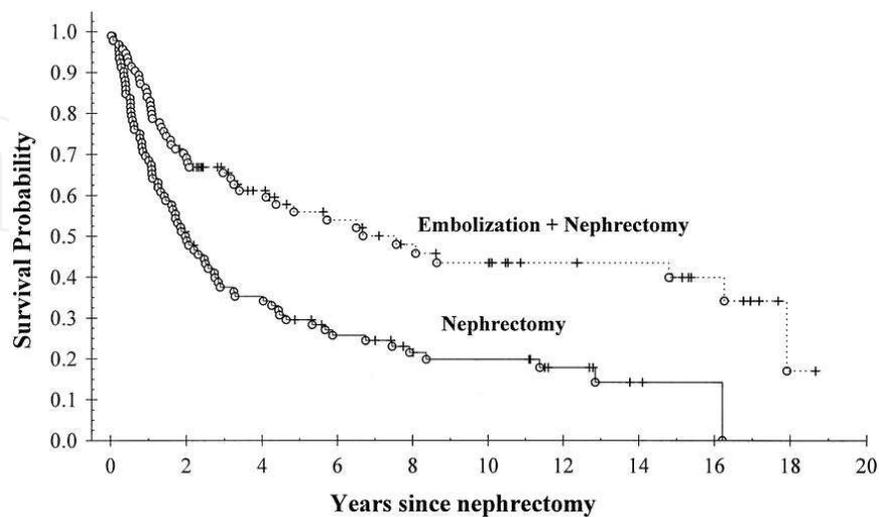

Figure 3. Estimated probability of survival in the 118 patients treated with preoperative embolization as compared to the 116 patients in radical nephrectomy alone group (matched patients).

The overall 5- and 10-year survival for 118 patients embolized before nephrectomy was 62% and 47%, respectively, and it was 35% and 23%, respectively, for the matched group of 116 patients treated with surgery alone (p = 0.01). The most important finding of this study was an apparent importance of preoperative embolization in improving patients' survival. This finding needs to be interpreted with caution and confirmed in a prospective randomized trial.

In conclusion, the available data suggest that RAE is a convenient, relatively tolerable management option in patients with unresectable renal tumours and in patients unfit or unwilling to undergo surgery as a means of palliation of local symptoms and improving clinical status. We believe there is also a role for this procedure in asymptomatic patients who have potentially resectable disease who are unfit or unwilling to undergo surgery, and in asymptomatic patients with inoperable metastatic disease.

4. Reaction of immune system to renal artery embolization

RC, with the tumor growth, and then the spread of tumor tissue beyond the original location, begins to affect the activity of the immune system [14]. Nakano et al [5] indicate the importance of cell proliferation inhibitory factor present in the serum of patients with RC. Lymphocytes in RC patients without any therapy, stimulated in vitro with PHA (phytohemagglutinin) in the presence of own serum responded very weakly to this mitogen. After RAE the impact of this inhibiting factor enhanced and proliferation of PHA-stimulated lymphocyte was still lowered [5]. Nephrectomy in patients not treated with RAE before surgery did not influence the ability of cells to stimulation by PHA. In contrary, patients who had RAE prior to nephrectomy the proliferation inhibitory factor quickly disappeared and proliferative response to PHA was normal already 2 months after surgery [5]. Catalona et al [34] reported that cell response to Con A (concanavalin A) is impaired in case of urological cancers, including RC, and the cells have a high immuno-suppressor activity. The abolition of the high suppressor activity may be necessary for effective treatment of RC [34]. Osada et al [35] in their study of 50 patients with RC confirmed a significant increase of helper and cytotoxic NK lymphocytes 10-12 months after RAE. This was very impressive, when compared to lowered values of these cells prior to RAE, suggesting that RAE enhanced the immune status [35]. Similar results were obtained by Bakke et al [13], who conducted a study of NK cell activity in patients with RC after RAE. Blood samples of 30 patients were taken before RAE and 24, 48, 72 and 96 hours after surgery. Surgery was performed to remove the kidney from 5 to 7 days after RAE. RAE resulted in increase in NK cells, with peak values observed after 48 hours [13]. RAE in patients with RC is performed in presence of potential existence of immune deficiency caused by cancer itself. Therefore, in this case, the immune responses (still poorly understood and inconsistent) observed at different times after embolization (usually few-several days after RAE) will be the result of the two, often different operating mechanisms: 1. response to ischemia and tissue necrosis and inflammation in the area of embolization of a probable stimulation of the macrophage-monocyte system; 2. release from tumor tissues of various factors affecting the immune system, at least some

