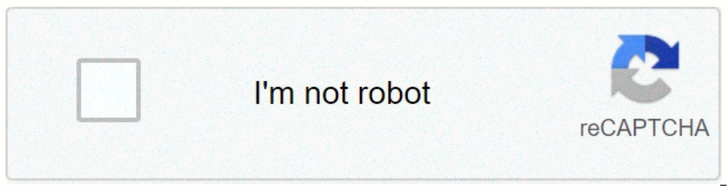

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Aua guidelines small renal mass

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J Urol 2014;191:907-12. 10.1016/j.juro.2013.10.099 [PubMed] [CrossRef] [Google Scholar]Page 2Patient and tumor characteristics to consider in guiding management of small renal massesManagement strategyOptimal candidatesContraindicationsActive surveillanceOlder patient at high risk of competing-cause mortality (multiple comorbidities, short life-expectancy)Young, healthy patient (long-term oncologic safety of surveillance is unproven, significant ionizing radiation exposure with periodic imaging)Severe renal dysfunction with risk of requiring hemodialysis after interventionNon-compliant patient unwilling to complete necessary radiographic imagingPatient refuses intervention–Hereditary RCC syndrome with neoplasm <3 cm (except syndromes associated with aggressive neoplastic behavior)–Focal ablationSmall, peripheral neoplasmYoung, healthy patient (long-term oncologic safety is unknown)Patient who is a poor surgical candidate who desires treatmentHilar mass (abutting vessels or collecting system)Patient desiring treatment who refuses surgeryLarger renal mass–Non-compliant patient unwilling to complete necessary follow-up radiographic imagingPartial nephrectomySolitary kidneyCoagulopathyPre-existing CKDComplex anatomyBilateral tumorsNon-compliant patient unwilling to complete necessary follow-up radiographic imagingHereditary RCC syndrome–Simple tumor anatomy–Radical nephrectomyComplex tumor in setting of normal contralateral kidneyHigh risk of post-operative CKD or end-stage bubrežna bolestOlder bolesnik s koobidnim stanjima s povišenim perioperativnim rizikom s djelomičnom nefretomijom– Sekcije 7.1.2 i 7.2.4.2 su The SR that all relevant published literature comparing surgical management of localised RCC (T1-2N0M0). Randomised or quasi-RST's are included. However, due to the very limited number of ERTs, non-randomised studies (NRS), prospective observational studies with controls, retrospective pair matching studies and comparative studies from databases of well-defined registries were also included. Historically, surgery has been a benchmark for the treatment of localized RCC.7.1.2.Surgical treatment7.1.2.1.Nephron-sparing surgery compared to radical nonfretomiesThis studies comparing the oncology outcomes of PN and RN are retrospective and include cohorts of varying and, overall, limited size [206]. There is only one potential RCT, including patients with limited-sized LTCs (< 5 cm), showing comparable CSS for PN versus RN [207]. Partial nonfretomy has shown that kidney function is better preserved after surgery, potentially reducing the risk of developing cardiovascular disorders [206,208-212]. Compared to the radical surgical approach, several retrospective analyses of large databases pointed to reduced cardiovascular-specific mortality [209,213] as well as improved OS for PN compared to RN. However, in some batches this was only true for younger patient populations and/or patients without significant combustion at the time of surgical intervention [214,215]. The Cochrane Review found that PN for clinically localised RCC was associated with reduced time to death of any cause compared to RN, while serious adverse event rates, CSS and time to recurrence were similar between the two groups [216]. Analysis of the Medicare database [217] could not prove the benefit of the OS for ≥ at age 75 when the RN or PN were compared with non-surgical management. Another series that addressed this issue and included Medicare patients suggested an OS benefit in the elderly population of RCC patients (75-80 years old) when they underwent surgery rather than non-military management. Shuch and Sur. compared patients undergoing PN for RCC with the Cancer-Free Healthy Control Group through a retrospective database analysis; OS benefit for cohort cancer [218]. These conflicting results may be an indication that unknown statistical confidantes interfere with retrospective analysis of tumour registries based on population. In contrast, only prospectively randomised but prematurely closed and severely weaker, the study did not show RN inferiority to PN in terms of OS [207]. Taken together, the OS advantage proposed for PN vs. RN remains an unresolved issue. Patients with normal preoperative renal function and reduced GFR due to surgical treatment (RN or PN), generally present with stable long-term renal function [212]. Harmful OS in patients with pre-existing GFR reduction