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Management of localized and locally advanced renal tumors. A contemporary review of current treatment options

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About 70% of patients with renal cell carcinoma present with localized or locally advanced disease at primary diagnosis. Whereas these patients are potentially curable by surgical treatment alone, a further 20% to 30% of patients are diagnosed with primary metastatic disease. Although over the past years medical treatment for metastatic patients has nearly completely changed from immunotherapy to effective treatment with targeted agents, metastatic disease still represents a disease status which is not curable. Also in patients with metastatic disease, surgical treatment of the primary tumor plays an important role, since local tumor related complications can be avoided or minimized by surgery. Furthermore, also improvement of overall survival has been proven for surgery in metastatic patients when combined with cytokine treatment. Hence, surgical combined with systemic treatment as a multi-modal, adjuvant, and neo-adjuvant treatment is also required in patients with advanced or metastatic disease. A growing number of elderly and comorbid patients are currently diagnosed with small renal masses, which has led to increased attention paid to alternative ablative treatment modalities as well as active surveillance strategies, which are applied in order to avoid unnecessary overtreatment in these patients. Since surgical treatment also might enhance the risk of chronic kidney disease with consecutive cardiac disorders as well as reduced overall survival, ablative techniques and active surveillance are increasingly applied. In this review article we focus on current surgical and none-surgical treatment options for the management of patients with localized, locally advanced, and metastatic renal cell carcinoma.

KEY WORDS: Carcinoma, renal cell - Nephrectomy - Ablation techniques.

*For the Renal Cancer Working Group of the Young Academic Urologists (YAU) working party of the European Association of Urology (EAU)

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Renal cell carcinoma (RCC) accounts for 2-3% of all cancers in adults in Europe with an annual increase in incidence of about 2% in most European countries as well as reduction in incidence rates in some others. Approximately 70% of patients present with localized or locally advanced disease at primary diagnosis and are potentially curable with radical nephrectomy (RN) or nephron-sparing surgery (NSS) alone. Furthermore, although over the past years medical treatment for patients with metastatic RCC (mRCC) has nearly completely changed from immunotherapy to effective treatment with targeted agents such as tyrosine kinase inhibitors (TKI), cure of metastatic disease is still not possible. Until now, surgical treatment of the primary tumorat a local or locally advanced disease stage represents the only curative treatment option in renal cell carcinoma. Besides surgery for localized RCC, surgical treatment of the primary tumor also plays an important role in patients with mRCC in order to avoid or minimize local tumor related complications as well as to improve survival which has been proven in combination with cytokine treatment. Hence, surgical treatment in combination with systemic treatment as a multi-modal, adjuvant, and neoadjuvant treatment is also required in patients with advanced or metastatic disease.

Beneath other reasons, based on enhanced sensitivity of modern imaging methods, a growing number of elderly and in a large fraction comorbid patients are diagnosed with small renal masses (SRM). Especially in these patients as well as in those with recurrent or multifocal disease and risk of chronic kidney disease (CKD), increasing attention is paid to alternative ablative treatment modalities such as cryoablation (CA) and radiofrequency ablation (RFA) as well as to active surveillance strategies (AS). Aiming at avoiding unnecessary overtreatment which harbours also an increased risk of CKD with consecutive cardiac disorders as well as reduced overall survival (OS), these techniques are increasingly applied.

In this review article we review the current state-of-the-art regarding treatment of localized and locally advanced RCC and provide a comprehensive overview on current evidence regarding surgical as well as non-surgical treatment strategies.

Surgical treatment in localized and locally advanced renal tumors

Radical nephrectomy

RN has been the standard of care for localized RCC over the last 50 years. However, indication for RN is restricted by two main issues. First, incidence of SRM has steadily increased. Second, with the improvement of NSS according to safety and oncological outcome and the development of alternative ablative treatment strategies, the indications for RN have decreased. Furthermore, novel systemic targeted molecules have an impact on timing and sequence of RN in either adjuvant or neoadjuvant setting.

RN is defined as a complete removal of the tumor bearing kidney. This approach has recently been questioned especially for smaller (<4 cm) and even larger tumors (4-7 cm) which present in a location where NSSmight be possiblefrom a technical point of view.[1-3] Besides, almost 20% of SRM are benign. Significant loss of renal parenchyma due to RN may predispose patients to CKD, which might lead to increased cardiovascular risk and shorter survival. Currently, RN is still indicated for non-metastatic T1 tumors when PN is not feasible and in tumors with a stage of at least T2.

The role of radical nephrectomy in T1 renal tumors

Urologic surgeons gradually adapted indications for NSS as a new and more complex procedure initially. Thus, primarily NSS was reserved for solitary kidneys only. Since growing experience showed that NSS had equivalent cancer specific survival (CSS) compared to RN for tumors <7 cm,[1-3] it became the preferred alternative to RN even in the elective setting. Besides oncological safety, NSS was associated with better pres-

ervation of renal reserve in a systematic review and meta-analysis by Kim *et al*.[4]

One European Organization for Research and Treatment of Cancer randomized trial showed NSS not to be inferior to RN with regard to OS, but superiority analysis showed that RN was superior to NSS, unexpectedly.[5] Although surgical trials are difficult in terms of enrollment and adherence, this study had several drawbacks to define the evidence as level one. Contrary to that surprising outcome, already earlier further retrospective studies showed that NSS conferred equivalent cancer control and decreased risk of overall mortality compared to RN.[6, 7] Recently, Tan *et al*. demonstrated that patients undergoing NSS were 50% less likely to die from any cause. Moreover, after eight years of follow-up, 7 NSS instead of RN avoided 1 death.[8] Finally, Kim *et al*. revealed that NSS was associated with a 19% risk reduction in all-cause mortality (hazard ratio [HR] 0.81), a 29% risk reduction in cancer-specific mortality (HR 0.71), and a 61% risk reduction in severe CKD (HR 0.39).[4]

NSS is now the standard treatment for renal masses up to 7 cm, as recommended by European Urology Guidelines.[9] Although the upper limit of tumor size beyond which NSS loses its advantage has yet to be defined, finally in T1 tumors RN is only indicated if NSS is not feasible or in special situations like RCC combined with end-stage renal disease or proven highly aggressive tumors (*e.g*., sarcomatoid, Duct-Bellini and medullary carcinoma). Laparoscopic RN in T1 tumors appears to have lower comorbidity and equivalent tumor control rates compared to open surgery.

The role of radical nephrectomy in T2 renal tumors

Current standard treatment for T2 tumors is RN. There is no high quality of evidence establishing different RN techniques to be superior to others yet. Hence, grade of recommendation regarding RN technique is low as most studies on that topic suffer from small cohorts with a short follow-up.[10] For laparoscopic RN equivalent recurrence-free survival (RFS) rates and lower morbidity rates in comparison to open RN have been reported. Current evidence on differences between open and laparoscopic as well as different laparoscopic approaches is inadequate. However, a recent systematic review proved that laparoscopic RN offers a shorter convalescence time and hospital stay, and requires less analgesia than open RN.[11] The evidence regarding the finest choice of approach and type of technique between standard, hand-assisted, robot-assisted or single-port is poor and should be decided on tumor location, previously performed surgery, surgeon preference, and capabilities of the centers.

