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Renal Cell Carcinoma: Clinical Surgery

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1. Introduction

Renal cell cancer is the third most common genitourinary tumour and the seventh most common cancer. It accounts for about 3% of all malignancies. After prostate cancer and bladder cancer it is the third most common urological tumour. Among urological cancers it shows the highest mortality [1]. Its incidence has geographic, ethnic and age differences, however over the last two decades there has been a rising incidence of renal cell carcinoma particularly of early-stage tumours leading to a paradigm shift in the therapeutic management.

An increased risk of disease is described with a positive family history and the following diseases: Von Hippel-Lindau (VHL) syndrome, tuberous sclerosis, polycystic renal degeneration, chronic renal insufficiency, dialysis and condition after renal transplantation, arterial hypertension, adiposity and diabetes mellitus. Other risk factors are drugs (phenacetinabuse, diuretics) and a number of environmental factors such as asbestos, lead, arsenic, cadmium and aromatic hydrocarbon compounds. Previously described as typical triad of flank pain, hematuria and palpable flank tumour (Virchow's triad) is nowadays rarely seen in far advanced tumour stages [2]. The same is true for B symptoms, which is usually a sign of metastasis already existing.

The increased availability and advances in diagnostic imaging (ultrasound, computed tomography and magnetic resonance imaging) (Fig.1) with an increase in the incidental diagnosis of renal tumours [3] and an improved understanding of the basic biology of renal cell carcinoma, led in recent years to an improvement in survival rates, however, in approximately one third of all patients when diagnosed there are metastasis [4] (mainly locoregional lymph nodes, lung, skeletal system, brain and liver) with a 5-year survival rate of less than 5%.

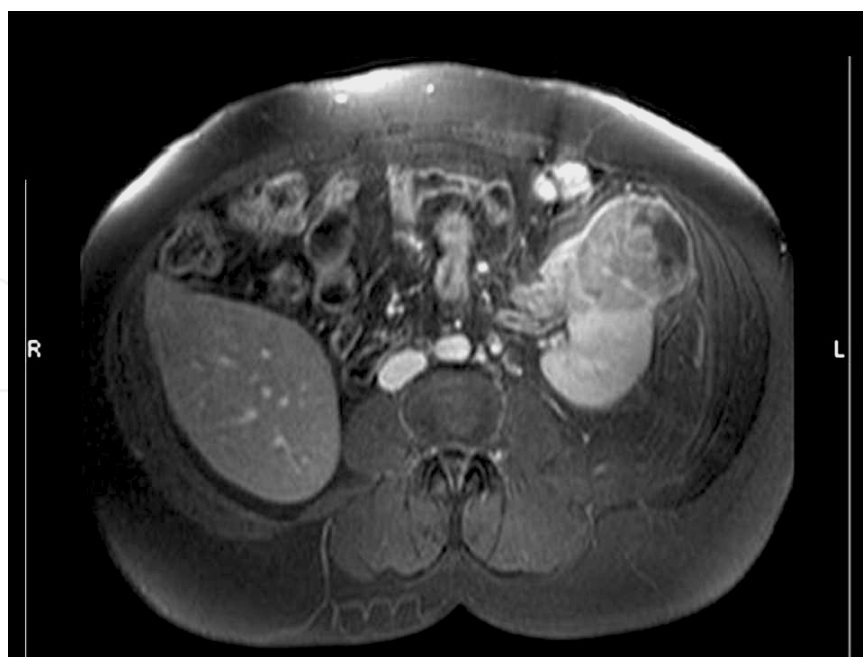


Figure 1. Abdominal magnetic resonance imaging (MRI): Renal tumour of the left upper pole: suspected renal cell carcinoma

Furthermore a third of patients that have been treated for a locally limited renal cell carcinoma (Fig. 2a,b,c) in the course show recurrence or metastasis. A tool to assess the risk of metastasis after a nephrectomy is the Mayo Scoring System (Tab.1).

