



Surgery in renal cell carcinoma—when, whom and how?

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Summary Surgical resection of RCC should be the aim for cure of localized or locally advanced RCC, either by partial or radical nephrectomy, depending on tumor size and patient's performance status. In cT1 stages partial nephrectomy is recommended. In metastatic stage, immediate CN can be performed in patients with good performance status, who do not need systemic therapy because of oligometastatic disease with feasibility of complete resection.

Keywords Treatment algorithm for renal cell carcinoma · Radical nephrectomy · Partial nephrectomy · Robot assisted nephrectomy · Robot assisted partial nephrectomy

Introduction

Surgical resection of renal cell cancer (RCC) is the standard procedure to cure localized (cT1/cT2) or locally advanced (cT3/cT4) RCC. Due to improved

imaging, the time of RCC diagnosis has been moved forward leading to more frequent incidental diagnoses, predominantly of early stage cancers (7% of all diagnosed RCC in 1971 up to 57% in 2005–2010). Thus, kidney-sparing approaches, such as nephron-sparing partial nephrectomy or minimally invasive procedures, have gained popularity, leading to a paradigm shift in RCC surgery: historically, radical nephrectomy (RN) was the standard technique and partial nephrectomy (PN) was reserved only for imperative indications like bilateral RCC or an affected solitary kidney. Nowadays, the treatment of choice for patients with a diagnosis of early stage (cT1 and cT2) disease is PN. Despite the stage shift towards localized disease, up to a quarter of patients present with locally advanced or metastatic disease. In these patients, a multimodal approach potentially involving surgical debulking and systemic treatment needs to be discussed, ideally in a multidisciplinary tumor board.

Treatment of localized RCC—partial nephrectomy and radical nephrectomy

In localized RCC (cT1/cT2), surgical resection by either PN or RN should be performed. The decision between PN and RN should be based on surgical feasibility, including tumor size, tumor location and maintenance of functioning renal parenchyma, yet the consensus is to attempt nephron-sparing surgery. Possible deterioration of renal function after RN needs to be taken into account.

The 2019 EAU (European Association of Urology) Guidelines recommend PN for all patients with cT1 tumors and cT2 tumors, when surgically feasible. Based on one systematic review by MacLennan et al., no differences for the 5-year and 10-year OS (overall survival) and CSS (cancer specific survival) respectively