Controversial discussion on the role of lymphadenectomy during surgery for localized renal cell carcinoma

The role of concomitant lymphadenectomy (LA) is controversial. Two recent studies have addressed this issue.[12, 13] In the first study by Blom *et al*., patients were randomly allocated to RN plus "not standardized" complete LA or RN alone.[12] OS was not different between both groups. In another non-randomized study by Herrlinger *et al*., patients underwent RN plus LAif macroscopically abnormal lymph nodes were present (facultative LA) or RN plus extended LA.[13] Patients with extended LA had significantly better 10-years survival rates compared to patients with facultative LA (80.2% *vs*. 54%). No definitive conclusions on the necessity of LA could be derived from available studies yet. On the other hand, in order to identify patients with indication for adjuvant targeted therapy trials, current LA practice will probably be modified particularly for high-risk patients in near future.

Concomitant adrenalectomy and nephrectomy

Until now, no randomized study has compared RN alone *vs*. RN plus adrenalectomy (AE). However, one prospective none-randomized study compared PN with AE *vs*. PN without.[14] Five-year survival rates were not different between groups (82% *vs*. 85%, respectively). Tumor size was significantly

predictive of adrenal involvement, which was, however, not confirmed in other studies. Finally, the impact of AE on survival remains to be determined.

Radical nephrectomy in locally advanced and metastatic tumors

Although benefit might be minimal, RN as a cytoreductive approach improves survival in mRCC patients prior to treatment with interferon alpha.[15, 16] In the last decade, molecular targeted agents such as TKIs, vascular endothelial growth factor (VEGF) antibodies, and mammalian target of rapamycin (mTOR) inhibitors have led to changed treatment paradigms in mRCCpatients. While most phase III studies for TKI and VEGFantibodies have actually included a high percentage of patients who underwent RN before treatment with TKI and it is generally assumed that data from cytoreductive treatment in the immunotherapy era can be translated also to patients treated with targeted agents, data from randomized trials on the definite role for cytoreductiveandneoadjuvantnephrectomy in the era of targeted therapy have to be awaited.[17-20] Likewise, trials testing targeted therapy as adjuvant treatment option are underway for high-risk patients after surgical treatment.

Nephron sparing surgery and simple enucleation

During the last decade, NSS evolved from an experimental procedure to the surgical standard treatment of SRM. Several studies were able to underline the benefit of a better renal function after NSS compared to RN.[7, 21] Furthermore, as already depicted above, the only prospective randomized trial for comparison of RN and NSS performed by the EORTC showed oncological equity of both procedures.[5] As RCC is a disease predominantly occurring in the 6th and 7thdecade, a significant proportion of patients already present with impaired renal function. From large scale studies we have learned that CKD is a risk factor for cardiac and vascular events as well asall-cause death.[6] These results underline the clinical importance of NSS, even more since almost 80 % of all renal masses are discovered incidentally, which furthermore will be of benign nature in up to 30% of cases. Finally, the way for increased survival of patients with metastatic disease is paved by a continuously evolving armamentarium of targeted therapies, which requires preserved renal function in most cases.

According to the 2013 edition of the European Association of Urology (EAU) guidelines on the treatment of RCC, NSS is recommended for the surgical treatment of T1 tumors whenever possible. However, NSS is also performed for larger tumors, mainly for relative and/or imperative indication. The respective data available suggests that NSS may be also reasonable for advanced tumors, but positive surgical margins (PSM) and complication rates should be expected higher in imperative cases compared to elective indication.[22]

A variety of approaches and techniques can be used when performing NSS: open surgery, laparoscopic and robot-assisted minimally invasive approach; wedge resection, simple enucleation, and enucleoresection as well as hemi-nephrectomy and finally work bench surgery in complex cases. Open and laparoscopic approach yield comparable perioperative, clinical, and oncologic results, and robot-assisted NSS, occasionally combined with near infrared fluorescence imaging, will bring the benefits of this minimally invasive approach also to patients harbouring complex tumors.[23, 24] Implementation of lasers in the field of NSS currently remains reserved for open surgery due to the lack of a suitable laparoscopic instrumentarium. However, initial reports of laser assisted laparoscopic NSShave already shown promising results.[25]

Although NSS is gaining increasing acceptance, there is still an unfortunate gross underutilization of NSS in clinical routine.[26] The underlying reasons are complex and seem to include limited patient access to high volume institutions as well as a possible preference of laparoscopic RN over open NSS due to shorter convalescence

and better cosmesis, as the more complex procedure of laparoscopic NSS may not be available at the respective institution. In this context, recent data also shows that robot-assisted NSS (robot-assisted partial nephrectomy; RAPN) is not only effective in overcoming the long learning curve of conventional laparoscopic surgery, but thereby also may increase the utilization of NSS.[27] Nevertheless, for the moment, open NSS remains the gold standard procedure for NSS.

As one preferential aim of oncologic surgery is to achieve negative surgical margins, a wide safety margin of regular renal parenchyma surrounding the excised tumor was historically recommended: eventually, this is no longer necessary. A minimal layer of regular renal tissue will provide the oncologic safety required, thereby making simple tumorenucleation and enucleoresektion of renal masses possible.[28] Margin width is irrelevant as long as a negative surgical margin is achieved. The surgical technique appropriate for the respective tumor may be determined by the use of recently published scoring systems (Renal nephrometry score, Padua score, c-index) which may aid in estimating the complexity of a planned NSS.

However, all these techniques share the same disadvantage: the detrimental effects of warm ischemia on renal function. Although exophytictumors can be excised without ischemia, the majority of NSS procedures will utilize renal artery occlusion to improve visibility of the intended resection margin. Data available suggests that warm renal ischemia should be kept as short as possible and irreversible damage may occurs as early as 20 minutes after clamping.[29] Various methods aimed to achieve local hypothermia in NSS, however, they all warrant improvement: crushed ice often only cools the renal surface while hypothermia needs to penetrate into the renal parenchyma sufficiently, and retrograde transureteral perfusion cooling of the renal pelvis seems to be even less efficient [30]. On the other side, renal artery perfusion cooling is highly efficient but complex and unsuitable for routine clinical use.[31] Therefore, NSS, irrespective of approach and technique, should be performed by an experienced surgeon able to adhere to the temporal requirements of warm ischemia. Auxiliaries utilized with varying evidence to protect renal function are intravenous mannitol, inhibitors of angiotensin converting enzyme, and topical papaverine.[32, 33] Finally, advancements in the surgical technique, such as the early unclamping technique and the use of barbed self-retaining running sutures, led to a significant reduction of warm ischemia time.

The oncological safety of NSS compared to RN was demonstrated in several studies. However, positive surgical margins (PSM) will be observed in up to 7 % of NSS performed for elective indication and in up to 18% in imperative indication.[34] PSM occur irrespective of surgical approach and tumor histology. The risk of disease recurrence is elevated if a PSM occurs in a highly malignant tumor, but only the minority of patients with PSM will experience such tumor recurrence.[34] Therefore, most patients with PSM following NSS can be spared sequelae of repeat surgery and possible renal function impairment. These patients should be closely monitored, as early salvage therapy upon local disease recurrence will be indicated rather than immediate RN. However, some controversy is still driven by the trend towards a narrowing of the recommended surgical margins. Several papers have been recently published on the necessary amount of normal tissue that should be excised with the tumor to avoid the risk of local recurrence, concluding that if the tumor is completely excised, the width of the resection margin is irrelevant and not correlated with disease progression.[35] The EAU Guidelines recommend the presence of a minimal tumor-free surgical margin of healthy renal tissue surrounding the resected tumor without specifying the exact minimum thickness of the healthy parenchyma to be removed.[9] At present, NSS can be performed either as standard partial nephrectomy (PN) defined as the excision of the tumor and of an additional margin of healthy peritumor renal parenchyma or as simple enucleation (SE), *i.e.*, a tumorectomy done by a blunt dissec-