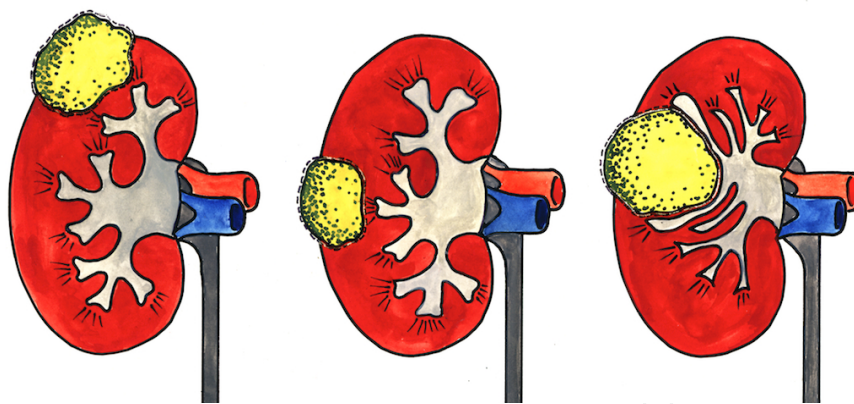


Figure 2. (a) Locally limited renal cell carcinoma of the upper pole; (b) Locally limited renal cell carcinoma in the lateral convexity; (c) Locally limited renal cell carcinoma with suppression of pelvicaliceal system

Of crucial prognostic importance is therefore the question of the presence of a locally defined or metastatic renal cell carcinoma with a median survival of about 50% one year after the diagnosis of metastasis. This underlines the importance of early detection. Because of lack of radiosensitivity and chemosensitivity of renal cell carcinoma surgical treatment (nephrectomy or partial nephrectomy) remains the only curative treatment option for locally confined tumours. Partial nephrectomy/nephron-sparing nephrectomy, minimally invasive

techniques, energy ablative techniques and active surveillance have been progressively used as an alternative option towards open radical nephrectomy which was the historical gold standard approach. Partial nephrectomy has demonstrated an equivalent oncologic outcome with an improved renal function and reduction of cardiovascular events. Over the past years laparoscopic and robot-assisted procedures gained in importance showing similar results in terms of oncologic control.

Feature	Score		
Pathologic T stage^a			
T1a	0		
T1b	2		
T2	3		
T3-4	4		
Regional lymph node status^a			
pNx/pN0	0		
pN1-2	2		
Nuclear grading			
G1-2	0		
G3	1		
G4	3		
Tumour size			
< 10cm	0		
> 10cm	1		
Histologic tumour necrosis			
No	0		
Yes	1		
^a According to the 2002 American Joint Committee in Cancer staging system			
Risk group	Score	Estimated metastasis-free survival after 3 years	Estimated metastasis-free survival after 10 years
Low risk	0-2	98%	92.5%
Intermediate risk	3-5	80%	64%
High risk	>6	37%	24%

Table 1. Mayo-Scoring-System (Leibovich BC, Blute ML, Cheville JC et al. Prediction of progression after radical nephrectomy for patients with clear cell carcinoma: a stratification tool for prospective clinical trials. Cancer 2003; 97:1663-1671)

In metastatic renal cell carcinoma the surgical removal of the primary tumour in the sense of reducing the tumour burden and metastasis respectively for palliative reasons or as part of a combined tumour therapy may be required. Through such combined therapy concepts in some cases significant extensions of survival times can be achieved. Integration of surgery and systemic therapy is essential in the treatment of metastatic renal cell carcinoma. The earliest possible diagnosis and careful selection of surgical procedure for each patient is the basis with the goal of curation and the best possible quality of life.

2. Therapy for localized renal cell carcinoma

For a long time radical nephrectomy was the standard treatment for normal contralateral renal function and absence of metastasis. The first successful nephrectomy took place on 2 August 1869 by the Heidelberg surgeon Gustav Simon. In the late 1960s the classic radical nephrectomy with the removal of kidney and adrenal gland within Gerota's fascia, including removal of the perirenal adipose capsule, of the proximal ureter and the ipsilateral lymph nodes with a 5-year overall survival rate of 66% for organ-confined tumours was described by Robson [5], (Tab. 2 and 3).

