# Urological literature review: November 2007 – November 2008. Part I

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## TRAUMAS

Many articles this year have been devoted to external traumas of the sexual organs and scrotum. The crucial element of the diagnostic procedure in closed trauma is an ultrasound examination with 100% sensitivity and 65% specificity. It may show the torn tunica albuginea of the testis and, as it is possible to visualize blurred testis borders which used to be sharp, a heterogeneous image of the parenchyma and sometimes its pouring outside the tunic. In some centres patients with visible haematomas are immediately explored without an ultrasound examination, whereas in other centres this examination is performed in all the cases of scrotum trauma [1, 2, 3]. The patients with a diagnosed haematoma or the torn tunic should always be operated on and conservative treatment may be applied only in a few cases, in which neither haematoma of the testis nor haeatoma of the tunica albuginea is found and tunica albuginea of testis is preserved.

In open traumas of the scrotum and genital organs conservative therapy may be introduced in patients with superficial traumas external to the tunica dartos. Mc Aninch et al. from Los Angeles, who specializes in trauma treatment, explored 78% of patients with scrotal injuries caused by gunshot wounds, as well 63% of the patients with stab wounds and 80% of patients bitten by animals. Saving treatment was applied whenever possible. It was possible to preserve 75% of testes (18 out of 24) with gunshot wounds, but only 24% in cases of self-emasculation and 20% of other stab wounds. Self-emasculation wounds made up half of stab wounds. It was possible to preserve the penis in 80% of patients with a complete amputation [4].

The Clinic of Paediatric Urology at the Collegium Medicum at the Jagiellonian University summarized its experience regarding the treatment of 187 children with renal injuries. An ultrasound examination and contrast computed tomography were used as the main diagnostic methods. According to worldwide tendencies 157 children received conservative treatment and only 30 children were operated on. Nephrectomies were performed in four children (slightly more than 2%), in three of them due to renal fragmentation and trauma of the large vessels and in one child due to a secondary haemorrhage after conservative treatment. In 15 children lesion was surgicaly repaired and in 5 the torn pole of the kidney were removed [5].

## IMAGING TECHNIQUES

There has been many controversial reports available recently regarding the applicability of positron emission tomography - PET (PET visualizes physiological and metabolic processes, characteristic features of which are different in normal and cancer cells, using positron-emitting substances, so called radionuclides, manufactured in a cyclotron) as a diagnostic method in the staging of primary neoplasms, local relapses and metastases in prostate, renal and bladder cancers. It was a consequence of insufficient experience in evaluation and interpretation of the findings obtained in the new diagnostic tool that is still not populari in Poland. Therefore it was common for surgeons to carry out surgical intervenions in patients in whom they found no lymph node metastases previously visible in PET, or in whom during a surgical procedure they observed highly advanced local cancer and lymph node metastases which had not been revealed in PET.

A review presented in the *Journal of Urology* summed up the current state of knowledge and the latest breakthroughs in the field. In prostate cancer PET was not highly effective in terms of detecting a primary tumour and had a limited role in evaluation of the stage of disease and in the detection of relapses after radical treatment. Promising results were obtained when PET was performed with the following substances: 11C-choline, 18F-fluorocholine, 11C-acetate, 18F-fluoride. The role and importance of other radionuclides remain the matter of ongoing studies. In bladder cancer PET with 18F-fluorodeoxyglucose was effective enough to detect metastases but was not able to visualize a primary tumour due to the fact that 18F-fluorodeoxyglucose was excreted in the urine. The 11C-choline and 11C-methionine are still in the experimental phase. In renal cancer PET with 18F-fluorodeoxyglucose could only be applied to a limited extent to detect a primary tumour. However, it was useful to evaluate the stage, local relapses and metastases after radical therapy. Further research is necessary to evaluate the applicability of 18F-fluoromisonidazole and 18F-fluorothymidine. New radionuclides and advances in the field of imaging methods may improve the diagnostic efficacy of PET in the future [6].