tion, using the natural cleavage plane between the tumor and normal parenchyma, with no ablation of the tumor bed.[36] In recent years, considerable data has emerged demonstrating good oncologic, functional and perioperative outcomes of SE.[36-38] Indeed, many studies have investigated the oncological results of SE, demonstrating local recurrence-free survival and cancer specific survival rates comparable to those reported in series of standard PN, for renal tumors with clinical diameter up to 7 cm.[39-41] However, no prospective randomized studies compared these two techniques from an oncological perspective to clarify controversies between surgeons about the right technique to perform a conservative surgery for kidney cancers. While two retrospective studies on large series with long FU have compared the oncological results to SE versus Standard PN and RN in T1 patients and showed that SE can achieve equivalent oncologic outcomes.[36, 38] Reports have also proven reduced incidence of positive surgical margins adopting the SE technique. This is probably due to the fact that SE provides a constant visual detection of the correct cleavage plane, whereas the sharp excision in case of standard PN can sometimes mislead the surgeon, especially in case of endophytic tumors. In the large multi-center series from SATURN-LUNA project on more than 1500 patients, the incidence of PSM was 3.4% and 0.2% after standard PN and SE, respectively.[36] At contrary, opponents to SE cite that a minimal rim of normal parenchyma around the resected tumor is recommended to ensure a complete tumor removal and reduce the risk of local relapse or progression and that the tumor capsule that serves as a landmark for SE is missing in some tumors.[40, 42, 43] Moreover, a recent paper also showed that patients who underwent SE for Fuhrman grade 4 disease had significantly worse cancer specific survival compared to those undergoing standard PN, however, this analysis was based on too small patient numbers (20 standard PN *versus* 4 SE) to draw an conclusions without validation in future prospective trials with more patients included.[36] The potential pathological concerns of incomplete tumor excision after SE were analysed in a recent study based on pathological examination of the surgical specimen obtained after SE that described the presence of tissue with a median thickness of 1 mm lying beyond the tumor capsule with signs of chronic inflammation. This precious microscopic layer of renal parenchyma allowed the presence of negative surgical margins in patients with tumors extending beyond the capsule as well.[44] Increased knowledge within the results of different renal cancer treatments strategies is a prerequisite for advances in patients care, however, only a prospective randomized study will be able to shed light on this dualism, in particular defining the best technique of NSS and parameters for a correct surgical decision between standard PN and SE.The complication rates observed with NSS are slightly higher but still very tolerable when compared with RN (level of evidence: 1b).[9, 38] Results regarding morbidity are extremely variable in the literature and the overall complication rate after NSS ranges between 4% and 37%. Several predicting factors for postoperative complications have been reported in the literature, the most relevant are: imperative indication for NSS, tumor stage ≥T1b (maximal tumor dimension >4 cm), perihilar localization of the tumor, length of WIT (>20 minutes), endophytictumor growth, and involvement of the collecting system.[45] Some authors have hypothesized that SE might be associated with a lower rate of major bleeding and urinary fistula, and, indeed, in a single-center series, a low incidence of postoperative complications requiring reintervention (3%) and also a low rate of urinary fistulas (3%) and ureteral stenting (0.5%) was demonstrated.[46, 47] However, no comparative studied have been published to date to compare the morbidity of SE and standard PN and therefore it is difficult to draw significant conclusions on the differences in adverse events rates between the two techniques. Finally also for SE, the PADUA score has been reported as a reliable toolto predict surgical results and morbidity.[48]

Partial versus *radical nephrectomy for cT1 renal cortical tumors: functional outcomes and impact on overall and cardiovascular mortality*

As already specified above, for RCC ≤4 cm, NSS has become the standard treatment of choice, since it provides excellent oncological outcomes and seems to reduce the risk of developing chronic kidney disease (CKD).[49-53] NSS has been considered as an alternative to RN also in patients with tumors>4 cm, who need to preserve renal function.[49, 50] Moreover, a recently growing body of literature has demonstrated that OS and CSS will not be compromised when NSS is done for 4 to 7 cm renal cortical tumors, adding the benefit of preserving renal function.[2, 3, 49, 50, 54]

Single-institution reports which retrospectively compared NSSwith RN in patients with a normal contralateral kidney by using postoperative serum creatinine levels as study end point have shown a higher likelihood of renal function impairment after RN. The Mayo Clinic experience using a matched comparison of patients who underwent NSS and RN has shown a higher risk for chronic renal insufficiency (defined as serum creatinine >2 mg/dL) after RN (HR 3.7; P=0.01).[55] Moreover, Huang *et al.* have analyzed 662 patients who underwent elective NSS or RN for <4-cm SRM with a normal preoperative serum creatinine and a healthy-appearing contralateral kidney on imaging. Multivariable analysis indicated that RN remained an independent risk factor for the development of new-onset CKD (HR 3.82; P<0.0001).[7]

The mechanism by which NSS offers an advantage over RN in preventing CKD in patients with T1 renal masses is certainly the result of a greater preservation of the nephron capital. Studies looking at independent predictors of renal function outcome after NSS have shown that larger renal volume reduction or percentage of resected parenchyma adversely influence renal function after NSS. Further predictors are either patient dependent (preoperative estimated GFR, solitary kidney status, advanced age, and male gender) or related to technique (length of ischemia time).[56-58]

Moreover, CKD was found to be an independent risk factor for the development of cardiovascular events (coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease), hospitalization, and death of any cause.[6] Since from the above data one can deduct that RN compared to NSS leads to a higher likelihood of CKD, a growing amount of literature has aimed to evaluate if patients treated by RN have a higher risk of cardiac events and lower survival rates.

From the SEER (Surveillance, Epidemiology and End Results) registry, Kates *et al.* identified 4216 patients with histologically confirmed RCC with a maximum size of 2 cm, who were treated with NSS or RN. When controlling for patient characteristics and surgery year, RN was associated with reducedOS (HR 2.24) and enhanced cardiovascular mortality (HR 2.53).[51]

Huang *et al.* addressed the issue of cardiovascular events and OS by analyzing a population-based cohort of 2991 patients older than 65 years treated by NSS (19%) or RN (81%) for renal cortical tumors <4 cm from the SEER-Medicare-linked data registry for the time period between 1995 and 2002. When controlling for demographic characteristics and patient comorbidities, type of surgery was not a statistically significant predictor of cardiovascular events or cardiovascular death. RN, however, was associated with an increased risk for all-cause-death (HR 1.46; P<0.001).[59] Contrasting with these results, in the Mayo Clinic series, a retrospective analysis based on 648 patients treated with NSS or RN between 1989 and 2003 for renal masses smaller than 4 cm, type of surgery was not significantly associated with an increased risk for all-cause-death. However, in a subset analysis limited to patients younger than 65 years, RN was associated with decreased OS (HR: 2.34; P=0.016).[54]

One further report from Cleveland Clinic compared OS, CSS, and cardiac specific survival in patients undergoing NSS or RN for cT1b tumors and reported patients under-

going RN to loose significantly more renal function than those undergoing NSS. The average excess loss of renal function observed with RNwas associated with a 25% (95% CI 3-73%) increased risk of cardiac death and 17% (95% CI 12–27) increased risk of death from any cause on multivariableanalysis.[2]

In summary, current evidence provided by literature supports the advantage of NSS over RN in reducing the risk of CKD and promoting the awareness of the importance of kidney preservation. However, the retrospective nature of most of the above mentioned studies comparing NSS to RN, limits the power of their results. Unknown selection biases may account for the observed differences in survival. For example, older and female patients are more likely to receive RN than younger and healthier patients. Furthermore, patients with multiple comorbidities might have been more likely to be treated with RN, which could have impacted OS results.