TNM stage ^a	5-year cancer-specific survival rate
T1	83%
T2	57%
T3	42%
T4	28%

^a According to the 1997 TNM system (AJCC)

Table 2. 5-year cancer-specific survival after nephrectomy/partial nephrectomy as a function of the 1997 TNM stage (AJCC) (Tsui KH, Shvarts O, Smith RB et al. Prognostic indicators for renal cell carcinoma: a multivariate analysis of 643 patients using the revised 1997 TNM staging criteria. J Urol 2000; 163:1090-1095)

Robson stage	5-year survival rate
I	75%
II	63%
III	38%
IV	11%

Table 3. 5-year survival rate after nephrectomy, depending on the Robson stage (Guinan PD, Vogelzang NJ, Fremgen AM et al. Renal cell carcinoma: tumour size, stage and survival. Members of the Cancer Incidence and End Results Committee. J Urol 1995; 153:901-903)

In the open surgical nephrectomy, the choice of the surgical approach should be taken depending on the location and size of the tumour as well as the experience of the surgeon. Basically the following methods are available: primary retroperitoneal approach to the lumbar

by use of sub- or intercostal incision, transabdominal or thoracoabdominal. There seems to be no difference in terms of oncological results.

The laparoscopic nephrectomy (transperitoneal, retroperitoneal or “hand-assisted”) is another method. This frequently surgical technique is especially used in T1 (up to 7cm tumour size) and T2 tumours (tumour larger 7cm, limited to the kidney). The surgical steps are basically those of the conventional open surgical approach. Comparable oncological results with open nephrectomy are seen in large tumours as well. [6].

The advantages of laparoscopic nephrectomy are reduction in postoperative pain symptoms with less pain medication and earlier mobilization. Furthermore faster recovery and better cosmetic results are mentioned. The frequently discussed risk of implantation metastasis in the abdominal puncture trocar has only been reported casuistic. A tumour cell spread by the applied pneumoperitoneum is not known.

The third and most recent method to be mentioned is the robotic-assisted laparoscopic nephrectomy. Major advantages of this method are the three-dimensional view for the surgeon, up to a 10-fold magnification of the surgical field, a suppression of tremor of the surgeon’s hands through a so-called tremor filter and the free movement of the instruments which are equivalent to those of the human wrist (so-called “endo wrist instruments”). Robot-assisted two approaches are possible: transperitoneal and retroperitoneal approach.

Specific complications of the nephrectomy, regardless of the surgical approach are mainly injuries to neighbouring organs in particular pleural lesions, spleen, pancreas and duodenal injuries and bleeding complications. Frequently occurring transient postoperative creatinine level elevation usually shows a rapid compensation with a healthy contralateral kidney.

As mentioned earlier, in recent years by increasing the availability and development of radiological examination techniques, there has been an increase of incidentally detected T1 renal tumours. After the first partial nephrectomy was done in 1887 by Vincenz Czerny at the University of Heidelberg, it is established today for tumours ≤ 4cm as the gold standard as well as for tumours up to 7cm in selected patients [7]. Becker et al. showed with the nephrectomy comparable oncologic results and low complication rates in tumours > 4cm [8] or ≥ 7cm [9] in selected patients. The 5- year tumour-free survival in this process is over 95%, the rate of local recurrence is < 1% [10], even though interestingly in section statistics up to 20% multifocal tumours are detected. A reason for this may lie in a different biological behaviour of tumours with a different aggressiveness. Whether the multifocal renal cell carcinoma is a primary multifocal tumour initiation or a secondary intrarenal metastasis is currently unknown. Careful preoperative imaging therefore is essential. Aim of the organ-preserving technique is a complete resection of the tumour with an optimal preserved renal function.

Tumour size	5-year cancer specific survival rate	10-year cancer specific survival rate
< 4cm (T1a)	96%	90%
> 4cm (T1b)	86%	66%

Table 4. 5-year and 10-year cancer-specific survival after partial nephrectomy depending on tumour size (Hafez KS, Fergany AF, Novick AC. Nephron sparing surgery for localized renal cell carcinoma: impact of tumour size on patient survival, tumour recurrence and TNM staging. J Urol 1999; 162:1930-1933)

Regarding the surgical procedure there is a distinction to be made, especially depending on tumour size and –localization between a number of techniques such as local tumour resection (Fig. 3 and 4) in which a safe distance of a few millimeters should be respected, the poleresection or segmentresection, the heminephrectomy up to nephrectomy with extracorporeal workbench tumour resection and subsequent autotransplantation of the kidney into the iliac fossa at very large central tumours and imperative implications.