does not appear to lead to further damage to renal function after surgery, but to other medical chronic kidney disease (CKD) [219]. However, especially in patients with pre-existing CKD, PN is the treatment of choice to limit the risk of developing an ESRD that requires haemodialysis. Only a limited number of quality of life studies (QoL) after PN versus RN are available, regardless of the surgical approach used (open vs. minimally invasive). Quality of life was ranked higher after PN compared to RN, but general patient health worsened after both approaches [220,221]. In terms of intra- and perioperative morbidity/complications associated with PN vs. RN, a randomized EORTC study showed that PN for small, easily resecutable, accidentally detected RCC, in the presence of a normal contralateral kidney, can be safely performed with slightly higher complication rates than after RN [221]. In view of the above, and since oncological safety (CSS and RFS) PN has proven similar for RN, PN is the treatment of choice for T1 RCC because it better preserves kidney function and in the long run potentially limits the incidence of cardiovascular disorders. Whether reduced mortality from any cause can be attributed to PN is still unresolved, but in patients with pre-existing CKD, PN is the preferred surgical treatment option as it avoids further deterioration in kidney function; the latter is associated with a higher risk of developing the ESRD and the need for haemodialysis. The study compared survival outcomes in patients with higher (≥ 7 cm) CCRCC treated with PN versus RN with long-term follow-up (median 102 months). Compared to the RN group, the PN group had a significantly longer median OS (p = 0.014) and median CSS (p = 0.04) [222]. SR and meta-analysis of comparative studies PN vs. RN for CT1b and T2 RNACSs observed that the PN group was less likely to repeat tumors (OR 0.6, p< 0.001), cancer-specific mortality (OR 0.58, p = 0.001) and all-cause mortality (OR 0.67, p = 0.005) compared to the RN group. For T2 tumours, estimated blood loss was higher for PN (p< 0.001), as was the likelihood of complications (RR: 2.0, p < 0.001). Recurrence rate (RR: 0.61, p = 0.004) and cancer-specific mortality (RR: 0.65, p = 0.03) were lower for PN [223].7.1.2.2.Related procedures7.1.2.2.1.Adrenalectomy Is the potential NRS comparing RN outcomes with or without, Ypsylateral adrenalectomy [224]. Multivariate analysis showed that the location of the upper pole is not predictive for the inclusion of the overhang gland, but the size of the tumor. No difference in OS after 5 or 10 years has been seen with or without adrenalectomy. Adrenalectomy is justified using criteria based on radiographic and intra-operational findings. Only 48 out of 2,065 patients underwent concomilate ypsilateral adrenalectomy, of which 42 were for benign lesions [224].7.1.1.1. 2.2.2.Dissection of lymph nodes for clinically negative lymph nodes (cN0)Indication for dissection of LN(LND) together with PN or RN is still [225]. Clinical assessment of LN status is based on the detection of CT/MRI VN enlargement or intraoperative palpability of extended nods. Less than 20% of suspected metastatic nodes (cN+) tested positive for metastatic disease in a histopathological study (pN+) [226]. CT and MRI are not suitable for detecting malignancy in nods of normal shape and size [227]. For clinically positive LN(cN+) see Section 7.2.2.Less retrospective studies have suggested a clinical benefit associated with more or less extensive LND preferably in patients at high risk of lymphogenic spread. In a large retrospective study, RN outcomes with or without LND in patients with high-risk non-mostatic RCC were compared by analyzing preference results. In this study, LND was not significantly associated with a reduced risk of distant metastases or mortality from cancer or all causes. Neither eLND nor LND scope was associated with improved oncology outcomes [228]. Number of LN metastases (< / > 4) as well as intra- and extracapacillar expansion of intra-nodal metastases correlated with clinical prognosis of patients in some studies [227,229-231]. Better survival outcomes were seen in patients with low positive LPs (< 4) and no extranodal enlargement. Based on retrospective analysis of the Surveillance, Epidemiology and End Results Database (SEER) > 9,000 patients, the effects of prolonged LND on disease-specific survival (DSS) of patients with pathologically restricted negative nods [232] were shown. However, in patients with pathologically proven lymphogenous spread (pN+), a 10 increase in the number