## BLADDER CANCER

The treatment of superficial bladder cancer using transurethral resection has two main goals: to reduce the relapse rate and to prevent manifestations of progression such as infiltration of the bladder muscular layer which requires cystectomy. pTa neoplasm relapses are burdensome for patients but progression is exceptional, therefore they are not life-threatening. In pT1 neoplasms, progression is the main risk as it may lead to tumor spreading, which unfortunately is common at the time of primary diagnosis. Early cystectomy directly after diagnosis, which is practiced in many centres, provides tumour-free survival in more than 90% of patients. However, the survival rate decreases to 60-70% when patients receive conservative treatment and cystectomy is postponed until progression can found. Nonetheless, such a procedure makes it possible to save the bladder in 70% of patients and for that reason is widely advocated for. In order to make this procedure more rational, scientists have been seeking markers which could predict the risk of progression and accelerate the decision of cystectomy. Several reports of the results have been published this year.

Incomplete resection of all the lesions during the first procedure is thought to be the main reason for fast relapses. The phenomenon of increased fluorescence of the neoplastic tissue following the exposure to photosensitizing substances has become the basis for fluorescence-based photodynamic resection (PDD) and it makes it easier to distinguish neoplastic lesions from the normal mucosa. Many reports proved that in pTa tumours photodynamic resection prolongs the relapse-free survival compared to classic white-light resection, especially due to the fact that the rate of tumours incompletely resected during the first procedure is reduced

(false relapses). For neoplasms at this stage progression is exceptional, therefore many centres abandoned PDD due to its high costs in favour of routine secondary resection to verify a primary histological diagnosis which also allows resection of remaining tumours. Urologists in Aachen published a prospective study on 191 patients with pT1 neoplasms (7-year follow-up period) and they studied benefits from using PDD in this group of patients with a high risk of progression. They demonstrated that both in pTa neoplasms and in pT1 tumours PDD increased the number of patients without fast relapses to 80% (52% for the white light); however, it had no effect on reducing the rate of progression and for that reason it cannot be used as another argument in favour of postponing cystectomy in patients with pT1 tumours [7].

The decision on more aggressive treatment for superficial bladder cancers may be enforced by the expression of survivin – a gene from the family of apoptosis inhibitors crucial for neoplastic progression. It was found that increased expression of survivin in the tissues prior to the tumour resection was associated with higher risk of relapse and progression; however, it had no effect on disease-specific survival [8].

A multicentre study from Japan had showen that oral administration of the *Lactobacillus casei* suspension accompanied by intra-bladder epirubicin infusions after the electroresection of superficial bladder cancers (pTa and pT1) statistically significantly decreased 3-year relapse-free survival. Several experimental studies indicated that preparations with different *Lactobacillus* species exerted the immunomodulatory effects and increased the antineoplastic response. Unfortunately, this treatment also had no effect on progression-free survival and the overall survival [9].

A large retrospective study that enrolled 121 patients in 1987-1988 with T1 neoplasms focused on the effects of different factors on the disease progression and the disease-specific survival (DSS). According to one-factor analysis the following factors were unfavourable in terms of progression: solid tumour, cancer cells present in the vessels, G3 histological grade, infiltration of the submucous membrane and coexisting endothelial carcinoma (CIS). According to a multi-factor analysis only solid tumour and the presence of cancer cells in the vessels were independent factors for the progression and DSS. It is not known yet whether intra-bladder BCG infusions may reverse this unfavourable prognosis in this group of patients [10].

In the editorial article in *European Urology* H. Herr from Memorial Hospital in New York, a world authority in the treatment for superficial bladder cancers, disputed about a currently used 3-year BCG maintenance therapy, a conservative treatement for stage pT1 G3 superficial bladder cancers. This current therapeutic regimen was based only on the results of one clinical study and two meta-analyses which, according to Herr, contained a large number of methodological mistakes. Other clinical studies comparing two methods did not confirm the superiority of maintenance therapy vs. induction therapy and in reports on induction therapy the progression rate was similar and in some reports even lower than for maintenance therapy. Maintenance therapy was more expensive; moreover, it was associated with a significant rate of serious adverse effects and for that reason Herr warned against its automatic use in all the patients with pT1 G3 tumours [11].