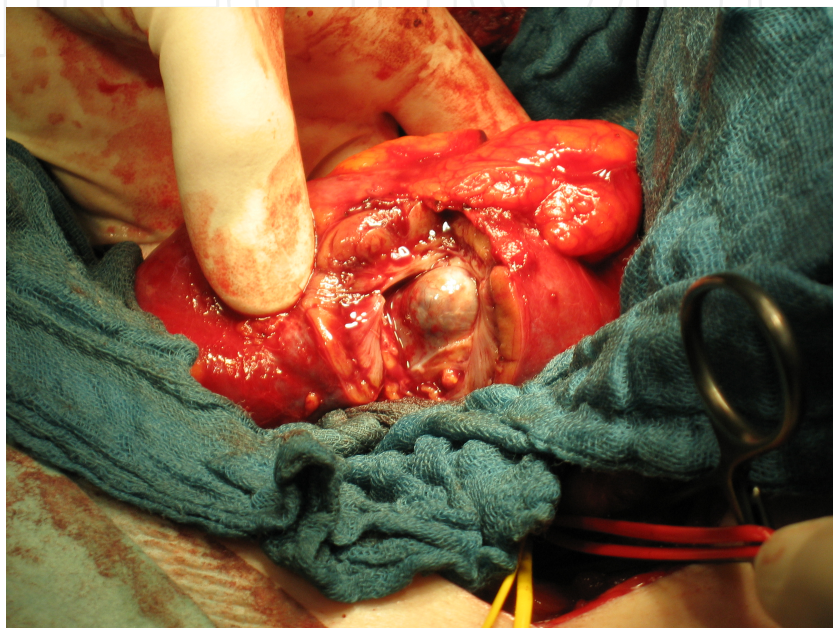


Figure 3. Local resection of a renal tumour

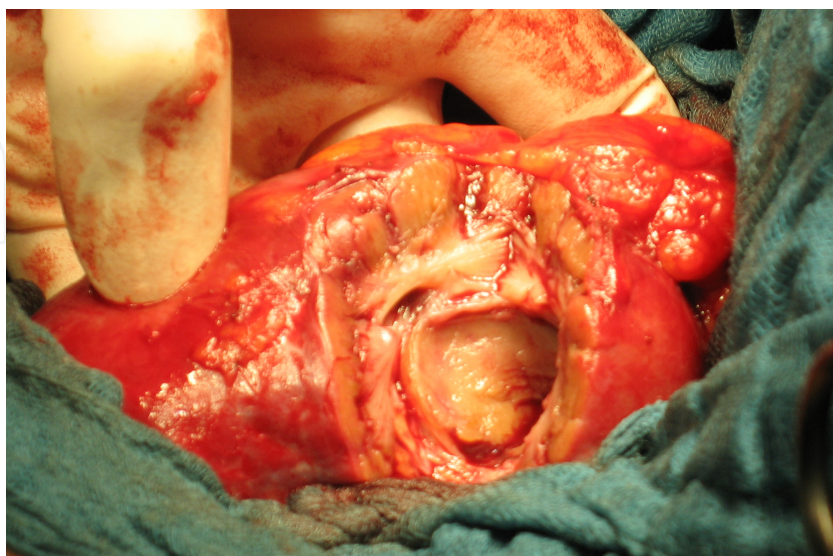


Figure 4. Local resection of a renal tumour (tumour has already been removed)

When doing a partial nephrectomy a differentiation is made between the most common existing elective indications for peripheral small unilateral tumours (≤ 4 cm, equivalent to a tumour stage pT1a or in specialized centres tumours up to 7 cm diameter, equivalent to a tumour stage pT1b) in a healthy contralateral kidney, the relative indication in impaired renal function or pre-existing renal insufficiency, synchronous bilateral organ involvement and genetic predisposition for multiple tumours as well as the absolute/imperative indication of an existing solitary kidney (anatomic or functional). Furthermore with this surgical procedure a distinction is made between a partial nephrectomy without ischemia, in a warm ischemia in an anticipated ischemic time of < 20 minutes by disconnection of the renal artery and the renal vein at the renal hilum and partial nephrectomy in cold ischemia (cooling kidney down to $15-20^{\circ}\text{C}$) in an anticipated ischemic time of > 20 minutes by the application of 4°C cold perfusion solution through the renal artery or by surrounding the organ with ice. Additionally the implementation of so-called renoprotective measures can follow. These include intraoperative administration of an ACE inhibitor for the reduction of post-ischemic vascular resistance and of mannitol 5% 5-10 minutes before clamping and reopening of the renal artery, with the aim of reducing the intracellular edema and increasing the diuresis and as needed heparin for the prevention of renal artery thrombosis.

