Postępy Nauk Medycznych, t. XXV, nr 4, 2012

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Surgical treatment of renal cell carcinoma

Leczenie chirurgiczne chorych na raka nerki

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S u m m a r y

Renal Cell Carcinoma (RCC) derives from various parts of the nephron. The incidence of RCC increases by an average of 2% per year and accounts for 2% to 3% of all adult malignant neoplasms. The implementation of ultrasonography and computed tomography increased the number of fortuitous diagnoses of RCCs which are called Incidental Renal Tumours (IRT). Such tumours are usually smaller than symptomatic ones. Surgical treatment is the best option for the primary tumour. The type of surgical treatment depends of the stage of the tumour. However, the technique of surgical treatment has changed recently. The trend is to decrease the extent and invasiveness of surgery without affecting the oncological safety in patients with localized RCC. On the other hand there is indication for aggressive treatment in patients with locally advanced disease. Tumour nephrectomy is also recommended for metastatic RCC patients with good performance status when combined with IFN – alpha. Complete removal of metastatic lesions or isolated local recurrences after partial nephrectomy or radical nephrectomy contribute to an improvement of clinical prognosis.

Key words: renal cell carcinoma, radical nephrectomy, partial nephrectomy

S t r e s z c z e n i e

Rak nerkowokomórkowy (RCC – *renal cell carcinoma*) powstaje zwykle z komórek nabłonka proksymalnych kanalików krętych nefronu. RCCs stanowią nie mniej niż 3% wszystkich nowotworów złośliwych, a zapadalność na ten nowotwór zwiększa się w Europie o 2% rocznie. Od czasu rozpowszechnienia ultrasonografii i tomografii komputerowej zwiększyła się liczba chorych, u których guzy nerki rozpoznaje się przypadkowo u osób, u których wspomniane badania wykonywane są z innych powodów niż „urologiczne". Guzy rozpoznane przypadkowo (IRT – *incidental renal tumors*), zwane także „guzami radiologicznymi", są zwykle mniejsze od guzów „objawowych". Jedyną metodą pierwotnego leczenia RCCs jest leczenie chirurgiczne, przy czym zakres i rodzaj operacji zależą głównie od stopnia zaawansowania raka. Zasady leczenia operacyjnego chorych na RCC uległy w ostatnich latach istotnym zmianom. Z jednej strony polegają one na ograniczeniu inwazyjności i zakresu operacji u chorych, u których rozpoznaje się guz ograniczony do nerki, aczkolwiek bez zmniejszenia jej skuteczności onkologicznej, z drugiej natomiast na możliwie jak najbardziej agresywnym leczeniu operacyjnym tych chorych, u których nowotwór jest zaawansowany miejscowo. Dynamiczne leczenie operacyjne ma także zastosowanie u chorych, u których stwierdza się współistnienie przerzutów odległych, jeśli stan chorych pozwala na poddanie ich operacji, a także u chorych, u których po częściowym wycięciu nerki wraz z guzem lub po nefrektomii radykalnej dochodzi do wznowy miejscowej nowotworu lub do przerzutów odległych, które można wyciąć.

Słowa kluczowe: rak nerkowokomórkowy, nefrektomia radykalna, częściowa resekcja nerki

In 2009, the incidence of malignant tumours arising from the renal parenchyma in Poland is estimated to have been 14.8/100 000 in men and 9.5/100 000 in women, while the associated death rates were 8.4/100 000 and 5.0/100 000, respectively (1). Among renal tumours, the dominating renal cell carcinoma (RCC) arises from the proximal canaliculi of the nephron. RCCs comprise at least 3% of all malignant neoplasms (2), while their incidence in Europe grows annually by 2% (3). RCC occurs 1.5-2 times more frequently in men compared to women (4), and the incidence rises in the sixth and seventh decades of life (5). The main risk factors of RCC are tobacco smoking, obesity and arterial hypertension (6, 7). In the majority of patients, RCC is a sporadic tumour, with only 2-3% occurring in a familial background (7).