of disseed nodes resulted in a 10% absolute increase in DSS. In addition, in a larger group of 1,983 patients, Capitanio and Dr. showed that prolonged LND results in a significant prolongation of CSS in patients with adverse prognostic features (e.g. sarcomatoid differentiation, large tumour size) [233]. As for the type of eLND-related pobola, a recent analysis of retrospective preference results from a large single-center database showed that eLND was not associated with an increased risk of Clavienic grade ≥ 3 complications. Furthermore, LND was not associated with length of hospital stay or estimated blood loss [234]. So far, only one prospective RCT has been published assessing the clinical value of LND in combination with surgical treatment of primary RCC. With an incidence of only 4%, the risk of lymphatic spread seems to be very low. Recognizing the latter, only the staging effect was attributed to LND [226]. This study involved a very high percentage of patients with pT2 tumours, who are not at increased risk of LN metastasis. In addition, only 25% of patients with pT3 tumours underwent complete LND. The LN template used by the authors is also not clearly stated. The optimal scope of the LND remains controversial. Retroactive studies suggest that extended LND should include ENs surrounding the Ypsilateral large vessel and interaortocoval region from the cross of the diaphragm to the common iliac arteries. Participation of interaortocacal LN's without participation in regional hilarity was reported in up to 35-45% of cases [227,235,236]. At least 15 LPs [233,237] should be removed. Sentinel LND is an investigative technique [238,239].7.1.2.2.3.EmbolisationBefore routine nonfretomy, tumor embolization has no benefit [240,241]. In patients who are unfit for surgery or with a disease that cannot be cut, embolisation may control symptoms, including visible haematuria or side pain [242,243]. These indications will be revisited in sections 7.2 and 7.3 with a cross reference to the summary of the evidence and recommendations below.7.1.2.2.4.Summary of the evidence and recommendations for the treatment of localised RCCSu summary of evidenceLECological outcome in OS-after PN terms is equivalent to that of RN in patients with c/p T1 RCC.1bIpsilateral adrenalectomy 1 during RN or PN does not have the advantage of survival in the absence of clinically obvious involvement of the canopy groove.3U patients with localised disease without evidence of LN metastases do not show an advantage of LND survival in combination with RN in randomised trials.2bRetrosspective studies suggest a clinical benefit associated with lymfadenectomy in high-risk patients.2bU patients unsuitable for surgery with massive haematuria or side pain, embolization may be a useful palliative approach.3RecommendationsStrength ratingOffer surgery to achieve cure in localized renal cell cancer. StrongOffer partial nonfretomy in patients with T1 tumours. StrongDo does not perform an ypsilateral adrenalectomy unless there is clinical evidence of an invasion of the outsmart gland. StrongOffer extended lymph node dissection for patients with adverse clinical features, including large diameter primary tumor. WeakOffer embolization to patients who are incapable of surgery with massive haematuria or pain on their side. Weak7.1.3.Radical and partial techniques of nonfretomy7.1.3.1.Radical nonfretomy techniques ERTs assessed the oncological outcomes of laparoscopic versus open RN. A cohort study [244] and retrospective database reviews, mostly of low methodological quality, showing similar oncology outcomes even for higher grade disease and locally more advanced tumors [245-247], are available. Based on SR, less morbidity was found for laparoscopic vs. open RN [206]. Data from one RCT [246] and two NRS [248,249] showed a much shorter hospital stay and a lower analgesic requirement for the laparoscopic RN group compared to the open group. Recovery time was also much shorter [249]. No difference was observed in the number of patients receiving blood transfusions, but periscope blood loss was significantly lower in the laparoscopic arm in all 3 studies [246,248,249]. Surgical complication rates were low with very wide confidence intervals. It wasn't complications, but surgery was significantly shorter in the open hand of nonfretomy. QoL's consdorative results were similar [248]. Some comparative studies focused on peri-operative outcomes of laparoscopic versus RN for kidney tumors ≥ T2. Overall, patients undergoing laparoscopic RN were shown to have lower estimated blood loss, lower postoperative pain, shorter length of hospital stay and recovery compared to those who underwent an open RN [247,249,250]. Intraoperative and postoperative complications were similar in the two groups and no significant differences were observed in CSS, PFS and OS [247,249,250] (LE: 2b). The second multilayered preference