Application of different surgical techniques for radical nephrectcomy and nephron-sparing surgery

Laparoscopic techniques and robot-assisted radical nephrectomy in renal cell carcinoma patients

Due to a widespread use of cross-sectional imaging, incidental diagnosis of SRM is frequent and the greatest increase over time across RCC tumor stages is among localized tumors.[60-62] A shift for localized RCC has occurred from open to laparoscopic RN. In the first case of laparoscopic which was described by Clayman *et al.* in 1991 a total of seven hours operative time was needed.[63] Since then, with more experience also operative times have decreased significantly. At that time the use of this technique for suspected RCC was still controversial and proposed to be most useful for benign disease. However, during recent years, laparoscopic techniques have improved dramatically and quickly became the standard for both benign renal surgery and for organ confined small RCC. Patients benefit from less postoperative pain and faster return to normal activities compared to open surgery, which was shown in a randomized controlled trial (RCT) by Burgess *et al.*[64] Further advantages may be less intraoperative blood loss and a shorter hospital stay. At first, the focus of laparoscopy was mainly on feasibility and on perioperative outcomes. Oncological outcome became more important with time when this technique was used also for treatment of larger tumors. However, no randomized studies have comparedopen and laparoscopic RN with regard to oncological oucome yet. Further alternative endoscopic approaches for renal cancer surgery, *i.e.* retroperitoneoscopic, hand-assisted laparoscopic, robot-assisted laparoscopic, and even single-port laparoscopic techniques have recently emerged. When choosing either approach, oncological safety is of utmost importance. Especially, tumor size, experience, and surgeon´s preference play an important role.

Oncological safety

With regard to oncological safety, for organ confined RCC up to 7 cm (pT1a-pT1b) laparoscopy has been proven to be safe. Nowadays, in patients with tumors >4 cm laparoscopic NSSis being performed increasingly more often with CSS rates equivalent to RN.[65] For SRM with a maximum size of 4 cm, RN was even found to be significantly associated with death from any cause compared with NSS.[59] In a prospective cohort study by Hemal *et al.* for cT2 RCC, similar oncological outcomes were found for laparoscopic and open RN with 5-year OS rates reported with 87.8% and 88.7% (P=0.87), respectively.[66] There was no evidence of any difference in CSS or RFS. Furthermore, laparoscopic RN was shown to be feasible also for larger tumors at advanced stages (pT3), with the expected advantages of laparoscopy for patient recovery, and similar long-term oncological outcome in the hands of experienced surgeons.[67]

Different laparoscopic techniques

Two RCTs comparing retroperitoneoscopic and transperitoneal laparoscopic RN were performed.[68, 69] Although a shorter operative time was found for the retroperitoneal approach (207 versus 150 min, P=0.001) in one study, other perioperative outcomes like blood loss, hospital stay, complications, analgesia requirements, and oncological outcomes were equivalent.[68, 69]

One quasi RCT and one database review compared hand-assisted and transperitoneal laparoscopic RN.[70, 71] No cancer-specific death or recurrence was reported in the first series, however, number of patients included was low with 11 patients only in each arm, and follow-up was short (median 20 months).[70] Gabr *et al.* performed a multivariable analysis revealing comparable 5-year RFS, -CSS, and -OS between hand-assisted and standard laparoscopic RN.[71] Perioperative outcomes were in favour of the laparoscopic arm with less blood loss, shorter hospital stay, and less time to recovery.

One prospective cohort study compared laparoscopic and robotic RN for cT1-2 RCC.[72] Perioperative outcomes were comparable in both groups, except for operative time which was significantly longer in the robotic group. There were no local, port-site or distant recurrences, but again follow-up was short and patient numbers were low (N.=30).

Only few cohort studies were reported on laparoendoscopic single-site RN.[73-76] Cosmetic satisfaction seems better after single site surgery. Furthermore, less pain, shorter analgesic times, and faster bowel recovery were reported. No recurrences or port-site metastases occurred during follow-up. However, patients in these studies had cT1 stage RCC, follow-up was short, and again patient numbers were small (N.<30). Larger patient series are required in order to evaluate the real advantages for single port surgery, preferably in a randomized trial.

In conclusion, laparoscopic techniques for RN are safe for localized RCC and oncologically justifiable also for larger tumors (pT2-T3) in experienced surgeons hands. Main patient related advantages include less postoperative pain and faster reconvalescence. New techniques like single-site surgery are evolving and may have promising results for cosmesis and postoperative pain, but larger patient series are required to confirm this. Robotic surgery for RCC is still undergoing further development with also increasing use of these techniques not only for RN but also for NSS.

Laparoscopic techniques and robot-assisted nephron-sparing surgery in renal cell carcinoma patients

Due to its wide spread use and acceptance, open NSS currently remains the contemporary standardtreatment in the management of SRM. Nevertheless, based especially on invasiveness, postoperative pain, scarring, longer hospitalization, and slower convalescence with open in comparison to laparoscopic techniques, in the forthcoming future also NSS procedures will be increasingly approached by laparoscopic or robot-assisted laparoscopic approaches. Firstly described by Winfield HN in 1993, laparoscopic NSS with several technical variationshas been standardized to a great extent during recent years.[77] Laparoscopic NSS is a viable treatment option with comparable outcomes like open surgery with even reduced intraoperative and postoperative morbidity.[78, 79] Proponents of laparoscopic NSS cite similar results like open surgery, nevertheless it continues to be performed in a minority of centersonly due to technical demands during the extirpative and in the reconstructive step of the procedure and a steep learning curve.[78-80] Indeed, laparoscopic NSS can offer the advantages of reduced blood loss and shorter hospital stay with similar oncologic outcomes when compared with the open NSS.[79] However, this technique has also been associated in some retrospective observational studies with longer ischemia time, increased postoperative complication rates, and an increased number of subsequent procedures required.[23]

First reported in 2004 by Gettman *et al*.[81] also RAPNusing the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA), represents an alternative procedure to standard laparoscopic open NSS for RCC treatment which has steadily gained acceptance between surgeons.[27] Recently, few studies have compared perioperative results of RAPN and standard laparoscopic NSS, and current evidence suggests that RAPN can reproduce the advantages of minimal invasiveness with shorter learning curves and excellent perioperative outcomes already after about 30 patient cases.[82] Recent studies have also shown that RAPN can be effectively utilized for the treatment of larger renal tumors (>4 cm) and more complex lesions, such as perihilartumors.[83] Ideally, every surgical option for renal tumors should be compared to open NSS that is the current standard of treatment and has the robustness of data regarding surgical and oncological results. Until now, only one prospective study has compared perioperative outcomes of RAPN and open NSS showing that RAPN was able to offer comparable perioperative and functional outcomes, including warm ischemia time and change in estimated glomerular filtration rate; furthermore, decreased hospitalization was shown for RAPN.[84]

Ablative treatment options and active surveillance strategies

Since a growing number of patients are diagnosed with SRM, increasing attention is paid to alternative treatment modalities besides surgical treatment. Especially in elderly and comorbid patients as well as in those with recurrent or multifocal disease and risk of CKD, increasing attention is paid to alternative ablative treatment modalities such as CA and RFA as well as to AS strategies. Aiming at avoiding unnecessary overtreatment which harbours also an increased risk of CKD with consecutive cardiac disorders as well as reduced OS, these techniques are increasingly applied.