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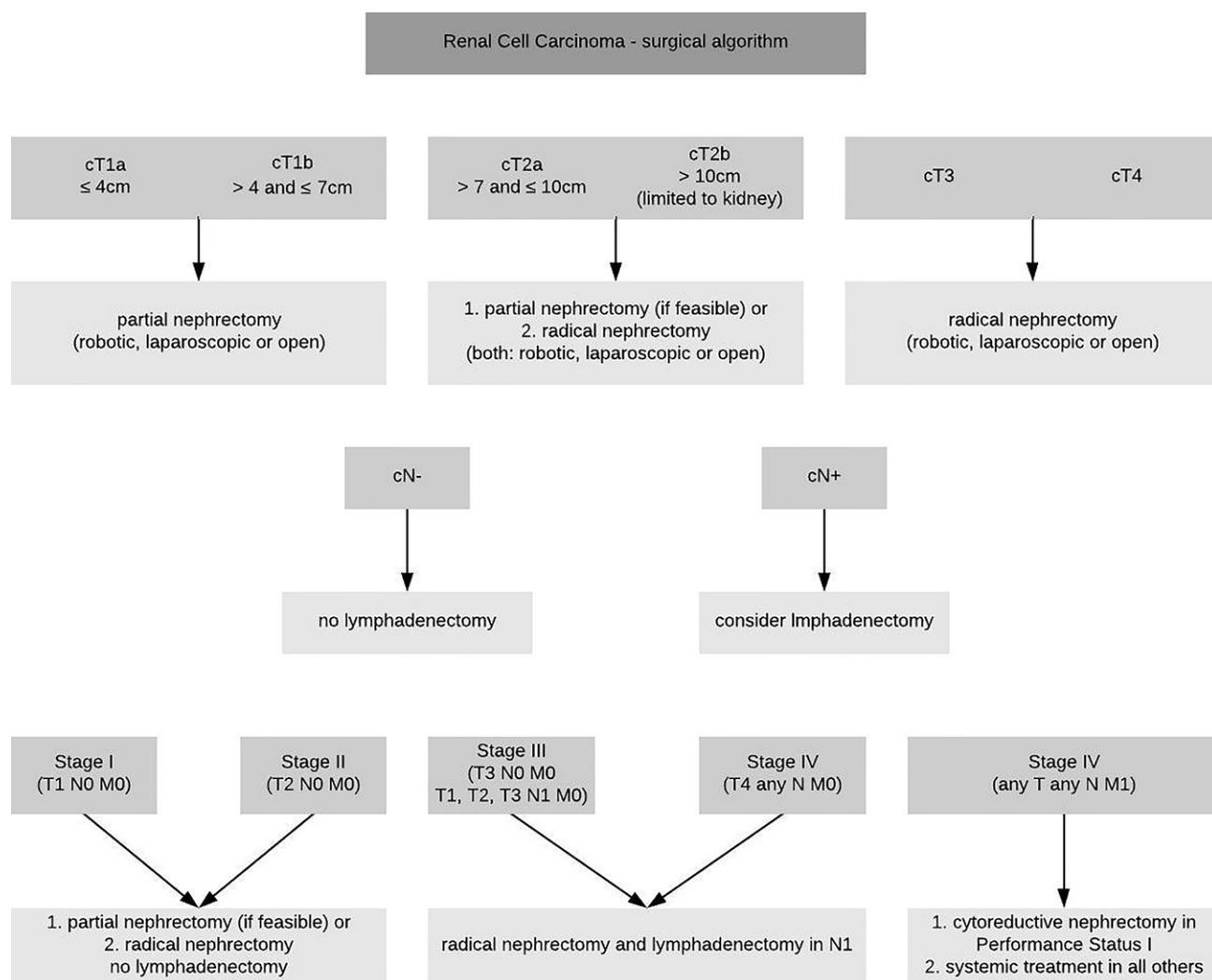


Fig. 1 Renal cell carcinoma—surgical algorithm

between open RN and open PN could be found, but when open and laparoscopic (lap.) approaches were considered together, an improved OS for patients with RCC <4 cm (\leq pT1a) for PN was found (5-year OS: open RN: 88.7%, lap. RN: 87.8%; 5-year OS \leq 4 cm: lap. PN: 74–97% vs open PN: 68–97%; lap. RN: 75–100%) [1]. Figure 1 depicts a surgical algorithm.

In the above mentioned review, several nonrandomized controlled trials were considered, showing slightly better 5-year OS for PN, irrespective of the surgical approach. Gill et al. showed an OS for PN after 7 years of 83.1% (lap.) vs. 83.5% (open), whereas Marszalek et al. showed a 5-year OS (only pT1 tumors) of 96% (lap.) vs. 85% (open) [2, 3]. Hemal et al. showed similar results in the 5-year OS and CSS for RN of 87.8%/95.12% (lap. RN) vs. 88.7%/94.36% (open RN) [4]. Tait et al. could not find differences in 5-year OS between open and laparoscopic RN in a meta-analysis of retrospective studies [5]. More than 20 further retrospective trials showed better OS for PN, but are limited by the retrospective design [6, 7].

Only one prospective multicenter, randomized controlled trial (RCT) assessed overall survival after PN and RN of RCC smaller than 5 cm in diameter in the EORTC trial 30904 [8]. Surprisingly, this study showed an improved OS for RN (81.1%, $n=273$) vs. PN (75.7%, $n=268$) ($p=0.03$) after 9.3 years of follow-up. No differences were seen in 10-year CSS (79.6% RN vs. 78% PN). Despite its multicenter design, the study was closed prematurely due to slow of recruitment. A total of 541 patients were randomized over a period of 11 years at 45 participating centers, resulting in an average recruitment of one patient per year per center. This study was criticized for not meeting the recruitment goal and for a potential selection bias. Despite these criticisms, this study is the only RCT available and showed an improved OS for RN in small RCCs, although more than 20 retrospective studies showed the opposite [6–8]. In 2017, this EORTC trial was tested for external validity with matching of baseline characteristics of the study population and the results were confirmed [9].