All examples presented above clearly show that despite the fact that we are able to detect a risk of progression more and more precisely and to delay progression, these actions do not lead to disease-specific survival (DSS).

It should be emphasized that a modified resectoscope has been introduced and the traditional movements of a cutting loop forwards and backwards have been replaced by rotational movements around the axis of a device. This modification is aimed to reduce the risk of a wall perforation while resecting bladder tumours and to make it easier to resect prostate adenoma in the area of the bladder neck and sphincter. The learning curve is simple. The instrument is in the last phase of tests in several selected university centres [12].

## CYSTECTOMY. URINE DIVERSION

At the end of 2007 two practical articles were published in *Urology,* which in a simple way may have made it easier to manage patients eligible for cystectomy.

Yet another time, but this time in a prospective trial, it was proved that special preparation of patients before cystectomy was not necessary, if urinary diversion using a small intestine was planned. Patients being prepared for cystectomy were divided into two groups: one was prepared for the surgical procedure in a classic way (a 3-day liquid diet, enemas until clear liquid, erythromycin and metronidasol for 2 days before the procedure) and the other received a 24-hour liquid diet and no oral administration of food and beverages for 8 hours prior to the procedure. No differences were observed between two groups in terms of the post-operative course and the number of complications [13].

Also another prospective trial proved that chewing gum since the first day after the procedure accelerates the appearance of peristalsis from 2.9 days to 2.4 days and the time to flatulence elimination from 3.9 days to 3.2 days. The suggested explanation was that vagus nerve-mediated hormonal and direct stimulation of smooth muscles was increased as well as saliva and bile secretion [14].

## RENAL CANCERS

Advances in the field of imaging techniques which contributed to the detection of renal cancer at more and more early stages did not contributed to the reduction in the mortality rate for a long time. On the contrary, the mortality rate tended to increase all the time and in the years 1990-1994 it reached the value of 4.8 deaths/100 000 among men and 2.1/100 000 among women. Nowadays, for the first time in a population study in 32 European countries we observed a decrease in the mortality rate from 2000-2004 by 13% among men (4.1/100 000) and 13% among women (1.8/100 000). However, the decrease in the incidence was less noticeable. The rate decreased mainly in the Western European countries, especially in Scandinavia, whereas in the Eastern European countries stabilisation was observed. The authors of the study claimed that the decrease in the mortality rate cannot only be a consequence of improved diagnostics and treatment, but it was mainly associated with a decrease in the rate of smokers as well as with other, yet not recognised conditions [15].

Two main topics were predominant in 2008 in other articles in the field of renal cancer. One of them was a nephron sparing surgery (NSS), and the other a targeted medical therapy (TMT) in the treatment of metastatic renal cell cancer.

## NEPHRON SPARING SURGERY (NSS)

The importance of NSS is growing more and more as recent reports contradict the belief which is common among urologists that a complete removal of a kidney with a tumour at the normal creatinine levels and with the other kidney normal in imaging tests is safe and does not lead to chronic renal failure. Today we already know that NSS minimally affects the glomerular filtration, whereas a complete kidney removal decreases the

creatinine clearance in a statistically significant way [16], and in younger patients has a negative effect on the risk of cardiovascular disease and on the increased mortality rate from any cause [17].

The importance of NSS will be growing more and more due to the fact that the rate of accidentally diagnosed moderate-sized tumours is still increasing. The analysis of data of 104150 patients with renal cell cancer from the *National Cancer Data Base* in 1993-2004 makes it possible to claim that it is feasible to diagnose tumours of smaller and smaller diameter. The average tumour diameter decreased from 4.1 cm in 1993 to 3.6 cm in 2004, and the rate of diagnosed tumours of this diameter decreased in the ratio 32.5% to 43.4% [18].