coincided with the analysis compared to laparoscopic and open surgery for PT3a RCC, showing no significant difference in the three-year RFS between the groups [251]. The best approach for RN was a retroperitonal or transperitoneal approach with similar oncology outcomes in two RTC's [251,252] and one quasi-randomized study [253]. Quality-of-life variables were similar for both approaches. Manually assisted versus standard laparoscopic RN was compared in one quasi-randomised study [253] and one database review and the estimated 5-year OSS, CSS and RFS rates were comparable [254]. The duration of the surgical procedure was much shorter in manually assisted access, while the length of hospital stay and the time for strenuous activities were shorter for the standard laparoscopic RN cohort [253,254]. However, the sample size was small. SR reported laparoscopic versus conventional robot-assisted laparoscopic RN, showing no significant differences in local recurrence rates, or in cancer-specific mortality [255]. Similar results were seen in observational cohort studies comparing port-free and 3-port laparoscopic RN, with similar perioperative outcomes [256,257].7.1.3.2.Partial nonfretomy techniques Of study comparing laparoscopic and open PN found no difference in PFS [258-261] and OS [260,261] in laparoscopic studies centers. However, laparoscopic to open PN oncology safety has so far only been addressed in studies with relatively limited monitoring. Gill and Sur. suggested comparable oncology efficacy even in the case of higher grade tumours (pT1b/pT3a). However, a greater number of patients treated with open surgery in this series may reflect selection bias by offering laparoscopic surgery in the event of a less complex anatomy [262]. Mean estimated blood loss was found to be lower with laparoscopic access [258,260,263], while postoperative mortality, deep vein thrombosis and pulmonary embolism events were similar [258,260]. Operational time is generally longer with laparoscopic access [259-261], and warm ischemia weather is shortened by open access [258,260,263,264]. Compared to pairs, the decline in GFR was higher in the laparoscopic PN group in the immediate postoperative period [261], but not follow-up of 3.6 years. In the second comparative study, the surgical approach was not an independent predictor predictor of CKD [264]. Retroperitoneal and transperitoneal laparoscopic PN have similar perioperative outcomes [265]. Simple tumour anointing also had similar rates of PFS and CSS compared to standard PN and RN in a large study [266]. Hand-assisted laparoscopic PN (HALPN) is rarely performed. A recent comparative open-to-HALPN study showed no difference in OS or RFS when monitoring for the medium term. The authors observed a lower rate of intraoperative and all-grade postoperative 30-day complications in HALPN than in patients with open PN, but there was no significant difference in complications of high clavien grade. Three months after surgery, the glomerular filtration rate was lower in HALPN than in the open PN group [267]. The feasibility of laparoscopic PN in one place has been demonstrated in selected patients, but larger studies are needed to confirm its safety and clinical role [268]. In a retrospective study that matched preference scores, comparing PN with the help of open, laparoscopic and robotic, with 5 years of median follow-up, similar rates of local recurrence, distant metastases and cancer-related mortality rates [269] were found. One study prospectively compared the perioperative outcomes of a series of robotically assisted and open PN performed by the same experienced surgeon. PN with the help of robots was superior to opening PN in terms of lower estimated blood loss and shorter hospital stay. Warm ischemia weather, operational time, immediate and short-term complications, variations in drug levels and pathological margins were similar among groups [270]. The second study involved 50 of the most recent patients undergoing laparoscopic and robotic PN for T1-T2 kidney tumors by two different surgeons with experience of over 200 procedures each in laparoscopic and robotic PN and robotically assisted partial nonfretomy (RAPN), at the beginning of the study. Perioperative and short-term