Retrospective studies have shown a benefit for partial nephrectomy compared to a nephrectomy with T1a tumours, which can be explained mainly by improved renal function with reduction of cardiovascular events [11]. Also Go et al. have demonstrated in a large prospective study that the loss of renal function is associated with an increase in cardiovascular mortality and shorter life expectancy [12].

Similar to the nephrectomy the partial nephrectomy is an established laparoscopic procedure performed for the first time in 1993 by Winfield and Clayman. When performing a laparoscopic partial nephrectomy the preparation of the renal hilum takes place after colon mobilization, identification of the ureter as well as the vena cava. Subsequently the excision of the tumour with scissors usually in warm, rarely performed in cold ischemia takes place. After attending to the tumour bed with sutures and/or hemostyptics follows an adaptation of the remaining parenchyma by using a continuous suture. Last is the recovery of the surgical specimen in the extraction bag. Similar to the laparoscopic nephrectomy this method shows the advantages of a lower mean blood loss, lower analgetic requirements postoperatively as well as shorter convalescence and hospitalisation times however at a heightened risk of postoperative hemorrhage and usually prolonged ischemic times. Regarding the oncological and functional outcomes there are comparable results between open and laparoscopic partial nephrectomy [13].

Similar to the robot-assisted nephrectomy, the laparoscopic robot-assisted procedure also used with the nephron-sparing surgery represents another possibility of minimally invasive surgery. After the introduction of the method in 2004 at first primarily small peripherally located tumours were considered to be particularly suitable for this technique [14]. With increasing experience the indication was extended to more complex tumours. Excellent results of robot-assisted surgical technique in relation to more complex lesions, such as centrally located renal tumours or directly at the renal hilum neighbouring tumours are described [15].

The three-dimensional view and the magnification of the surgical field has the advantage of a more precise excision of the tumour. In addition, the robotic-assisted partial nephrectomy has a much shorter learning curve and shorter ischemic times than the conventional laparoscopic procedure. A special technique for the reduction of the ischemic time is the so-called “sliding clip renorrhaphy” during renal reconstruction. In this technique a continuous absorbable suture with clips for securing both ends is used. These clips can then be moved along the sutures and this way the renal defect can be closed. With this the warm ischemic time could be reduced significantly [16]. Another method through which the warm ischemic time can be reduced is the early removal of the vascular clamps, so-called “early unclamping”. Few sutures are used in order to avoid more bleeding before removal of the vascular clamps, to then care for the remaining still bleeding vessels without ischemia [17]. Also the selective disconnection of the tumour supplying segmental arteries can reduce the ischemic time, but at an increased risk of injury during preparation of the hilar vessels. While early experience with robotic partial nephrectomy have demonstrated no advantages of this surgical method compared to the conventional laparoscopic approach [14], recent work showed equivalent results in terms of oncologic outcomes for benefits such as a lower intraoperative blood loss and shorter warm ischemic times compared to those of conventional laparoscopy. A multicenter study showed comparable results in terms of the following parameters: duration of surgery (laparoscopic partial nephrectomy 174 min vs. robotic-assisted partial nephrectomy 189 min), cavity opening (54 vs. 47%), R1-status (3.9 vs. 1%) and postoperative complications (10.2 vs. 8.6%) [18].

The criticism of the robot-assisted partial nephrectomy are essentially two:

1. Dependency of the surgeon on the assistant during surgery
2. High purchase and maintenance costs for the surgical robot

The surgeon sits at the console and does not stand at the operating table, therefore communication between him and his assistant surgeon is extremely important, especially during critical surgical steps such as the setting of vascular clamps and clips.