The prognosis of disease-free survival (DSS) does not depend only on one factor which until now was thought to be the tumour diameter <4 cm, but it depends on a great number of factors, and a multivariate analysis cannot be replaced by prognosis based on only one element, namely the tumour size. While prognosis of DSS for tumours with the diameter <4 cm (T1a) is better than for the ones >4 cm and <7 cm (T1b), prognosis for Tb1 tumours does not depend on the fact whether a NSS or radical nephrectomy were performed. In other words, disease metastases that would develop in the future do not depend on the fact whether there was a partial or complete removal of the engaged kidney, but do depend on the fact whether during a surgical procedure there were metastases which we were not able to diagnose [19].

The removal of a larger tumour is associated with an increased rate of perioperative bleedings, transfusions and urethral fistulas; however, the total rate of complications and the length of hospitalisation do not differ between the two groups to such a significant extent that NSS should be abandoned in the group of patients with T1b cancers. It can be said that in 2008 the decision whether to perform NSS in patients with T1b tumours (diameter <7 cm) would depend not on the tumour size, but on its localisation, patient's general condition, underlying diseases and mainly on surgeon's experience.

We can expect that along with the growing experience the indications for elective NSS will include all tumours limited to a kidney; as a consequence, a large extent of T2 tumours and T3a tumours with only adipose tissue infiltration, as well. Nowadays, it is known that the prognosis of DSS in the T3a group with only perirenal adipose tissue infiltration for tumours <7 cm is the same as the prognosis for T2 tumours [20, 21].

The larger the tumour diameter, the more certain preoperative diagnosis is, which is based on imaging tests, and the greater belief that the tumour should be removed, not only observed. In T1a tumours (diameter <4 cm), the smaller tumour diameter, the higher tendency to postpone a surgical procedure is, as there is a higher likelihood that it is a benign tumour, because of the fact that a natural history of small renal tumours remains unknown. When a natural history of small, accidentally detected renal tumours is analysed, it is easily to notice that the majority of them grow slowly, with the rate of 0.14-0.24 cm/year, while 1/3 of them do not grow at all in short or moderate time periods with rare progression in such patients. As a consequence, the introduction of active observation programmes based on the initial tumour diameter and the rate of its growth would be considered more and more often.

Below we present one of the reports where the authors tried to determine the tumour diameter which would minimalize the risk of synchronous metastases and the risk of progression. In order to do that, they compared medical documentation of 110 patients with histologically confirmed renal cancer metastases and of 250 patients with localised cancer without metastases (4.5 cm, 0.3-17.5 cm on average). Metastatic patients had larger tumours (8 cm, 2.2-20.0 cm on average), than patients without metastases (4.5 cm, 0.3-17.5 cm on average). In none of the patients with tumours smaller than 2 cm metastases were observed, and metastases were present only in 5% of patients with tumours smaller than 3 cm. Each 1 cm of tumour growth was associated with the increase in the risk of metastases of 22% [22].

Such reports are published more and more often; however, their main weakness is the risk of bias selection. Knowledge based not on reports with randomly chosen patients but on reliable statistical studies (10420 patients from the SEER register) have proven the presence of metastases in respectively 6.3%, 4.7%, 5.2% and 7.2% patients with tumours of the diameter below 1 cm, 1-2 cm, 2-3 cm and 3-4 cm [23].

Moreover, a surgical procedure cannot be abandoned due to only the observation of the tumour diameter growth rate. In a study of 61 patients with small renal cell cancers who were operated on, authors found a complete lack of correlation between the growth rate and the fact whether the tumour was benign or malignant in a post-operative histopathological test; 5 out of 6 tumours which did not grow were malignant tumours [24].

For that reason, it is too early to introduce active observation programmes for small renal tumours, as we have no knowledge of reliable progression markers. Finding such markers is crucial for the observation programmes to be safer and based on the most reliable factors such as the tumour growth or tumour doubling time. In clinical trials conducted so far the most frequent causes of abandoning observation and making a decision to proceed with a surgery were as follows: tumour growth, patients' anxiety, improvement of general condition which made it impossible to conduct a surgery in the past.

The surgery of small renal cancers is abandoned most frequently in the elderly. If it is not a result of underlying diseases or patient's poor general condition, it has to be explicitly stated that such a decision is unjustified. In a large European multicentre study it was proven that old age is an independent, unfavourable prognostic factor for DSS, irrespective of a disease stage, Furman scale score, tumour size and histological subtype [25].