oncology and functional outcomes seemed broadly comparable between RAPN and LPN when performed by experienced surgeons [271]. A multicenter French perspective database compared the outcomes of 1,800 patients undergoing open PN and PN with the help of robots. Although monitoring was shorter, there was reduced pobola in the PN group with the help of robots with fewer overall complications, fewer major complications, fewer transfusions and a much shorter hospital stay [272]. Meta-analysis, including a range of NSS with variable methodological quality, compared the perioperative outcomes of robotically assisted and laparoscopic PN. The robotic group had a much lower conversion rate to open surgery and radical surgery, shorter warm ischemia weather, a smaller change in estimated GFR after surgery and a shorter length of hospital stay. No significant difference was observed between the two groups in terms of complications, serum anacrein change after surgery, operating time, blood loss and positive surgical margins [273]. In a recent analysis of 8,753 patients PN, an inverse non-linear hospital volume relationship with PN morbidity was observed, with a plateau of a total of 35 to 40 cases per year and 18 to 20 cases for robotic access [274]. A retrospective study by the US National Cancer Database looked at the prognostic impact of hospital volume and robot-assisted PN outcomes, including 18,724 cases. This study shows that undergoing RAPN in higher volume hospitals may have better perioperative outcomes (open conversion and length of hospital stay) and lower positive surgical margin rates [275]. The French study, including 1,222 RAPN, showed that hospital volume was the main predictive factor of Trifecta's achievement after adaptation for other variables, including surgeon volume [276].7.1.3.3.Positive margins on histopathological specimens of resected tumors Positive surgical margin is encountered in about 2-8% PNS [273]. Studies comparing surgical margins with different surgical approaches (open, laparoscopic, robotic) are inconclusive [277,278]. Most studies showed that the analysis within the operational frozen part did not affect the risk of certain positive surgical margins [279]. Positive surgical margin status occurs more frequently in cases where surgery is imperative (lone kidneys and bilateral tumours) and in patients with adverse pathological characteristics (pT2a, pT3a, grade III-IV) [280-283]. The potential negative impact of positive margin status on the oncology outcome is still controversial [277]. Most retrospective analyses reported so far have shown that positive surgical margins do not translate into a higher risk of metastasis or reduced CSS [281,282]. On the other hand, another retrospective study of a large individual institutional series showed that positive surgical margins were an independent predictor of PFS due to a higher incidence of remote and local relapses [284]. However, only a fraction of patients with precarious margin status actually have the remaining malignanducy [285]. In patients with positive surgical margins compared to 3% in patients with negative margins [280], patients with positive surgical margins were found to have local tumour beds at 16% compared to 3% in those with negative margins [280], therefore RN or re-reaction of margins may result in overtreats in many cases. Patients with positive surgical margins should be informed that they will need more intensive monitoring of surveillance (imaging) and are at increased risk of secondary local therapies [281,286]. On the other hand, relapse protection is not ensured by negative surgical margins [287].7.1.3.4.Summary of evidence and recommendations for radical and partial techniques of nonfretomyWith the evidenceLELaparoscopic radical nefracrect (RN) has a lower morbidity than open nonfretomy.1bShort-thermal oncology outcomes for T1-T2a tumours are equivalent to laparoscopic and open RN.2aPartial nonfretomy can be performed, Whether open, pure laparoscopic robotically assisted access, based on the expertise of surgeons and nephrectomy is associated with a higher percentage of positive surgical margins compared to RN.3RecommendationsStrength ratingOffer laparoscopic radical nephrectomy (RN) in patients with T2 tumors and localized masses that cannot be treated with partial nephrectomy (PN). StrongDo does not perform minimally invasive RN in patients with T1 tumours for whom PN is feasible by any approach, including open. StrongDo does not perform minimally invasive surgery if this approach may compromise oncological, functional and