Comparative data on the ratio of the costs for an open, conventional laparoscopic and robotic partial nephrectomy are limited. Mir et al. compared the costs of open, laparoscopic and robotic partial nephrectomy in 33 patients. They showed laparoscopic partial nephrectomy to be more cost effective than open partial nephrectomy due to a shorter hospital stay. Moreover they demonstrated that the laparoscopic procedure is more cost effective compared the robotic approach because of lower instrumentation costs [19]. Studies on robotic-assisted cystectomy and prostatectomy however showed significantly higher costs of robotic surgeries [20, 21].

In summary it can be stated that the preservation of functioning renal parenchyma and therefore a reduction in renal dysfunction is a clear advantage of partial nephrectomy compared to nephrectomy. The laparoscopic as well as the robotic-assisted partial nephrectomy in studies with small numbers of patients (Fig. 5 and 6) represent a safe alternative with low morbidity for selected patients at appropriate centres with special expertise. Specific complications with a partial nephrectomy, regardless which type of surgical approach, most likely

are postoperative hemorrhage and extravasation of urine (urinoma) which can be treated by a transient ureter splint or nephrostomy. These complications occur more frequently in patients with imperative indications than in elective indications.

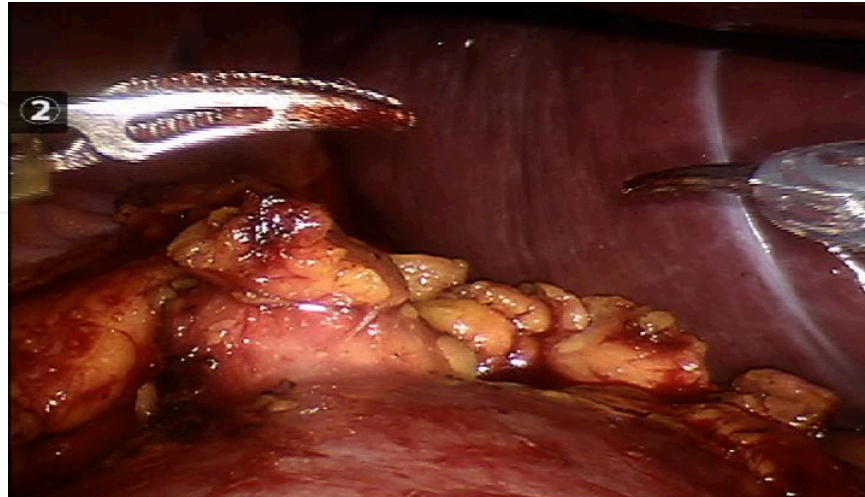


Figure 5. Robot-assisted laparoscopic partial nephrectomy

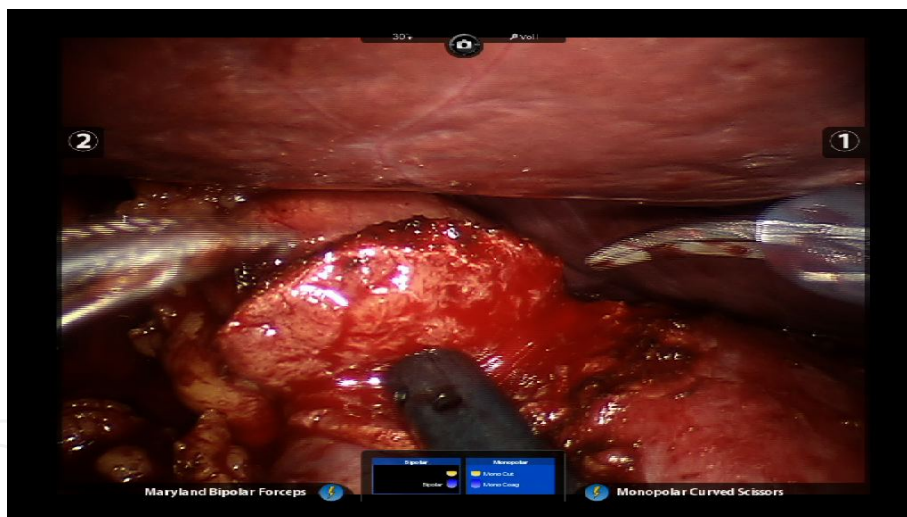


Figure 6. Robot-assisted laparoscopic partial nephrectomy (during enucleation of the tumour)