For that reason, in 2008 the appropriate procedure in patients with small renal tumours as well as with an atypical cyst of Bośniak grade II-IV is NSS, irrespective of the tumour size and patient's age, provided that the general condition and underlying diseases are not the reason why the procedure has to be abandoned.

The attempts to develop observation programmes based on more reliable factors than the observation of the tumour growth alone resulted in a renewal of biopsies of small renal tumours. Replacing ultrasound-guided biopsy (difficulties in detecting small isoechogenic tumours) with spiral CT-guided biopsy, changing fine-needle biopsy with 2 or 3 core biopsies with 18 gauge needle resulted in the increased diagnostic precision up to more than 90%. Using thicker needles did not cause any significant increase in the complication rate. Small, harmless complications occured in less than 5% of patients, 1-2% patients required blood transfusion, but renal removal was rare and the implantation of neoplastic cells in the injection canal did not exceed 0.01% [26].

Apart from classic histological tests which make it possible to distinguish renal lymphoma from clear cell cancer and to introduce chemotherapy instead of surgical treatment, biopsy material is a subject of numerous immunohistochemical and molecular tests. The tests for the presence of melanocytic markers (e.g. HMB45) make it possible to identify atypical angiomyolipoma with a low amount of adipose tissue, while the presence of cytokeratins makes it possible to distinguish oncocytoma from chromophobic cancer and the presence of carbonic anhydrase IX makes it possible to diagnose clear cell cancers of higher aggressiveness, the

ones associated with the VHL gene mutation. Finally, FISH genetic testing increases the likelihood of diagnosing oncocytoma up to 95%. Biopsies will be more and more important and data obtained in immunohistochemical and molecular tests on biopsy material will probably allow the introduction of program to observe small renal tumours using more reliable prognostic factors [27].

The data above indicate growing importance of a thick needle biopsy in the diagnostics of small renal tumours; however, *Guidelines EUA* for 2008 do not recommend biopsies as routine procedures. Biopsies are not recommended in the diagnosis of atypical cysts of Bośniak grade II-IV. A diagnostical mistake is very likely, due to the fact that the neoplasm may be located in small foci between benign cystic lesions and, what is more, the risk of metastases due to the rupture of the cystic neoplastic lesion is highly possible.

In 2008 a relatively young and healthy patient who wants to avoid a complete lack of diagnostic certainty which is still present and the risk of complications following a biopsy of a small renal tumour is treated with a surgical tumour removal (NSS). The same rule applies to the atypical renal cysts with Bośniak grade II-IV. There is a risk of about 20% that the removed tumour is benign. However, this approach minimizes the risk of metastases that exist even in the case of quite small tumour for the observation. Nephron saving techniques will provide such a patient with the oncological safety and will protect them from the development of renal failure in the future.

The majority of authors think that wedge excision or enucleation with a margin of healthy looking tissue will provide the greatest protection against a real relapse in the site of a tumour removal, especially in small tumours in which a pseudocapsule is not formed yet. The analysis of the local relapse rate and disease-free survival allowed to estimate that 1-2 mm of healthy renal parenchyma left around the tumour will provide oncological safety during the procedure [28, 29].

There is no unified opinion on the usefulness of the pathological examinations during surgical procedures. Controversy is a result of difficulties associated with the histological evaluation of the frozen sections during procedures: the sections from a removed kidney tissue or those from tumor base in the kidney. There were reports on many diagnostic mistakes when an anatomopathologist did not find cancer cells in the resection margin in emergency tests and in the final histological evaluation and the patient developed a local relapse; or there were reversed situations, where cancer was diagnosed, the kidney was removed and the final histological evaluation was negative or benign neoplasm was diagnosed [28].

These doubts translate into routine practice. In a large American study with 7507 patients in whom NSS was performed, histological examination during a surgery was performed only in 11.2%. In the majority of urological centres the applicability of the regular frozen sections is uncommon because the costs and lack of undoubted information achieved in the procedure . It was never proven that histological examination during surgery decreass the rate of positive margins in a final histological examination. It seems that practice of frozen sections comes from surgical traditions rather than evidence based medicine [28, 30].