Radiofrequency ablation

Technique of RFA

Technically, RFA involves a high-frequency alternating current, 300-500 kHz, which induces coagulative necrosis of tumor tissue via needle electrodes.[84] Mostly, RFA is performed percutaneously under computed tomography (CT) or ultrasound (US) guidance. Monitoring of this procedures difficult because neither CT nor US allows real time imaging of the ablation zone. Some authors suggest using fiberoptic probes to monitor the procedure and to allow for equal radiofrequency energy distribution within the tumor.[86] The use of RFA is also possible during laparoscopic or open interventions.

Advantages and drawbacks of RFA

Percutaneous RFA is one of the minimally invasive treatment options for patients with renal tumors. Importantly, this minimal-invasive approach does not appear to negatively affect CSS. The procedure has already been performed in many oncological centers, and mostly reported treatment outcome was satisfactory particularly in the management of SRM.[87-90] Recently, Psutka *et al.* describe their single-institution experience with CT–guided RFA for single, biopsy-proven (T1a and T1b) RCC.[87] The authors retrospectively analyzed the outcomes of 274 patients with 311 mostly exophytic renal masses with a median size of 3 cm. Final oncologic outcome was provided for 185 patients (143 T1a and 42 T1b RCC). RFA was shown to be highly efficacious in managing T1a RCC, even over a follow-up of 10 years. In this group, the authors reported a 5- and 10-year RFSto be as high as 96% and 93%, respectively. 5-year DFS and CSS rates were 91% and 100%, respectively. Outcome of RFA in T1b tumors was less spectacular, with a 5-year DFS rate of 74%, suggesting that RFA in tumors >4 cm should be considered only in clinically infirm patients unfit for surgery. Similarly encouraging results for RFA in T1a tumors were reported by Olweny *et al*.[88] RFA performed in T1a tumors

resulted in 5-year RFS and DFS rates of 92% and almost 90%, respectively. Importantly, Olweny *et al.* showed that 5-year OS and CSS was similar for RFA and PN, each reported at >95%.

Percutaneous procedures are not only more convenient for patients but also lead to reduction of morbidity. Complications of RFA are rare; the most common include pain and paraesthesis and are reported in less than 5% of cases. The economic aspects of RFA are also encouraging. Hospital stay and overall costs are often reduced, mainly because of a quick recovery. Pandharipande *et al.* described increased cost effectiveness of RFA compared with NSS.[91] The ease of retreatment is another advantage of RFA compared with other minimally invasive techniques such as CA. Retreatment and/or salvage RFA remain possible following the incomplete (residual tumor on follow-up imaging) or unsuccessful procedure.

The lack of adequate oncologic follow-up (in many of the large RFA series, the reported mean follow-up is generally short and does not exceed 3-yrs), the questioned accuracy of pre- and postablation biopsy (following RFA procedure, the ablated renal tumor is left in situ and it is not available for complete pathological evaluation), and the high rate of benign pathology in SRM (around 20-30%) are amongst the main limitations of RFA.Another problematic issue is the lack of standardization of RFA, since many authors do not provide a detailed description of their RFA protocol, which limits comparability of different series. Furthermore, follow-up after renal ablative therapy remains difficult. There is no perfect tool to detect local progression; and, according to some studies, the absence of contrast enhancement on CT does not exclude the presence of viable cancer cells.[92] Importantly, the application of a minimally invasive approach for treating larger organ-confined kidney tumors exceeding 4 cm remains controversial. According to above cited study, outcome for patients with T1b tumors undergoing RFA appears unsatisfactory.[87] Finally, reliable data on comparative effectiveness of RFA and other treatment options, i.e., partial nephrectomy, surveillance, or CA based in prospective studies or matched cohorts is currently missing.

In conclusion, recent studies have shown that RFA can provide durable oncologic control in patients with T1a biopsy-proven RCC. Therefore, percutaneous RFA remains a promising minimally invasive treatment approach for appropriately selected patients with up to 4 cm and at best exophytic tumors. Nevertheless, further prospective studies are necessary to establish the role of RFA as an equivalent to surgery for the definitive management of small kidney tumors.

Cryoablation

Widespread use of US and CT scan has increased incidental diagnosis of SRM ≤4 cm by up to 60%.[93] Besides RFA also CA represents a minimally invasive technique and preferable option to ensure preservation of renal function and avoid the morbidity associated with surgery. Furthermore, CA can be an alternative treatment option in patients unfit for surgery and those with congenital diseases or renal masses in solitary kidneys.[94]

Technique of cryoablation

CA is based on the Joule-Thomson phenomenon. When tissue and extracellular fluid freeze, the osmotic pressure in the extracellular space increases. The resulting fluid shift leads to dehydration, accumulation of toxins, change in pH and denaturation of proteins. The cellular membrane is disrupted and the intracellular fluid crystallises; the endothelial damage leads to ischemia, thrombosis, and coagulative necrosis, ending with cell death.[95]

CA is delivered through two freeze-thaw cycles: a first rapid cycle to -40 °C with the formation of an initial ice ball extending up to 1 cm beyond the tumour mass, followed by a slow-thaw phase. Afterwards, the cycle is repeated. The temperature is controlled by the placement of thermosensors at the mar-

gins of the tumour or by direct visualisation of the ice ball.[96] Third-generation 17-gauge cryoprobes use argon gas, which cools on expansion. Probes are available in different sizes (1.5-8 mm) and in three shapes (standard, elliptical and bulb shaped).[97]

CA for RCC can be performed during open surgery as well as laparoscopically or percutaneously. CT scan and MRI are the most common imaging techniques for follow-up to ensure optimal reduction of tumour size and to detect tumorrecurrence or persistence. Optimally, CT scan after CA should be performed every 3 months for the first 2 years, followed by long-term imaging until the lesion has completely resolved.[98] Stein *et al.* demonstrated that presence of enhancement beyond nine months after CA is not frequent and furthermore not necessarily associated with persistence of malignancy.[99] Complications of CA include bleeding and perinephric hematoma in about 10% of cases, which can be avoided by slow removal of the probes only during the thawing phase.[94] Extra-renal complications include injury to spleen, liver or bowel, and paraesthesia at the probe entry site. Mid-term follow-up results have confirmed that laparoscopic CA iseffective from an oncological and functional point of view. In a recent series of 100 tumours treated by CA with a median follow-up of 30.2 months, Beemster *et al.* reported CSS and metastasis-free survival rates of 100%.[100] In a single-surgeon series of 80 laparoscopic CA, Aron *et al.* reported a CSS rate of 95% after 5 years and 83% at 10 years, respectively.[101]

Lin *et al.* compared laparoscopic NSS and CA in patients with multiple ipsilateral tumours. Both patient groups presented with similar findings with respect to complications, renal function, and survival, but the laparoscopic NSS group had higher rates of blood loss and a longer hospital stay.[102] In another single-institution report, Desai *et al.* did not observe significant differences in hospital stay, blood loss, operating time, and complications and recommended laparoscopic NSSas standard treatment based on the lack of long-term survival results for CA only.[103]

Different approaches for cryoablation

Minimally invasive CA can be performed by the laparoscopic or percutaneous approach. In case of anterior tumours, the laparoscopic approach has the advantage of direct visualisation of the tumour, which permits use of US to monitor the size of the ball and avoid injury to healthy tissue.[104] The laparoscopic approach entails mobilisation of the kidney and the perinephric fat. Identification of the tumour by US is required, and a biopsy should be taken for pathology. Use of US also can guide optimal placement of the probes. It is recommended that probes are inserted into the kidney at a right angle to minimise the risk of renal injury. At the end of the second thaw cycle, the probes are gently withdrawn to avoid bleeding.