"Renal cell carcinoma" is a broad term. It encompasses several histologically dissimilar tumours. The one with the highest incidence is clear cell carcinoma (CCC), which makes up 70-80% of all RCCs. The remaining types are papillary cancer (10-15%), chromophobic cancer (3-5%) and an exceptionally malig-

nant cancer arising from the collecting duct epithelium (collecting duct carcinoma), also known as Bellini's tumour (< 1 %) (8).

The signs and symptoms associated with solid renal tumours are not characteristic. The main ones include pain, haematuria, and a palpable mass in the kidney region, collectively known as Israel's triad. Tumours found when diagnostic workup was induced by symptoms are usually advanced. Ever since ultrasound and computed tomography imaging became widely available, there is a growing number of cases identified accidentally by studies performed for "non-urological" indications. Incidental renal tumours (IRT), also called "imaging tumours", are usually smaller than "symptomatic" tumours. The proportion of fortuitously diagnosed tumours in the total number of diagnosed renal tumours is currently approx. 60% (9,10).

The only method of primary treatment of RCC is surgery, while the type and scope of the operation depend chiefly on the disease stage. The grading of the cancer based on a four-grade Fuhrman scale (11) can be determined after tumour excision, since percutaneous lesion biopsy is not deemed to be a part of standard preoperative management. The latter is only applied when the tumour is to be removed by a minimally invasive method executed through thermal ablation.

Less advanced stages and smaller sizes of RCCs at the time of diagnosis as well as a better understanding of the biology of these tumours has encouraged the search for surgical methods that would be less invasive and more limited in scope compared to the classic radical nephrectomy (RN), which has been the mainstay of treatment. Currently, in cases with a favourable anatomical location of the tumour, which measures no more than 7 cm in its largest diameter, nephron-sparing surgery is advocated (NSS).

PARTIAL NEPHRECTOMY

The pioneer of partial nephrectomy (PN), also known as kidney resection, is Vincent Czerny, who performed a renal parenchyma-sparing operation in 1887. However, this method was not broadly adopted due to numerous complications. Currently, PN is recommended for tumours measuring up to 4 cm in diameter (cT1a) and is a method of choice for tumours measuring between 4 and 7 cm, which are limited to the kidney (cT1b), provided that it is technically feasible (12-24). The occurrence of major complications, which were reported earlier, has been greatly reduced by the advent of new techniques, devices and materials, however, the risk of their emergence should not be ignored. They can include secondary bleeding from the resected kidney, and urinary or arterio-venous fistulas, which may lead to serious haematuria. The fundamental advantage of PN is the preservation of the unaffected part of the kidney. This markedly reduces the risk of chronic renal failure, which may emerge with varied delay following total nephrectomy, especially in patients with diabetes, atherosclerosis or arterial hypertension (25). According to some authors, the quality of life of patients subjected to PN is superior to that of patients treated by radical nephrectomy (26, 27). Moreover, the execution of surgery with a short period of renal ischaemia usually does not impair renal function (28).

Until recently, the indications for PN were limited to the so-called absolute kind and included tumours developing in an anatomically or functionally single kidney (i.e. absence of the contralateral kidney or failure or complete lack of function of the contralateral kidney), as well as a bilateral RCC. Currently, these have been broadened to include relative indications, which regard patients with a risk of future failure of the contralateral kidney; or with a genetic defect, which increases the risk of renal tumours developing in the future, as in syndromes like von Hippel-Lindau, hereditary papillary RCC, familial leiomyomatosis, Birt-Hogg-Dubé (29, 30); as well as elective indications, such as the technical feasibility and safety of PN in patients, whose contralateral kidney is intact (12).