Contrary to logic and rules of proceedings valid so far in surgical practice absolute necessity to expand the site of resection (secondary NSS) or to perform secondary nephrectomy in the case of cancer cells in the resection margin in a final histological examination on post-operative paraffin-processed material is not being confirmed in more and more numerous reports and collected evidence.

In the last report from the Memorial Sloan Kettering and Mayo Clinic on 1390 partial renal resections, cancer cells in the resection margin in a final histological examination were found in 77 patients (5.5%.) All the patients underwent a secondary surgery. The result analysis excluded patients with a secondary nephrectomy. Statistical differences in 10-year local relapse-free survival or metastasis-free survival were not observed in the group of patients with "positive and negative margins." The authors claimed that patients with massive infiltration of the resection margin in a final histological examination should be reoperated on, whereas the patients with microscopic infiltration may be safely observed. A large number of "positive margins" were observed in patients with one kidney and in this group the tumour diameter tended to be lower, which was associated with a subconscious attempt to limit the extent of the resection in these patients.

There are many theories why the presence of positive margins does not mean a poor prognosis. A positive margin may be a result of histological artefacts. Some small tumours have a favourable phenotype that implies their low biological aggressiveness. Cancer cells that are more metabolically "demanding" may not survive ischaemia during a surgical procedure and may be destroyed either during coagulation of the site following resection or as a result of secondary lesions associated with sutures causing local necrosis and tissue fibrosis [31].

The multivariate analysis based on the postoperative determination of the creatinine levels and glomerular filtration rate (GFR) in 1049 patients following NSS indicated that the extent of renal function decrease is influenced by the following factors: the operation on the only kidney, low preoperative GFR, tumour diameter and patient's age. The following factors do not influence renal function: duration of the operation, tumour location (exophytic or central) and operation type (open surgery or laparoscopic procedure) [32].

The main factor is the duration of renal ischaemia during a surgery. It is thought that warm ischaemia below 30 minutes is safe for a kidney with normal preoperative function. However, all efforts must be made to make warm ischaemia as short as possible. The latest tests based on the observation of 537 patients with only one kidney being subject to NSS indicated that extending the duration of warm ischaemia above 20 minutes and of cold ischaemia above 35 minutes was associated with the increased risk of renal failure (from 19% to 41%) and the increased postoperative creatinine blood levels above 0.5 mg% (from 15% to 42%); constant dialysis was necessary more frequently, as well (the increase from 4% to 10%) [33].

Contrary to common beliefs functioning of a kidney subject to warm ischaemia is not affected by artery only claming or the whole renal peduncle (claming the whole renal peduncle facilitates a surgery as there is no venous backflow), the method of clamping (tourniquet or clamp) or using interrupted ischaemia. If only possible, NSS without renal peduncle clamping should be performed and, if ischaemia is necessary, furosemide and mannitol should be used in order to improve renal perfusion and increase postoperative diuresis [34].

Until the beginning of 2008 more than 2000 laparoscopic NSS procedures were performed and it is a method in rapid developement, widening indications to centrally located tumours and tumours in the renal hilus. The main disadvantages of this method included so far the following: the increased rate of postoperative complications, mainly urological (urinary fistulas) and secondary bleedings requiring reoperation and longer duration of warm ischaemia when compared to open surgeries. However, as the laparoscopic technique was mastered, the duration of warm ischaemia in experienced teams is currently below 20 minutes for 94% of procedures and never exceeded 30 minutes. Moreover, the number of secondary bleedings decreased to 1-2% [35].

The undoubted benefits of laparoscopic procedures when compared to open surgery include statistically shorter procedure time, a lower intraoperative blood loss and shorter hospitalization time. In experienced centres in patients with single renal tumours <7 cm the number of positive margins, 3-year oncological relapse-free survival and the results of renal functions are comparable [36].

Even in the centres with extensive experience in laparoscopic procedures it is thought that in patients with a single kidney and with renal failure NSS during an open surgery is a method of choice [37].