peri-operative outcomes. Strong7.1.4.Therapeutic approaches as alternatives to surgery7.1.4.1.Surgical compared to non-surgical treatment Studies based onpopulation compared oncological outcomes of surgery (RN or PN) and non-surgical management of tumors < 4 cm. Analyses showed significantly lower cancer-specific mortality in patients treated with surgery [217,288,289]. However, patients assigned to the supervisory group were older and likely more fragile and less fit for surgery. The mortality rates of other causes in the no-surgical group significantly exceeded the surgical group rate [288]. Analyses of elderly patients (> 75 years) did not show the same benefit in cancer-specific mortality for surgical treatment [290-292].7.1.4.2.SurveillanceElderly and comorbid patients with random small renal masses have low RCC-specific mortality and significant mortality from competing causes [293,294]. Active surveillance is defined as initial tumour size monitoring by serial abdominal imaging (US, CT or MRI) with delayed intervention reserved for tumours showing clinical progression during follow-up [295]. The concept of AS differs from the concept of waking waiting; vigilant waiting is reserved for patients whose co-offenders contraindications to any subsequent active treatment and do not require follow-up scans unless clinically indicated. In the largest as-reported series, renal tumour growth was low and progression to metastatic disease was reported in only a limited number of patients [296,297]. A single-sided comparative study evaluating patients at age > 75 showed reduced OS for those undergoing surveillance and nonfretomy compared to NSS for clinical T1 renal tumors. However, multi-variate analysis, a type of management was not associated with OS after age, energy and other variables were adjusted [293]. A statistically significant difference in OS and CSS was not observed in the second RN vs. PN study versus AS for T1a renal masses with a follow-up of 34 months [298]. Recently, the results of the Registry of Multiinstitutional Delayed Interventions and Monitoring for Small Renal Masses (DISSRM) were published. This potential NRS enrolled 497 patients with solid renal masses < 4 cm who chose AS or primary active intervention. Patients who chose AS were older, had poorer ECOG results, more coorbidity, smaller tumours, and more often had multiple and bilateral lesions. In patients have chosen AS in The total median rate of small kidney mass growth was 0.09 cm/year with a median follow-up rate of 1.83 years. The growth rate and variability decreased with longer monitoring. No patients developed metastatic disease or died of RCC [300]. Total survival for primary intervention and AS was 98% and 96% after 2 years, and 92% and 75% respectively after 5 years (p = 0.06). At 5 years old, CSS was 99% and 100% respectively(p = 0.3). Active surveillance did not foresee OS or CSS in regression models with relatively short monitoring [299]. Overall, short-term and intermediate oncology outcomes suggest that in selected patients with advanced age and/or coobidities, AS is suitable for initial monitoring of small renal masses, followed, if necessary, by treatment of disease progression [295-297,301-304]. A multicenter study evaluated QoL patients undergoing emergency intervention versus AS. Patients who underwent emergency intervention had higher QoL results at baseline, especially for physical health. The perceived benefit in physical health lasted at least a year after the intervention. Mental health, which includes the domains of depression and anxiety, has not been adversely affected while AS [305].7.1.4.3.Ablative therapy7.1.4.3.1.CryoablationCryoablation is performed using a percutaneous or laparoscopic assisted approach. In comparative studies, there was no significant difference in overall complication rates between laparoscopic and percutaneous cryoablation [306-308]. One comparative study showed similar OSS, CSS and RFS in 145 laparoscopic patients with longer follow-up compared to 118 patients treated percutaneously with shorter follow-up [307]. A shorter average length of hospital stay was found percutaneously [307-309]. A recent systematic review, including 82 articles, reported complication rates ranging between 8 and 20%, with most complications minor [310]. Although a precise definition of tumor recurrence is lacking, the authors reported lower RFS compared to PN.7.1.4.3.2.Cryoablation versus partial nephrotomyStudies compared open, laparoscopic or robotic PN with percutaneous or laparoscopic cryoablablia. Oncology outcomes were