Partial nephrectomy can involve the resection of the inferior, superior, or even central fragment of the kidney, which contains the tumour, together with a margin of macroscopically unaltered renal parenchyma (a margin of 1 mm is sufficient). It is performed retroperitoneally via lumbotomy (open surgery) or, with increasing frequency, by laparoscopy or retroperitoneoscopy (endoscopic surgery without opening of the peritoneal cavity). Surgery is performed in conditions of ischaemia achieved after clamping the major vessels of the renal pedicle, or preferably, if possible, the selective clamping of vessels supplying the resected fragment of the kidney. The duration of ischaemia is critically important for the later function of the resected kidney. In the case of so-called "warm ischaemia", its duration should not exceed 20 minutes (31). On the other hand, if "cold ischaemia" is applied by packing the kidney with sterile crushed ice, its duration can be safely extended up to 60 minutes (32). PN reduces the risk of renal failure. McKiernan et al. performed a 10-year prospective study, which enrolled 290 patients with RCC measuring up to 4 cm, in whom the contralateral kidney was normal. The study compared 173 patients treated by radical nephrectomy (RN) with a group of 117 patients treated by PN. The former group had a higher risk of developing chronic renal failure, compared to the latter group (33). Dash et al. performed a prospective study, which followed 196 subjects with RCC measuring 4-7 cm, in whom either RN or PN was performed. They found that 3 months post-op, creatinine levels were significantly lower in patients treated with PN (20). Nevertheless, the most important goal regarding PN is to achieve long-term oncological outcomes that match classic radical nephrectomy. Lee et al. compared PN and RN outcomes in patients with RCC tumours measuring < 4 cm finding that 5-year survival without local recurrence is comparable for both types of treatment (34). Many other papers have reported similar outcomes of PN and RN in

patients operated for tumours measuring < 7 cm (13, 17, 18, 20, 22, 24).

The alternative to and open PN is endoscopic surgery (LPN – laparoscopic partial nephrectomy). Recently, LPN has been gaining increasing popularity and specialised centres use it to treat the majority of patients operated for small RCCs. The choice of endoscopic approach to the kidney depends on the tumour's location. In the majority of cases, surgery is performed transperitoneally. If the tumour is located on the posterior or postero-medial aspect of the kidney, it can be accessed by retroperitoneal approach (retroperitoneoscopy) although this involves technical difficulties due to a limited surgical field (35). With LPN, the ischaemic kidney is not cooled. Therefore, the planning of LPN must consider whether the fundamental part of the procedure can be performed during an appropriately short ischaemic period. Oncological outcomes of LPN in an excellent nephro-oncology centre are similar to those achieved with open PN (36) but it should be borne in mind that LPN requires technical skill and a significant experience in laparoscopy. Authors from the above-mentioned centre have recently presented an interesting report on the outcomes of LPN performed in 1,000 patients with RCC operated over 9 years. The patients were split into 3 groups by time the period in which they were treated. Comparing the group treated in the earliest period with the two other groups, the authors found that the recently excised tumours were more challenging for the surgeons (they were larger, measuring > 4 cm and were located closer to the vascular pedicle of the kidney). This points to a significant impact of experience on the safety and effectiveness of the surgery. Despite being a more technically difficult group, these patients had a shorter time of warm ischaemia during surgery and less complications. The proportion of positive surgical margins in that group was only 0.6%. The 5-year recurrence-free survival for the three groups was 90%, 99% and 97%, respectively (37). The comparison of open PN with LPN in a group of 1,800 patients showed that the laparoscopic surgery took less time (200 min vs. 258 min – p < 0.0001), it involved less blood loss (300 ml vs. 376 ml – p. < 0,0001), however, the duration of warm ischaemia was longer (31 min vs. 20 min – p. < 0,0001), and the proportions of patients developing "urological" complications, requiring further surgery as a result or suffering a post-op bleed were higher. The percentages were 9.2% vs. 5.0% (p < 0.006), 7.0% vs. 3.5% (p < 0.0001) and 4.2% vs. 1.6% (p < 0.0002), respectively (38). Nevertheless, the risk-benefit ratio suggests that LPN applied to treat well-selected patients is more attractive for them compared to open PN. Hence, the list of indications for LPN is gradually expanded. Initially the procedure was applied for small tumours (cT1a), while currently, it is used for tumours measuring 4-7 cm (cT1b), and even tumours that are larger (cT2) (39). At the same time, it is underscored that if difficulties emerge during LPN, the procedure should be converted to open access and completed with the kidney preserved rather than continued as LPN with kidney excised (40). The latest technique used for endoscopic PN is robotic partial nephrectomy (RPN). The outcomes in patients treated that way seem promising (12).