The guidelines of the European Association of Urology for 2008 claim that laparoscopic NSS is the an alternative to recommended open NSS for T1a tumours (<4 cm) and feasible only in centres with the highest experience in T1b-T2 tumours.

The preliminary results of robot-assisted laparoscopic NSS come from about dozen cases. The procedures were performed because of different indications and by surgeons of different experience. However, the results were encouraging, although sometimes the duration of warm ischaemia was too long. Robot-assisted laparoscopic NSS in especially difficult cases may be an alternative that allows the kidney preservation owing to a minimally invasive procedure. Nonetheless, it is still an experimental method whose relation to traditional laparoscopic NSS needs to be defined [38, 39].

The necessity to make an incision into a well-vascularised renal stroma during an open and laparoscopic kidney resection and complications such as intra- and postoperative bleedings triggered the development and more and more extensive use of tumour ablative techniques that use energy from different sources. These are called needle energy-ablative techniques, energy ablative techniques or thermal ablative techniques. The most frequently used is cryoablation and a thermal therapy, in which the energy source is radio frequency waves (radio frequency ablation). The technique which is used rarely as it is still experimental is ablation using high-intensity focused ultrasound [40].

The methods to apply these techniques are various. They might be used transcutaneously or laparoscopically and during open surgeries (for centrally located tumours), as well. There is no agreement as for the number of needles placed in the tumour, the levels of required energy for the procedure to be successful or the fact whether energy should be provided constantly or in several stages (during one procedure), method of tumour detection, and last but not least, the evaluation of the completeness of the procedure in imaging techniques. Laparoscopic cryoablation is thought to be the most effective, worse results are obtained transcutaneously. Moreover, for the latter method there are limitations when treating tumours located on the anterior renal surface. Contrast computed tomography is considered to be the best method of detection as it allows to evaluate the completeness of the procedure through enhancement or its lack along the borders of the tumour which were not completely necrotized during a procedure. The best assessment of completeness during postoperative follow-up is thought to be a lack of tumour growth and lack of enhancement of a postablative lesion after contrast administration [41].

None of these new techniques have been compared in prospective and randomized trials with resection techniques; but routine practice indicates that the latter are more effective. In the case of open and laparoscopic surgery cancer cells are present in the resection margin in 2.4% (1.6-2.9) of cases and the rate of local relapses is from 0 to 1.7% [42].

However, it is sufficient enough to compare these data with the results of ablative techniques from the Cleveland centre, one of the most referenced worldwide. The assessment of margins was not technically feasible, but the number of local relapses was evaluated at 7.4% (13 out of 175 patients) following cryoablation and 25% (26 out of 104 patients) following a thermal therapy. Nonetheless, it should be emphasised that in great number of reports the rate of local relapses was significantly lower. A patient who decide to be treated with ablative techniques has to be fully informed about the fact that the risk of reoperation is significantly higher than in the case of partial kidney resection. A revision procedure is possible in 2/3 of patients and due to very large and dense scars, as a result of an inflammatory reaction following ablative techniques, a laparoscopic reoperation is often impossible and in more than 50% of patients the only surgical procedure possible to be performed is a kidney removal. For that reason, a patient choosing the treatment with new techniques may lose a possibility of kidney preservation, which could have been possible in case of partial resection performed originally. However, such methods may be an alternative for elderly patients, those in a poor general condition or with additional contraindications [43].

Moreover, these new techniques may be very attractive for other patients, for example recently a new technique, single port access (positioned in the umbiliculus) renal laparoscopic cryoablation, has been introduced [44].

Secondary NSS following primary partial renal resection is currently assessed differently in various centres; however, the nephrectomy number is significantly lower than in case of reperation following ablative techniques. On the other hand, ablative techniques may be a tempting alternative for secondary NSS in case of a local relapse following primary NSS [45].