3. Surgical features

Adrenalectomy: After the ipsilateral adrenalectomy over a long period of time on the grounds of radicalism was seen regardless of size and extent of the renal tumour as essential, the indication for performing a routine adrenalectomy during a nephrectomy is not a standard these days. As an important aspect the fact is that an adrenal tumour rarely grows

per continuitatem, but most likely it is a sign of haematogenous metastasis with poor prognosis. On the other side the safety of imaging by using CT is at 97%. The likelihood of adrenal metastasis in small T1 tumours is less than 1% [22]. After Robson in the 1960s described a survival benefit for patients that had a standard adrenalectomy [5], were not detected in subsequent studies [23]. The indication for removal of the adrenal gland is given in case of a very large renal tumour, an upper pole tumour and a suspected metastasis in the adrenal gland (preoperative imaging studies or intraoperative finding).

Lymphadenectomy: For a long time conducting a regional lymphadenectomy (paraaortic/paracaval) was an important part of the nephrectomy. The improved survival times when performing a lymphadenectomy were proven in part by the work of Robson. Especially in view of conversion of patients to small asymptomatic renal tumours, the removal of the ipsilateral lymph nodes is critical discussed similarly to the adrenalectomy. Though diagnostically useful, the value of the hilar ipsilateral lymphadenectomy due to few studies regarding their prognostic significance remains unclear. The therapeutic benefit has not been proven. Interestingly in autopsy studies it was proven that the result of lymph node metastasis usually shows an occult distant metastasis.

Renal vein thrombus and vena cava thrombus: A special feature of the renal cell carcinoma is the tendency of ingrowth into the venous system. A tumour thrombus in the vena cava is found in about 4-10% of all cases, a tumour thrombus with growth up into the right atrium in 0.4% of all cases. Surgical removal of the thrombus should be sought in principle. The surgical procedure must be scheduled in this case depending on the extent of the thrombus.

Level I: Infiltration of the renal vein

Level II: Infiltration of the infrahepatic vena cava

Level III: Infiltration of the intrahepatic vena cava

Level IV: Infiltration of the suprahepatic vena cava

Renal vein thrombi are removed by clamping the junction into the vena cava, thrombi of the vena cava below the diaphragm by a cavotomy. If there is an expansion beyond the hepatic hilum the use of a heart-lung machine is necessary. If there is an expansion to the right atrium the use of extracorporeal circulation is required. An important aspect in the planning and implementation of these procedures is the interdisciplinary collaboration between urologists and cardiac surgeons. The prognosis of patients with a tumour thrombus after a successfully carried out surgery is not dependent on the size and extent of the thrombus, but the metastasis stage. After thrombectomy in a non-metastatic stage 5-year tumour specific survival rates up to nearly 70% can be achieved [24]. However almost half of all patients with an extensive vena cava thrombus at diagnosis show lymphatic or haematogenous metastasis.

Bilateral renal tumours: The incidence of synchronous bilateral renal tumours is at 1.6-6%. In principle a two-stage procedure is desirable, where initially the smaller and unifocal tumour can be treated in terms of a partial nephrectomy, with the aim to avoid dialysis in case a subsequent contralateral nephrectomy is required.

Local recurrence: The discovery of local recurrence in condition after partial nephrectomy without evidence of systemic metastasis is seen in <3% of all cases. In this case higher local recurrence rates are seen with imperative indications, which may be explained by a greater number of advanced tumours. In principal surgical removal should be made after exclusion of other metastasis.

4. Other techniques

Energy ablative therapy: The energy ablative method is based on tissue destruction by using cold or heat. Especially cryoablation (CA) and radiofrequency ablation (RFA) are to be mentioned. There are percutaneous and laparoscopic techniques available. Essentially the indication for performing the energy ablative method is limited to palliative situations or as an alternative for high-risk patients with small, conveniently located renal tumours. Potential benefits represent mainly the reduced morbidity and the possibility of treating multimorbid patients in an outpatient setting. The problem is, among other things, the increased risk of local recurrence [25].

LESS/NOTES: After establishing laparoscopic and robot-supported methods now further developments of the methodology in terms of a reduction of the required trocars (LESS = Laparoscopic Single Site Surgery) and the use of so-called "natural orifices" (NOTES = Natural Orifice Transluminal Endoscopic Surgery) take place. Concerning this matter so far however there are only casuistics and small case series available.