of which appear to have an immunosuppressive effect. The main task of the immune system is to maintain homeostasis. The basic unit, often defined as "immune orchestra conductor" is thymus-dependent T lymphocyte, which, based on the phenomenon of restriction major histocompatibility complex I and II expresses the phenomenon of violence against its own unnormal or changed antigens, and the phenomenon of tolerance to its own antigens [32, 33]. Embolization may lead to stimulation of the immune system in the following mechanism: close off blood supply to the tumor leads to necrosis which gives a chance to enhance antigenicity of cancer cells and evoke the potential amplification of the immune system [14]. This leads in turn to destruction of tumor tissue by infiltration with cytolytic immunocompetent cells.

Recent studies in patients with metastatic RC have shown a small survival advantage in patients undergoing radical nephrectomy followed by immunotherapy; however, these studies are biased towards patients with good performance status aqccording to ECOG (Eastern Cooperative Oncology Group) scale status 0 or status 1. This small survival benefit should also be viewed in light of the morbidity and mortality associated with a large surgical procedure. The increased morbidity associated with radical nephrectomy may preclude or delay the administration of systemic immunotherapy, which has demonstrated reproducible response rates of 10–20% [15].

In two randomized trials with identical design, patients who underwent nephrectomy followed by interferon alpha (IFN-α) therapy had improved survival (median 13.6 months) compared with those treated with IFN-α alone (median 7.8 months) [15, 16]. The antivascular endothelial growth factor (VEGF) antibody; the multityrosine kinase inhibitors, sorafenib, sunitinib, and pazopanib; and the mammalian target of rapamycin (mTOR) inhibitors, temsirolimus and everolimus, have become the mainstay of therapy for the vast majority of patients with metastatic renal cell carcinoma (mRCC). Large randomized controlled clinical trials have shown improved progression-free survival with these agents and improved survival in selected populations, but the majority of these study patients had prior nephrectomy and good performance status [16, 17, 20, 21].

In own studies [14] we examined functional status of immunocompetent cells isolated from peripheral blood of patients with advanced RC treated with RAE. Blood samples were collected by vein puncture and peripheral blood mononuclear cells (PBMC) were isolated on Ficol-Paque gradient, and after determination of cell viability (usually no less than 80% viable cells), the microcultures were set up in triplicates (10^5 cells/0.2 ml RPMI + 15% autologous inactivated serum) in Nuncoln microplates. Respective triplicates were left without stimulation or stimulated with phytohemagglutinin (PHA, HA16, Murex Biotech Ltd Dartford U.K., 0.4 µg/cult.) or with concanavalin A (Con A, Sigma, 8 µg/cult.). The plates were placed inside the anechoic chamber in the ASSAB incubator at 37° C and 5% CO_2. An identical plate of control cultures was also set up and placed in the ASSAB incubator beyond the chamber. At 24h of incubation, rearrangements of the cultures were performed as described elsewhere [32,33].

As a result of rearrangements of cultures performed at 24 h, the following parameters of T cell and monocyte activities were measured at the end of cultures: T lymphocyte response to PHA and to Con A, saturation of IL-2 receptors, T cell suppressive activity (SAT index), and the index of monocyte immunogenic activity (LM) related to the ratio of produced monokines (IL-1β versus IL-1ra) [32]. For the last 18h of incubation, 3H-thymidine (3HTdR, Amersham, U.K., spec act. 5Ci/mM) was added into the cultures in a dose of 0.4 µCi/cult.