However, PN should be considered the gold standard in localized disease, since OS is at least comparable and perioperative outcomes should be considered too.

Another review by McLennan et al. analyzed the perioperative outcomes following surgery in localized RCC of 7 randomized controlled trials and 22 non-randomized trials. PN resulted in significantly better preservation of renal function and has a potentially lower risk of cardiovascular morbidity [10, 11]. Especially patients with pre-existing chronic kidney disease and with comorbidities, like hypertension or diabetes, will benefit from PN [12, 13] and experience a decreased risk of end stage renal disease [11, 14, 15].

Rates of osteoporosis and fractures as well as metabolic changes, like anemia or acidosis, has been shown to be lower for PN than RN, especially in tumor masses <2 cm [16, 17]. Capitano et al. confirmed these results in a multicenter, retrospective trial on 1331 patients with cT1a–T1b tumors and showed decreased risk of cardiovascular events related to RN, independently of PN techniques and that the split of curves of cardiovascular events occurred very early after surgery (PN: 1, 5, and 10 years: 5.5%, 9.9%, and 20.2%; RN: to 8.7%, 15.6%, and 25.9%) [18]. Since the decline of GFR occurred early after surgery, pre-existent renal function impairment seems to indicate the need for nephron sparing surgery. A study by Marszalek et al. showed higher early impairment after 24 h for the laparoscopic group than for the open group (8.8% vs. 0.8%, $p \leq 0.001$) but a similar impairment after 3–6 years for both groups (10.9% vs. 10.6%, $p = 0.8$) [3]. Gill et al. and Gong et al. confirmed these results [2, 19].

Postoperative complication rates are difficult to compare, since reporting was heterogeneous, but complication rates were generally low. Whereas some studies, like Gill et al. and Gong et al. showed higher complication rates for the laparoscopic approach (Gill et al., lap. 24.9% vs. open 19.2%; Gong et al.: 39% vs. 22%, $p = 0.026$), differences diminish when complications are standardized according to the National Cancer Institute Common Toxicity Criteria (14/100 vs. 19/100, $p = 0.8$) [2, 19]. This comparability could be confirmed by Marszalek et al. [3].

Blood loss, analgesic requirement and infection rates were lower in the laparoscopic groups [4, 20, 21]. Hospital stay was shorter for laparoscopic RN, shown in three studies with a difference of five days in favor of laparoscopic RN in one RCT by Peng et al. (median: –4.5 days). [20].

Any comparison between the open and laparoscopic or robotic approach is hampered by the absence of any prospective randomized clinical trial. Robotic approaches have been performed for more than 10 years but only one prospective cohort study is available showing similar results regarding blood loss, hospital stay and local cancer control between the laparoscopic and robotic approach [22]. One retrospec-

tive study showed no increased risk of complications but was associated with prolonged operating time and higher hospital costs compared with laparoscopic surgery [23]. In some studies, robotic surgery showed decreased morbidity with fewer complications, lower transfusion rates and shorter hospital stay too, but no difference in creatinine levels or positive surgical margins compared to open PN [24–26].

Several nephrometry scoring systems exist for assessing renal tumor masses, based on cross-sectional imaging findings, for aiding in the decision making of surgical strategies and patient's follow-up (P.A.D.U.A. [preoperative aspects and dimensions used for anatomic classification] score, R.E.N.A.L. [Radius, exophytic/endophytic location, nearness to collecting system, anterior or posterior location, location relative to kidney pole] score or C-Index [centrality index]), but the relevance of these scores in clinical routine remains unclear.

Treatment of locally advanced RCC (cT3/T4)

Open surgical approach remains the standard of care, even though a laparoscopic or robotic approach can be considered, when surgically feasible. Figure 1 depicts a surgical algorithm. The 5-year relative survival rate for locally advanced RCC is 69%, according to the SEER database [27].