Many papers confirm that the oncological outcomes in patients treated by PN vs. RN are comparable. Moreover, they point to the lower risk renal failure in patients with preserved renal parenchyma. However, none of these studies was randomised. A recent report discusses the first randomised study to compare the oncological outcome in 541 subjects who underwent PN (n=268) or RN (n=273), for tumours measuring no more than 5 cm in diameter. Surprisingly, a slightly higher proportion of 10-year survival was found in the RN group, compared to PN (79.4% vs. 75.2%, statistically insignificant). Nevertheless, both methods offered very good oncologic outcomes (41).

RADICAL NEPHRECTOMY

The first nephtectomy for a renal tumour was performed by Gustav Simon in 1869. Until the mid-1900s, the surgery was executed via a retroperitoneal approach (lumbotomy), because at the time, laparotomy carried a high risk of peritonitis. As of 1950, the transperitoneal approach gained popularity. In 1969, Robson presented his concept of the scope of radical nephrectomy (RN), which was accepted for many years. It involved the laparotomy approach, removal of the kidney with its fatty capsule, the suprarenal gland, regional lymph-nodes and both laminae of Gerota's fascia (42). As oncologic follow-up data of this broad radical nephrectomy were collected, and as the numbers of patients with early-stage disease grew, the range of RN was revisited. Gradually, the indications for lymphadenectomy and adrenalectomy, as part of RN, became limited. Currently, adrenalectomy is performed only where there is direct renal tumour spread to the adrenal gland or if the gland is believed to harbour metastases. Regional lymphadenectomy is performed whenever the intraoperative evaluation and/or preoperative diagnostics are consistent with lymphadenopathy. This followed the finding of evidence that a routine performance of an extensive lymphadenectomy in the absence of macroscopic lesions in the lymph nodes does not improve cancer-specific mortality. The excision of macroscopically unchanged regional lymph nodes is meaningful for the pathological staging of RCC. It must be underscored that the presence of metastases in lymph nodes is one of the most important predictors of poor risk in RCC patients without distant metastases.

Earlier, in the case of very large tumours, especially ones that created a venous thrombus of malignant tissue, the renal artery would be embolised prior to surgery in order to limit bleeding during the operation. For over a decade, thanks to the development of surgical technique, this solution is no longer advocated. How-

ever, embolization remains indicated, when reccurent haematuria occurs in connection with a renal tumour, which cannot be treated with RN (12).

Open RN is indicated for a renal tumour that infiltrates the perirenal fatty tissue, the adrenal gland, the renal vein and/or the vena cava as well as neighbouring structures (43). If RN is performed for a large tumour, its success depends on an unrestricted access to the kidney and its vascular pedicle. This is provided by laparotomy, which allows for expedited ligation and division of the renal artery. The choice of the surgical incision (Chevron, hemi-Chevron or even an abdomino-phreno-thoracic incision) depends on the size and location of the tumour as well as the urologist's preferences. In some patients, access via lumbotomy is sufficient, although the majority could be successfully treated with laparoscopic RN (LRN). The risk of complications related to RN is high, however, it depends on the size and stage of the tumour and the patient's preoperative condition. Van Poppel *et al*., in a prospective randomised clinical trial (comparison of open RN with LRN in patients with RCC measuring < 5 cm), found that the loss of < 500 ml or > 1000 ml of blood during surgery occurred in 96 % and 1.2 %, respectively, while damage to the pleura and spleen during open RN was noted in 9.3 % and 0.4 %, respectively (44).

The first LRN was performed by Clayman in 1990, in Washington. Currently, this procedure is the standard of care in patients with RCC clinically staged as locally advanced, i.e. cT2 (tumours > 7 cm in diameter, limited to the kidney) as well as smaller tumours, if PN is not feasible (12). Nonetheless, in specialised centres, LRN is performed for large, locally advanced tumours (cT > 2), and even tumours that have spread into the renal vein, and in debulking treatment (45). The procedure can be performed through a trans- or retroperitoneal approach. Two prospective studies have shown that the time needed to perform retroperitoneal LRN is shorter in comparison to transperitoneal LRN, although the outcomes and complications of the two procedure types turned out to be identical (46, 47).