At 72h the cultures were harvested and incorporation of 3HTdR was measured in Packard Tri carb 2100 TR scintillation counter. The results were calculated as a mean value of dpm (desintegrations per minute) per triplicate of cultures ± SD. The experiments were repeated 10 times, and the results observed in the exposed cultures were compared with those obtained in the control cultures. The data were analyzed with STATGRAPHICS PLUS 6.0 version. The differences between the mean values were assumed statistically significant if the p values, calculated withthe use of U Mann-Whitney's test, were lower than 0.05.

The results obtained in this study are summarized in Table 1 and described in detail elsewhere [14].

In the analysis of 50 patients with RC treated with RAE, we selected 30 patients where RAE was the only form of treatment. In this group of patients the immune response was studied at different times after the palliative RAE (output test, the test after 2-6 weeks and at 12 weeks after RAE) successive assessment of significant differences in the magnitude and direction of change of parameters characterizing the efficiency of the immune system. It was found that RAE performed in patients with advanced RC exerts immunomodulatory effect on the immune response manifested by the increase of the proliferative response to PHA and the percentage of CD4 + cells, and significant increase in the value of saturation of the receptors, IL-2, a cytokine with protrophic properties (Table 1). After RAE significant increase was observed in inflammatory response manifested by the increase of T regulatory cells, which can be a potential source of IL-10, cytokine inhibition of the function of the inflammatory response (Table 1).

It was found that RAE lowers the suppressive action of neoplastic cells on the immune system, results in normalization of disordered proportion of lymphocyte subpopulations (CD4, CD8) and enhances the antiinflamatory response (increases levels of certain cytokines- IL-10 and IL-1ra). All together, the result reveal stimulation of certain functions of immunocompetent cells isolated from blood of RAE-treated RC patients. Clinical relevance of these findings and concluding whether or not RAE improved immune status of patients needs further studies [1, 14].

The changes in the immune system may, however be heterogeneous and multidirectional and individually changebale. This would indicate that the systemic inflammatory response is not only associated with the release of cytokines from a kidney tumor, and it rather results from the defective immune response in patients with advanced cancer [14].

Investigated parameter	RAE-treated RC patients (T 3 and 4) N=30
PHA	Lowering after 2-6 weeks * Increase after 12 weeks
ConA	Lowering after 2-6 weeks * Lowering after 12 weeks
IL-2	Lowering after 2-6 weeks Increase after 12 weeks
LM	No significant differences after 2-6 weeks Lowering after 12 weeks
SAT	Increase after 2-6 weeks No significant differences after 12 weeks
CD3$^+$	Increase after 2-6 weks No significant differences after 12 weeks
CD4$^+$	Increase after 2-6 weeks Increase after 12 weeks
CD8$^+$	Lowering after 2-6 weeks * Lowering after 12 weeks
CD4$^+$/CD25^{high}	Increase after 2-6 weeks Increase after 12 weeks
NK	No significant differences after 2-6 weeks No significant differences after 12 weeks
IL-1β	Increase after 2-6 weeks Lowering after 12 weeks
IL-6	Increase after 2-6 weeks Lowering after 12 weeks
TGF-β	Lowering after 2-6 weeks * Increase after 12 weeks
IL-1ra	Lowering after 2-6 weeks * Increase after 12 weeks
IL-10	Lowering after 2-6 weeks * Increase after 12 weeks

Table 1. Summary of changes in investigated functional parameters of immune system in a group of 30 patients with advanced RC treated with RAE ($p<0.05$).

5. Summary and conclusions

In summary, the present authors conclude that patients with advanced RC benefit from RAE with longer survival. RAE applied prior to nephrectomy facilitates surgery and additionally prolongs survival. Additionally, RAE appears to be a potent immunostimulatory agent. It is our strong feeling that in specialistic urologic centers RAE is a safe procedure which suc-cours the complex therapeutic process in patients with RC.

Author details

H. Zielinski[1], T. Syrylo[1*] and S. Szmigielski[2]

*Address all correspondence to: tsyrylo@wp.pl

1 Department of Clinical Urology, Military Institute of Medicine, Warsaw, Poland

2 Military Institute of Hygiene and Epidemiology, Warsaw, Poland

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