Tumor stage plays an important role in timing of recurrence, with pT3 tumors generally recurring between 17 and 28 months following initial nephrectomy [28, 29]. After nephrectomy, the incidence of RCC recurrence has been reported to be 39% with a median time to recurrence at 17 months for T3 tumors, 7% at 38 months for T1 tumors and 26% with a median time of 32 months for T2 stages [29].

Tumor thrombus in the vena cava inferior implies worse prognosis, but the presence of thrombi is not associated with increased lymph node invasion or distant metastasis [30, 31]. The management of thrombus resection is associated with higher risk of complication. No surgical technique seems to be superior for thrombus excision [32, 33].

In case of nonresectable tumor burden, embolization of the renal artery can control symptoms (e.g. pain, hematuria) [34]. Systematic adrenalectomy is not recommended when abdominal CT shows no evidence of adrenal invasion.

Lymphadenectomy

The role of lymphadenectomy is still controversially discussed. There does not seem to be a benefit of systematic and extended lymphadenectomy during surgery of RCC—not in locally confined or in advanced disease without suspicious lymph node involvement (cN0 cM0) on preoperative staging. In those with enlarged regional lymph nodes, lymphadenectomy can be performed, mainly for staging

reasons. Less than 20% of suspected metastatic lymph nodes are finally malign in the histopathological examination [35]. Whether lymphadenectomy in these patients has an impact on survival remains to be determined; more recent studies, however, suggest that this is not the case [36, 37]. However, the EAU Guidelines recommend lymphadenectomy in patients with clinically enlarged lymph nodes for staging purposes.

Cytoreductive nephrectomy

Cytoreductive nephrectomy (CN) is defined as the removal of the primary RCC lesion in metastatic cases (mRCC). In the cytokine era, CN in mRCC was the standard for patients with good performance status and low metastatic burden [38]. In recent years, however, tyrosine kinase inhibitors (TKI) have become first-line treatment. This indicates the need for studies contributing to this paradigm shift. Two randomized trials analyzed the role of CN in the TKI therapy era (CARMENA study, SURTIME study) [39, 40]. The CARMENA study compared immediate CN + adjuvant sunitinib 4–6 weeks afterwards (A: $n=226$) vs. sunitinib (B: $n=224$) with a follow-up of 50.9 months. The median overall survival was 18.4 months in the sunitinib-alone group and 13.9 months in the nephrectomy–sunitinib group. While the SURTIME study was underpowered, the CARMENA study showed that OS for immediate CN in MSKCC intermediate- and poor-risk patients with asymptomatic primary tumors was worse than initial therapy with sunitinib and thus, immediate CN should no longer be considered the standard of care for these patient groups. Based on this RCT, indications for immediate CN adhere to good performance status, small lung metastases, single metastases, severe symptoms linked to the primary tumor and any indication for delayed initiation of systemic therapy. Since first-line systemic therapy has changed again towards immunotherapy, studies comparing this with the standard systemic treatment are needed.

The EAU guidelines recommend immediate CN for patients with good performance status and in patients with oligometastases, when complete resection of the metastases can be achieved. CN should not be performed in MSKCC intermediate-risk or poor-risk patients, who have an asymptomatic primary tumor and are accessible for systemic treatment.

Metastasectomy

Surgical metastasectomy (SM) may play a role in prolonging survival, as retrospective studies consistently show benefits for complete SM in terms of OS, CSS and delay/avoidance of systemic therapy. Six non-RCT reported a significantly longer median OS or CSS following complete metastasectomy (median OS/CSS: 40.75 months, range 23–122 months) compared to incomplete and/or no metastasectomy (me-

dian OS/CSS: 14.8 months, range 8.4–55.5 months) [41, 42]. The EAU guidelines postulate a weak recommendation for offering metastasectomy to patients, when complete resection is achievable.

Conflict of interest S. Lenart, I. Berger, N. Hartig, S. Madersbacher and A. Ponholzer declare that they have no competing interests.

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