## TARGETED MEDICAL THERAPY (TMT) IN THE TREATMENT OF THE PATIENTS WITH METASTATIC RENAL CELL CANCER (MRCC)

In previous years many clinical trials proved that treatment for metastatic renal cell cancer complemented with tyrosine kinase inhibitors (sunitinib, sorafenib), mTOR inhibitors (temsirolimus), or monoclonal antibodies to vascular endothelial growth factor (VGEF) (bevacizumab) prolonged progression-free survival and total survival in this group of patients previously resistant to any kind of treatment.

Despite the fact that the efficacy of these medicines were proven, the majority of issues associated with their usage are the subject of intensive trials. These drugs were registered at the beginning as a drugs of the second choice in post-nephrectomy patients who did respond neither to the immunotherapy with a single agent (sorafenib) nor to the combination therapy with interferon (bevacizumab), but now they are being tried in different combinations with respect to the order of administration, combination of two drugs and the role of nephrectomy and metastasectomy combined with TMT.

An idea to use TMT before kidney removal used to raise many doubts due to concerns of its effects on secondary bleedings and interference with normal wound healing following nephrectomy. These doubts were dispelled by the oncologists from the Anderson Cancer Center, Houston, Texas. They applied TMT in 44 patients with mRCC before cytoreductive nephrectomy. They used sunitinib, sorafenib or bevacizumab. They did not find any statistically significant difference in the number of reoperation, thromboembolic or cardiovascular complications, infections or abnormal postoperative wound healing when compared to the control group of 58 patients. The type of medicine used did not influence the presence and the type of complications. However, the therapy with bevacizumab cannot last more than 4 weeks before nephrectomy and with sorafenib and sunitinib more than one day, due to different half life times of these medicinal products [46].

A spectacular case of applying TMT before a surgical procedure was described by Karakiewicz. A 75-year-old woman with the renal tumour

**Table 1.**

| Patients | | First choice medicinal products | Alternative treatment |
|---|---|---|---|
| I choice | Low or moderate risk | Sunitinib<br>Bevacizumab + INFα | HD IL-2<br>Sorafenib<br>Clinical trials<br>Observation |
| | High risk | Temsirolimus | Sunitinib<br>Clinical trials |
| II choice / resistance | Cytokines | Sorafenib | Sunitinib<br>Bevacizumab + INFα |
| | VEGF-tyrosine<br>kinase inhibitors mTOR | Everolimus<br>Clinical trials | |

diameter of 11 cm and a neoplastic thrombus reaching the right heart atrium refused to agree on a surgery due to the concerns about sternotomy and cardiopulmonary bypass. Following two sunitib cycles the tumour decreased its diameter to 8 cm and the thrombus in the inferior vena cava underwent involution and regressed to the level below the hepatic vessels, which made it possible to perform a simple surgical procedure using the transperitoneal access [47].

As a result of such experiments, nowadays several clinical trials are being performed in order to assess the role of TMT before nephrectomy [48].

Despite the fact that during the initial era of using TMT in mRCC the role of cytoreductive nephrectomy was not clear, more and more frequently it is thought that its performance will increase the efficacy of the subsequent targeted therapy. We know more and more in the field of using new agents in case of individual patients. Sunitinib and bevacizumab are active in all prognostic groups, whereas temsirolimus has the best properties in high-risk patients, especially in case of neoplasms other than typical clear cell cancer. Better responses to treatment are observed in patients with the VHL gene mutation (48%) when compared to those without this mutation (28%) [49].

An excellent example of possibilities created by TMT in post-nephrectomy patients is a case described at the end of 2007 in *European Urology*. A 69-year-old patient with bilateral renal cancer with metastasis to the humeral bone and the pathological fracture of the femoral bone, in a general poor condition (ECOG 3, pain scale 3), as a result of immunotherapy failure was the subject of the left-side nephrectomy, a tumour removal from the right kidney, a metastasis removal and femoral stabilization and a radiation therapy to the humeral bone. After the procedures no adverse effects were observed and the patient was treated with oral sorafenib at the dose of 400 mg/day. After one year no local progression and no metastasis progression was observed and his general condition significantly improved (ECOG 1, pain scale 1) [50].

Based on clinical experience obtained so far and preliminary clinical observations on the way the order of using TMT medicinal products were determined [51] (Tab. I).

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