Percutaneous CA offers enhanced advantages in patients with posterior tumours. The procedure is usually done under general anaesthesia, but in unfit patients also local anaesthesia with sedation can be performed instead. US, CT scan, and MRI can be used for tumour localisation, biopsy and placement of the probes. A final image can be obtained to confirm the precise placement of the probes. The standard double freeze-thaw is applied and ice ball formation and progression is monitored with real-time ultrasonography. A meta-analysis published by Hui *et al.* included 46 series (28 percutaneous and 18 surgical) and concluded that the percutaneous approach is safer than the open or laparoscopic approach, and equally effective.[105] However, more than one single procedure was needed to treat the tumour completely.[105] Comparing the laparoscopic and percutaneous approaches, published series have revealed lower rates of blood transfusion, shorter hospital stay, and shorter operative time with the latter, but on the other hand, high analgesic requirements.[106] Bandi *et al.* suggested that percutaneous ablation in carefully selected patients is associated with early convalescence compared with laparoscopic ablation.[107] Also, Mues *et al.* reported lower complication rates and no significant change in renal function after

CA, with inclusion of patients with a solitary kidney.[108]

To date, CA has not gained widespread recognition owing to a lack of long-term results. Short- and intermediate-term results have shown that CA represents an alternative treatment option worthy for consideration especially in elderly and unfit patients. Initial results of laparoscopic and percutaneous approaches can be optimised by employing the appropriate approach depending on the location of the tumour, i.e. in patients with posterior tumours the percutaneous approach should be employed, while in those with anterior tumours, laparoscopy or single port access should be used.[94]

Active surveillance and percutaneous renal tumor biopsy

Active surveillance for the management of small renal masses

The rationale for AS is based on the hypothesis that active treatment for SRM may not influence OS in patients with limited life expectancy. In fact, recent studies have shown that non-RCC related mortality after surgical removal of SRMs is significant and correlates with age and comorbidities.[109, 110] Lane *et al*. assessed oncological outcomes of a series of 537 patients aged >75 years treated either by surgery or observation and showed that surgical treatment was not associated with a significant survival advantage, confirming a role for conservative management in selected elderly patients and patients with high-risk for surgery who present with SRMs.[110]

AS is defined as initial monitoring of tumor size by serial abdominal imaging (US, CT or MRI) with delayed intervention in tumors showing progression during follow-up. Progression of a SRM during AS is generally defined as tumor volume doubling time <12 months, reaching a tumor diameter that is considered to provide risk for development of metastasis (3-4 cm) and/or new onset of tumor-related symptoms. Several experiences have shown that the growth rate of SRMs under AS is overall slow and progression to metastatic disease is rare (0-2%) (Table I).[111-140] Although most reported series are retrospective, single institutional and relatively small, the results of a large, prospective, multi-institutional Canadian trial of AS confirmed a slow growth rate (0.13 cm/year) and a low tendency to metastasize (1.1%) in 209 SRMs followed with serial imaging with an average follow-up of 28 months.[112] Other studies have shown that delaying intervention does not compromise the feasibility of nephron sparing surgery and the oncologic outcomes.[113]

Limitations of current AS series are the relatively short follow-up and the lack of pathological diagnosis in a significant number of cases. Currently, AS is not recommended for young and healthy patients, but is considered an appropriate strategy for the elderly or patients with significant comorbidities who are not proper surgical candidates.[49, 114, 115] Gill *et al*. suggested that AS seems also a reasonable option for renal masses that are 1 cm in diameter or smaller, regardless of patient's life expectancy.[116]

There is no clear consensus on the best imaging technique and the optimal follow-

TABLE I.—*Outcomes in selected series of patients undergoing active surveillance of small renal masses.*

	Patients (SRMs), n	Mean tumor size (cm)	Mean follow-up (mo)	Growth rate (cm/year)	Progression to metastasis N. (%)
Volpe *et al*. Cancer 2004 [134]	29 (32)	2.48	27.9	0.1	0
Chawla *et al*. J Urol 2006 [135]	49 (61)	2.97	36	0.2	1 (2)
Abouassaly *et al*. J Urol 2008 [136]	110 (-)	2.5	24	0.26	0
Crispen *et al*. Cancer 2009 [137]	154 (172)	2.5	31	0.28	2 (1.3)
Rosales *et al*. J Urol 2010 [138]	212 (223)	2.8	35	0.34	1 (0.5)
Jewett *et al*. Eur Urol 2011 [139]	178 (209)	2.1	28	0.13	2 (1.1)
Patel *et al*. BJU Int 2012 [140]	71 (93)	2.2	34	0.21	1 (1.4)

up schedule that should be adopted in AS protocols. The typical recommendation is to perform repeat imaging at intervals of 6-12 months.[117] CT and MRI are generally preferred based on their superior accuracy and lower variability in determining tumor size, but there are no studies showing their superiority over abdominal US. When US visibility of the renal mass is good, it is possible to alternate cross sectional and US imaging to reduce radiation exposure.

The role of percutaneous renal tumor biopsy in the management of small renal masses by active surveillance and ablative treatment strategies

The role of percutaneous renal tumor biopsy (RTB) in the management of SRM is expanding. Historically, RTBs have been rarely used because of concerns about their safety and accuracy.[118] Several large series of RTBs have been recently published, confirming that the procedure is characterized by low morbidity in centers with expertise. Clinically significant bleeding is reported in <1% of cases with the use of modern biopsy techniques and only 6 cases of renal tumor seeding have been reported in the literature. All recent series of RTBs reported high diagnostic rates and excellent accuracy for the diagnosis of malignancy (Table II).[140-148]

Aim of biopsy is to determine malignancy, histological type, and grade of a SRM in order to support treatment decisions.[118] Needle biopsy can avoid unnecessary surgery for benign renal tumors that cannot be accurately identified by modern abdominal imaging, such as oncocytomas and fat-free angiomyolipomas.[119, 120] Furthermore, percutaneous biopsy can be useful to guide surveillance strategies.[114, 121] Histologically proven, high grade RCCs may not be optimal candidates for AS based on their higher risk of progression during follow-up, while benign tumors can be followed with a less rigorous imaging schedule. Finally, percutaneous biopsy should always be performed before ablative treatment of a SRM [49, 114] and can be useful to monitor the success of minimally invasive therapies such as RFA and CA in combination with CT and MR imaging.

Several issues with renal tumor biopsies have still to be resolved. Overall, 3-30% of biopsies fail to provide a diagnosis. Further improvements in biopsy techniques and in the definition of optimal patterns of biopsy are required. At present, when a biopsy of a radiologically suspicious renal mass is negative or non-diagnostic, surgical exploration or repeat biopsy should be recommended.