The comparison of open RN with LRN performed for tumours confined to the kidney has found no significant differences with regard to oncological outcomes (48). Burgess *et al*. performed the first randomised study comparing open RN with LRN. The mean maximum diameter of the tumours was 8 cm. Both groups consisted of 45 patients. No significant differences were found regarding blood loss, mortality, surgery duration, or duration of post-op hospital stay. However, patients operated by laparoscopy suffered less post-op pain and their rehabilitation period was shorter (49). Another prospective study comparing patients operated for stage cT2 RCC by open RN or LRN, found that 5-year survival in either group was identical, whereas the laparoscopy group suffered less blood loss, required less analgesic treatment, had a shorter hospitalisation and rehabilitation time (50).

There is a modification of LRN, which is worth mentioning. This involves surgery that is assisted by the surgeon's hand, which is introduced through a small, air-tight incision in the abdominal integument (H-ALRN – hand-assisted LRN). Matin et al. performed a retrospective analysis of 271 patients operated either by H-ALRN or LRN. They found that with H-ALRN the duration of surgery was shorter but post-op pain intensity was higher and post-op hospital stay was longer (51). Ultimately, it seems that the use of H-ALRN should not be advocated.

On the other hand, great expectations are associated with robotic radical nephrectomy (RRN). Hamal et al., in a prospective comparison of RRN and LRN, found that the results, including oncological outcomes, were similar, although the RRN procedure involved higher costs and took longer to complete. The study found no advantages of RRN compared to LRN (52).

LOCALLY ADVANCED RENAL CANCER

Despite of the increased proportion of small, asymptomatic tumours in the overall number of cases, locally advanced and/or metastatic RCCs continue to be diagnosed. In some patients, the renal vein or the vena cava contain ingrown tumour masses, and/or the tumour has spread to neighbouring organs including lymph nodes. RCCs are also classified as advanced in patients who sustain local tumour recurrence following prior surgical treatment (53).

In about 10% of RCC patients, the tumour has spread into the lumen of the renal or caval vein, while in 1 % the malignant growth reaches the right atrium (54). Intraluminal tumour growth is best identified and assessed for scope with MRI. Such imaging allows for the planning of surgical tactics (55). The only treatment option for patients with a venous tumour thrombus is the surgical removal of the tumour with the whole venous ingrowth (56). In itself, the presence of the ingrowth is not an independent prognostic factor and post-op survival chiefly depends on the specific characteristics of the primary tumour, less on the size of the ingrowth (57).

If lymph nodes are involved, lymphadenectomy may be therapeutically beneficial. In such cases, lymph node excision improves patient survival and helps identify those who qualify for systemic adjuvant treatment. If distant metastases are present, lymphadenectomy comprises an additional cytoreduction measure (40). Pantuck et al. found that in patients with RCC metastases to the lymph nodes and distant organs, lymphadenectomy and systemic immunotherapy with interleukin 2 prolongs survival by a mean of 5 months compared to patients treated by RN alone (58).

Renal tumours, which infiltrate neighbouring structures without causing distant metastases, are rare and comprise about 1-1.5% of all locally advanced RCC cases (59,60). Capitanio et al. presented a series of 310 patients with T4N0-2 stage RCC, of whom 246 were treated surgically and 64 were treated con-

servatively. The survival of the surgical patients was 48 months, while the symptomatically treated survived only 6 months (61). Overall, patients with RCC tumours, which infiltrate neighbouring structures should undergo a broad nephrectomy with the removal of all involved tissues in one block (40).

SUMMARY

The principles of surgical treatment in patients with RCC have recently undergone significant changes. On the one hand, the invasiveness and the scope of the surgery have been limited in patients diagnosed as having an organ-confined tumour with no loss of oncological effectiveness. On the other hand, highly aggressive surgery is advocated for patients with locally advanced tumours. A dynamic course of surgical management is applicable in patients who are found to have distant metastases, whenever the patient's condition allows for surgery. A similar approach is suggested for patients who, having undergone partial or radical nephrectomy, develop a local recurrence or distant metastases amenable to resection.

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received/otrzymano: 25.01.2012
accepted/zaakceptowano: 29.02.2012

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