5. Surgical treatment of metastatic renal cell carcinoma

Given the fact that a third of patients who are suffering from a renal cell carcinoma have a synchronous and another third after curative intent therapy have a metachronous metastasis, the following shows the possibilities and the importance of surgical therapy for metastatic renal cell carcinoma.

Basically in metastatic renal cell carcinoma a distinction must be made between the sole palliative and the cytoreductive nephrectomy. Indication criterias for palliative nephrectomy for example are conservative uncontrolled pain or recurrent bleeding. In symptomatic multimorbid patients with a high surgical risk the possibility of a tumour embolization should be evaluated. Important here is a sufficient analgesic therapy after completion of the procedure, because severe pain is a common local complication. An impact on the survival rates cannot be seen with surgical procedure nor with tumour embolization. In the era of immunotherapy it was shown that cytoreductive nephrectomy followed by immunotherapy opposed to receiving only medical therapy shows significantly better survival rates (7.8 months for interferon vs. 13.6 months for nephrectomy plus interferon) [26]. Whether a nephrectomy in metastatic stage in the post-immunotherapy era is up-to date needs to be

evaluated. Results of prospective randomized trials for example CARMENA study (“Clinical Trial to Assess the Importance of Nephrectomy”) are still pending.

With regard to the surgical treatment of metastasis themselves this indication must be made primarily in response to the location, size and extent of metastasis findings, the symptoms and the overall situation of the affected patients.

Solitary pulmonary filiae should be checked for resectability. Are there only a few (up to three) localized metastasis, then a nephrectomy plus complete resection of metastasis can lead to a significant survival benefit. Basically patients with synchronous pulmonary metastasis have a significant worse prognosis than those with a metachronous metastasis. If it is a disseminated metastasis the initiation of a targeted therapy for (long-term) stabilization of the disease should be discussed with the patient. The basis for this inhibition of tumour growth is a modification of growth signaling inside the tumour cell and the (neo)angiogenesis. Currently seven substances (in different indications) are available: tyrosine kinase inhibitors such as sunitinib, sorafenib, pazopanib and axitinib, antibody-based therapies such as bevacizumab plus interferon-alpha and mTOR (“mamillian target of Rapamycin”) inhibitors as temsirolimus and everolimus. The use of drugs in the adjuvant setting with advanced renal cell carcinoma with a high risk of disease progression is currently being evaluated in clinical trials.

In case of hepatic filiae with a median survival rate of 6-18 months the indication for resection in case of a solitary metastasis with a diameter <5 cm should be evaluated if liver function is intact. It is essential to inform the patient about this procedure’s high morbidity. For non-resectable liver metastasis it is possible to perform a CT-guided percutaneous radiofrequency induced thermal ablation (RITA).

In the detection of brain metastasis a surgical approach is to be discussed especially with the onset of neurological symptoms. The indication for resection of metastasis through stereotactic radiosurgery (GammaKnife, CyberKnife) or radiation therapy is to be weighed individually. When limited in size and number of brain metastasis very good results can be achieved in this case with regard to the local control of metastasis.

An indication for surgery in bone metastasis may present neurological deficits in a myelon compression, pain, and fracture risk in instability of the bone. However survival time extensions are described in an osseous metastasis only in individual cases.

Metachronous adrenal metastasis without evidence of further metastasis should be surgically removed.

6. Conclusion

Surgical therapy remains the only curative approach in the treatment of renal cell carcinoma being resistant opposite radiation and chemotherapy. (Radical) nephrectomy was the standard surgical procedure over a long period of time. The spread and further developments of

imaging diagnostics resulted in an earlier diagnostic of incidentally detected small renal masses therefore an increase of the performance of nephron-sparing procedures. In the meantime partial nephrectomy represents the standard surgical technique in pT1a renal cell carcinomas (size of tumour ≤ 4 cm). Over the past years laparoscopic procedures (laparoscopic nephrectomy and laparoscopic partial nephrectomy) showing similar results in consideration of the oncological outcome compared to open-surgical procedures gained in importance. Long-term results of the rather new technique of robotic nephrectomy and partial nephrectomy are encouraging but remain to be seen. LESS (Laparoscopic Single Site Surgery) and NOTES (Natural Orifice Transluminal Endoscopic Surgery) are first steps towards modifying established minimal invasive procedures.

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