Although the diagnosis of histological subtype is possible in the majority of RTBs, differential diagnosis between oncocytoma and chromophobe RCC remains particularly challenging on biopsy specimens.[119] The use of immunohistochemistry panels, FISH and RT-PCR can increase the accuracy of diagnosis in uncertain cases.[122, 123] Finally, assessment of Fuhrman grading is challenging on RTBs and accuracy is not optimal. This can be partially explained by interobserver variability and by grade heterogene-

TABLE II.—*Outcomes in recent series of patients undergoing percutaneous biopsy of renal tumors.*

	No. tumors biopsied	Mean tumor size (cm)	Image guidance	% diagnostic biopsies	Accuracy for malignancy	Accuracy for RCC subtype	Accuracy for grading
Shannon *et al.* J Urol 2008 [141]	235	2.9	CT/US	78%	100%	98%	NR
Schmidbauer *et al.* Eur Urol 2007 [142]	78	4.0	CT	97%	Sensitivity 93.5% Specificity 100%	91%	76%
Lebret *et al.* J Urol 2007 [143]	119	3.3	CT/US	79%	86%	86%	46/74%°
Maturen *et al.* AJR 2007 [144]	152	4.1	CT/US	96%	Sensitivity 97.7% Specificity 100%	NR	NR
Volpe *et al.* J Urol 2008 [145]	100	2.4	CT/US	84%	100%	100%	66.7/75%
Wang *et al.* Urology 2009 [146]	110	2.7	CT/US	90.9%	100%	96.6%	NR
Veltri *et al.* Eur Radiol 2011 [147]	103	3.4	US	100%	NR	93.2%	NR
Leveridge *et al.* Eur Urol 2011 [148]	345	2.5	CT/US	80.6%	99.7%	88%	63.5%

ity in the tumor. Enhances accuracy in the assessment of Fuhrman grade can be obtained when tumors are simply classified as low (Fuhrman I-II) or high (Fuhrman III-IV) grade.

In summary, adequate biopsies can provide histological information that can be combined with clinical tumor and patient characteristics to assist in the choice of the appropriate treatment for each individual patient. In the future, molecular and cytogenetic information from RTBs may be integrated with further histological and clinical variables in algorithms and nomograms to be used for counseling and treatment decision-making in patients with SRMs.

Medical treatment in localized tumors

Adjuvant treatment of localized and locally-advanced renal tumors after primary curative treatment

Approximately 70% of patients present with localised or locally advanced disease and are curable with surgery or ablative treatment alone. Standard therapy of organ-confined and locally advanced RCC is surgical resection. Additionally, as described above, over the recent years further minimally invasive and ablative treatment options have advanced treatment options in RCC patients. However, recurrence rates after primary curatively intended treatment range between 35-65% depending on several parameters, including pathological stage, Fuhrman nuclear grade, and Eastern Cooperative Oncology Group performance status (ECOG-PS).[124] Data on this issue retrieved from several trials clearly demonstrate the need for adjuvant treatments for tumor control, adjusted to the individual oncological risk profile.

Contrariwise, until 2004 no adjuvant treatment could reveal efficacy in the adjuvant treatment of localized and locally advanced RCC. Although treatment with cytokines has been the standard treatment for patients with mRCC until 2006, adjuvant immunotherapeutic treatment with cytokines alone or in combination with chemotherapeutic agents failed to show oncologic benefit compared to observation alone in the adjuvant setting. Until now, the only treatment which has proven efficacy in the adjuvant setting is an autologous tumor vaccine (Reniale®) which improvedRFS especially in patients with pT3 tumors based on results of a randomized controlled trial published in 2004.[125] However, until now this substance has not been regularly approved based on insufficiencies in the trial design (such as missing central radiological review and missing adaption to the current TNM classification). Further adjuvant approaches such as hormonal treatment and adjuvant radiotherapy after surgery did neither reduce the risk of recurrence nor improve survival of patients.[126, 127] In addition, it has to be mentioned that in most published studies, except the vaccination trials, patients in the trial arms had worse prognosis compared with patients in the control arms. Finally, outside clinical trials until now no approved adjuvant therapeutic approach has been defined. Recent advances in understanding the molecular biology of RCC led to the development of several targeted agents showing impressive anti-tumor efficacy and prolongation of PFS in mRCCpatients,[128-131] but to date no data are available regarding their applicability and efficacy in the adjuvant setting after nephrectomy. However, according to the established activity of TKI targeting vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) in metastatic RCC, currently ongoing phase-III trials are exploring the role of these agents also in the adjuvant setting aiming at reducing the risk of tumour recurrence in high-risk patients after treatment with curative intention. Furthermore, different immune-modulatory characteristics of the TKI sunitinib and sorafenib have been shown in vitro, which makes it reasonable to further evaluate in vivo immune-modulatory effects of these agents.[132, 133] However, until results from the ongoing phase-III trials are available it remains unclear, whether treatment with antiangiogenic agents will be able to enhance RFS after curative treatment. Trials

assessing the influence of mTOR inhibitors in the adjuvant setting are not available.

Neoadjuvant and multimodal treatment of locally-advanced and metastatic renal tumors

Although benefit might be minimal, RN as a cytoreductive approach improves survival in mRCC patients prior to treatment with interferon alpha.[15, 16] During the cytokine era, the role of cytoreductive nephrectomy was defined in order to improve survival and to reduce local complications by the tumor. Currently, it is generally assumed that data from cytoreductive treatment in the immunotherapy era can be translated also to patients with mRCC treated with targeted agents, which is furthermore corroborated by limited retrospective data of smaller patient series. Furthermore, in most clinical phase III trials for TKI and VEGF antibodies a high percentage of patients underwent RN before treatment with TKI (*e.g.*, for sunitinib 91% *vs.* interferon alpha 89%).[17] However, data from prospective randomized trials on the definite role for cytoreductive and neoadjuvant nephrectomy as well as on multimodal treatment in the era of targeted therapy have to be awaited.[18, 19] Applying systemic therapy prior to surgery could possibly also guide us to select patients who most likely benefit from surgery based on response to treatment. Moreover, RN with extraction of tumor thrombosis is the only chance for survival in patients with locally advanced tumor with tumor thrombus in the V. cava, which might be facilitated in some cases by neoadjuvant treatment only.[20] Role and timing of application of these novel agents in combination with surgical treatment have yet to be defined.

Comment

Over the past few years, treatment options for localized as well as metastatic RCC have expanded. Beside paradigm changes in the systemic treatment for metastatic disease, also local treatment modalities for the primary tumor as well as for metastases have changed and previously established ways of treatment have been altered.

— Over the last 50 years, RN has been the standard of care for localized RCC, however, this approach has recently been questioned especially for T1 tumors smaller than 4 cm and even for larger tumors. The rationale that about 20% of these SRM are benign and significant loss of renal parenchyma due to RN may predispose patients to CKD, increased cardiovascular risk, and shorter survival, has led to increasing use of NSS in patients with smaller tumors. In summary, current evidence provided by the literature supports the advantage of NSS over RN in reducing the risk of CKD and promoting the awareness of the importance of kidney preservation. Furthermore, also simple enucleation of the tumor displays a proper treatment option at least in small lesions. However, RN is currently still indicated for non-metastatic T1 tumors when PN is not feasible and in tumors with a stage of at least T2 as well as in complex smaller tumors.

— The open approach for RN as well as NSS for smaller localized tumors has been the standard treatment for several years. Recently also laparoscopic techniques for RN have been shown to be safe for localized RCC and oncologically justifiable also for larger tumors (pT2-T3) when performed by experienced surgeons. Main patient related advantages include less postoperative pain and faster reconvalescence. New techniques such as single-site surgery and robotic-assisted surgery may further improve cosmesis and reduce postoperative pain, but larger patient series are required to confirm this. Due to its wide spread use and acceptance, open NSS currently remains the contemporary standard treatment in the management of SRM. Nevertheless, based especially on invasiveness, postoperative pain, scarring, longer hospitalization, and slower convalescence with open in comparison to laparoscopic techniques, also NSS procedures will be increasingly approached by laparoscopic or robot-assisted laparoscopic approaches, since laparoscopic NSS

can offer the advantages of reduced blood loss and shorter hospital stay with similar oncologic outcomes when compared with open surgery.[79] However, longer ischemia time, increased postoperative complication rates, and an increased number of subsequent procedures required should be considered as current drawbacks of minimally invasive NSS.[23] Recently, few studies have also compared perioperative results of RAPN and standard laparoscopic NSS, and current evidence suggests that RAPN can reproduce the advantages of minimal invasiveness with shorter learning curves and excellent perioperative outcomes also in patients with more complex and larger tumors.[82, 82]

— Since a growing number of elderly and comorbid patients are diagnosed with SRM, increasing attention is paid to alternative treatment modalities besides surgical treatment such as CA and RFA as well as to AS strategies. Aiming at avoiding unnecessary overtreatment which harbours also an increased risk of CKD with consecutive cardiac disorders as well as reduced OS, these techniques are increasingly applied. Recent studies have shown that RFA can provide durable oncologic control in patients with T1a biopsy-proven RCC and that it represents a proper minimally invasive treatment approach for appropriately selected patients with up to 4 cm and exophytic tumors. Another minimal-invasive treatment modality is CA, which is currently not widely used owing to a lack of long-term results. Short- and intermediate-term results have shown that CA represents an alternative treatment option which should be considered especially in elderly and unfit patients. Nevertheless, further prospective studies are necessary to establish the role of both RFA and CA as an equivalent to surgery for the definitive management of small kidney tumors.

— The rationale for AS is based on the hypothesis that active treatment for SRM may not influence OS in patients with limited life expectancy. This is underlined by results of resent studies, which have shown that non-RCC related mortality after surgical removal of SRMs is significant and correlates with age and comorbidities and that growth rate of SRMs under AS is overall slow and progression to metastatic disease is rare.[119-122] Further studies have shown that delayed intervention does not compromise the feasibility of NSS and deteriorate oncologic outcomes.[113] However, limitations of current AS series are the relatively short follow-up and the lack of pathological diagnosis in a significant number of cases. Finally, to date AS is not recommended for young and healthy patients, but is considered an appropriate strategy for the elderly or patients with significant comorbidities who are not proper surgical candidates.[49, 114, 115] Furthermore, there is no clear consensus on the best imaging technique and the optimal follow-up schedule that should be adopted in AS protocols.

— The role of percutaneous renal tumor biopsy in the management of SRM to assist in the choice of the appropriate treatment for each individual patient and especially in patients undergoing surveillance is expanding. Historically, RTBs have been rarely used because of concerns about their safety and accuracy.[118] Several large series of RTBs have been recently published, confirming that the procedure is characterized by low morbidity and oncological safety in centers with expertise. Needle biopsy can avoid unnecessary surgery for benign renal tumors that cannot be accurately identified by modern abdominal imaging, such as oncocytomas and fat-free angiomyolipomas.[119, 120] However, several issues with renal tumor biopsies have still to be resolved. Further improvements in biopsy techniques and in the definition of optimal patterns of biopsy are required, since overall, 3-30% of biopsies fail to provide final diagnosis. Although the diagnosis of histological subtype is possible in the majority of RTBs, differential diagnosis between oncocytoma and chromophobe RCC as well as assessment of grading remains particularly challenging on biopsy specimens.[119]

— Although benefit for patients might be minimal, RN as a cytoreductive approach improves survival in mRCC patients when combined with systemic treatment with in-

terferon alpha.[15, 16] During the last decade, molecular targeted agents such as TKIs, VEGF antibodies, and mTOR inhibitors have led to changed treatment paradigms in mRCC patients. Generally it is assumed that data from cytoreductive nephrectomy can be transferred also to the era of targeted treatment. However, data from randomized trials on the definite role for cytoreductive and neo-adjuvant nephrectomy in the era of targeted therapy have to be awaited.[17-20]

— Trials assessing the effect of targeted therapy as adjuvant treatment option after surgery in patients with high-risk localized and locally advanced tumors are also underway and results might change current treatment practice further, since until now outside clinical trials no adjuvant treatment option is available for RCC patients despite considerable recurrence rates after primary surgery.

Finally, local treatment in patients with localized as well metastatic RCC plays a considerable role for adequate patient management. In the near future, minimally invasive surgical treatment options such as laparoscopic and robot-assisted laparoscopic surgery will be increasingly applied based on promising results with regard to patient related benefits such as cosmesis as well equivalent oncological outcome in comparison to standard surgical treatment. Also ablative treatment options such as CA and RFA as well as surveillance strategies might be applied more often in order to avoid unnecessary overtreatment, development of chronic kidney disease, and reduced overall survival especially in patients with small kidney tumors. For the future, every new surgical and ablative treatment option for renal tumors needs to show robustness with regard to surgical and oncological results in comparison with the current standard treatment. For patients with advanced and metastatic disease results of prospective trials assessing the efficacy and role of multimodal, neo-adjuvant and adjuvant treatment as well as of cytoreductive surgery in the era of targeted treatment have to be awaited and might further change currently established treatment pathways. In order to individualize treatment on an individual patient level, which might further improve treatment management and patient outcome, in the future integration of molecular and cytogenetic information from renal tumor biopsies and further histological and clinical variables in algorithms and nomograms should be considered for patient counseling and improved treatment decision-making in RCC patients.

Riassunto

Gestione dei tumori renali localizzati e localmente avanzati. Un riesame contemporaneo delle attuali opzioni di trattamento

Circa il 70% dei pazienti con carcinoma renale presenta una patologia localizzata o localmente avanzata alla diagnosi primaria. Mentre tali pazienti sono potenzialmente curabili mediante il solo trattamento chirurgico, un ulteriore 20%-30% dei pazienti presenta una diagnosi di malattia metastatica primaria. Sebbene negli ultimi anni la cura medica dei pazienti metastatici sia quasi completamente passata dall'immunoterapia al trattamento efficace con agenti mirati, la malattia metastatica rappresenta ancora una patologia incurabile. Anche nei pazienti con malattia metastatica, il trattamento chirurgico del tumore primario svolge un ruolo importante, in quanto le complicanze locali correlate al tumore possono essere evitate o minimizzate attraverso l'intervento chirurgico. Inoltre, la chirurgia ha dimostrato anche il miglioramento della sopravvivenza globale dei pazienti metastatici, se abbinata al trattamento con citochina. Quindi, l'intervento chirurgico, abbinato alla cura sistemica come trattamento multi-modale, adiuvante e neo-adiuvante, è richiesto anche in pazienti con malattia avanzata o metastatica. Attualmente un numero crescente di pazienti anziani e comorbidi presenta una diagnosi di piccole masse renali e ciò ha comportato una maggiore attenzione per modalità alternative di trattamento ablativo, nonché per strategie di sorveglianza attiva, applicate in modo da evitare un inutile accanimento terapeutico su questi pazienti. Dal momento che il trattamento chirurgico potrebbe anche aumentare il rischio di malattia renale cronica con disturbi cardiaci consecutivi, nonché una riduzione della sopravvivenza globale, si applicano sempre di più tecniche di ablazione e di sorveglianza attiva. In questo articolo ci concentriamo sulle opzioni attuali di trattamento chirurgico e non chirurgico per la gestione dei pazienti con carcinoma renale localizzato, localmente avanzato e metastatico.

PAROLE CHIAVE: Carcinoma, cellule renali - Nefrectomia - Ablazione, tecniche.

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