mixed and some studies showed no difference in OSS, CSS, RFS, disease-free survival (DFS), local recurrence or progression to metastatic disease [311,312], with some showing significant benefit for PN techniques for some or all of these outcomes [313-316]. Not all studies reported all of the above outcomes, and some were small and included benign tumors. No studies have shown an oncological benefit for cryoablation over PN. Peri-operating outcomes, complication rates and other QoL measures were mixed. Some studies have shown that the length of hospital stay is shorter and surgical blood loss is lower with cryoablablom [311-313], while at the same time no differences were found in other peri-operational outcomes such as complication rates or postoperative serum. Serum. Levels. Two studies [315,316] reported specific rates of Clavien, with mostly non-significant differences, which were mixed for intraoperative versus postoperative complications. The estimated GFRs did not differ significantly in the two studies, but in favour of cryoablation in a third [314-316]. Estimates of the new CKD were also mixed, with one study in favour of cryoablation [314], another strongly in favour of PN [315], and a third not showing a difference [316]. One study compared PN with ablation therapy, either cryoablation or RFA [317], and showed significantly improved DSS in 5 and 10 years for PN. The study compared 1,057 PN-treated patients with 180 RFA and 187 treated with cryoablation for the cT1 tumour and found no differences in RFS between the three techniques. Met metastase-free survival was superior after PN and cryoablation compared to RFA for patients with cT1a. However, monitoring of patients treated with thermal ablation was shorter [214].7.1.4.3.3.Radiofrequency ablationRadiofrequency ablation is performed laparoscopically or percutaneously. Four studies were compared in patients with T1a tumours treated with laparoscopic or percutaneous RFA [318-321]. Complications occurred in up to 29% of patients, but were generally minor. Complication rates were similar in patients treated laparoscopicly or percutaneously. One study with a limited number of patients showed a higher rate of incomplete ablation in patients treated with percutaneous RFA [320]. However, three comparative studies found no differences in relapse or CSS.7.1.4.3.4.Radiofrequency ablation versus partial nonfretomyThis publications on RFA are retrospective cohort studies with a small number of patients and limited follow-up. Some studies compared RFA retroactively with surgery in patients with T1a tumours [322-324]. One study compared patients with T1a who underwent RFA (percutaneous or laparoscopic) or PN and found no difference in OS and CSS [298]. The second study retroactively examined 105 patients with T1a treated with percutaneous RFA or RN. Cancer-specific survival was 100% in both groups [322]. Overall survival was lower in the RFA treatment group, but patients treated with surgery were younger [322]. A retrospective evaluation comparing RFA with LPN concluded after a median follow-up time of 27.5 months that both methods achieved equivalent secondary efficacy rates. Radiofrequency ablation involved several treatments, but session and hospitalization times were shorter and complications were less common than for LPN. Differences remained after adjusting for the complexity of the kidney tumour [325]. Methanalysis reported comparable complication rates and postoperative estimated glomerular filtration (eGFR) rates between RFA and PN [326]. The local tumour recurrence rate was higher in the RFA group than in the PN group = 1.81), but there was no difference in the occurrence of distant metastases. Retrospective analysis of 264 patients treated with RFA or PN and a median follow-up of 78 months showed that patients with T1b ccRCC had less favourable outcomes for percutaneant RFA compared to PN. However, percutaneant RFA provides comparable oncological outcomes of PN in patients with T1b non-ccRCC. The authors conclude that sub types of RCC may need to be taken into account when choosing PN or percutaneous RFA as a surgical approach to the treatment of T1b RCC [327]. Recent major systematic screening and meta-analysis, including 3,974 patients undergoing an ablation procedure (RFA or cryoablation) or PN, showed higher all-cause mortality and ablation-specific mortality rates than for PN (HR: 2.11 and 3.84, respectively). No statistically significant difference in local recurrence rates or risk of metastases was seen. Complication rates were lower for ablation than for PN (13% vs. 17.6%, p< 0.05). A significantly higher decrease in eGFR was observed after PN versus ablation therapy [328].7.1.4.3.5.Cryoablation and thermal ablation compared to delayed therapyAn analysis of the SEER registry included 733 patients with histo localised T1a ccRCC who either received cryos surgery (n = 315) or thermal ablation (n = 155), as well as patients who had delayed therapy (n = 263) [329]. Patients treated with cryosusus and thermal ablation benefited statistically significantly from CSS compared to those who had delayed therapy (cryosu operation HR: 0.25, 95% CI: 0.14-0.45, p< 0.001; heat ablation HR: 0.27, 95% CI: 0.13-0.55, p< 0.001, after adjusting age at diagnosis, tumor grade and size). However, in a systematic review and meta-analysis of 99 studies representing 6,471 small renal lesions, no statistical differences in the incidence of metastatic progression were found regardless of whether the lesions were cut, encryption or radiofrequency or observed [330].7,1,4,3,6.Cryoablation versus radio frequency ablationDwo studies compared RFA and cryoablation [331,332]. No study reported significant differences for OS, CSS or RFS. For local RFS in 5 years, one study [331] reported improvement with RFA, while another [332] reported benefit with cryoablation. One study [331] reported no difference in Clavien complication rates between the techniques. A recent retrospective series in including 384 patients (mean age 71; range 22 to 88 years) evaluated peri-operative heat ablation outcomes by microwave, RFA and cryoablation for stage T1c RCC. Complication rates and current changes in renal function were similar among the three ablation modalities. Microwave ablation was associated with significantly reduced ablation time (p< 0.05), procedural time (p< 0.05) and dose of sedative drugs (p< 0.05) compared to RF ablation and cryoablom. The authors conclude that CT-guided percutaneous microwave ablation is comparable to RF ablation or cryoablation for the treatment of phase T1N0M0 RCC with respect to response and is associated with shorter treatment times and less sedation than RF ablation or cryoablation [333].7.1.4.3.7.Other ablation techniquesMode studies have shown feasibility of other ablation techniques, such as microwave ablation, laser ablation, High Intensity American Ablation and irreversible electropocracy. However, these techniques are considered experimental.7.1.4.3.8.Summary of evidence and recommendations for therapeutic approaches as an alternative to surgerySu summary of evidenceLEVa population analyses show significantly lower cancer-specific mortality for patients treated with surgery compared to unruly management.3U active surveillance cohort, small renal mass growth is in most cases low, progression to metastatic disease is rare (1-2%).3Quality of available data does not allow definitive conclusions on morbidity and oncological outcomes of ablation cry and radiofrequency ablation.3Ni quality studies indicate a higher local reci rate of recitals treatments compared to partial nephrectomy.3RecommendationStrength ratingOffer active surveillance, radio frequency ablation or cryoablation on fragile and/or coorbid patients with small renal masses. Vulnerability When radiofrequency ablation, cryoablation and active surveillance are offered, they inform patients of a higher risk of local recurrence and/or tumour progression. Weak7.2.Treatment of locally advanced RCC7.2.1.IntroductionIn summary of the evidence and recommendations listed in Section 7.1 for localised RCC, certain therapeutic strategies arise in specific situations for locally advanced disease.7.2.2.2.Management of clinically positive lymph nodes (cN+)In the presence of clinically positive LPs (cN+), LND is always justified [23]. However, the scope of the LND remains controversial [227]. Systematic screening and meta-analysis attempted to assess the role of retroperitoneal LND in non-methic and mRCC [334]. The review included several studies recruiting patients at high risk of LN metastases, including patients with cN1. Diction of the lymph nodes was not associated with any survival benefit. However, LND may provide additional information about the staging. A recent analysis also shows that LND is not associated with improved oncology outcomes in patients with radiographic amphetamines (cN1) and over increasing thresholds of pN1 disease probability [228].7.2.3.Managing locally advanced non-resexctable RCCIn patients with non-resexctable disease, Embolism can control symptoms, including visible haematuria or pain on the side [242,243,335]. The use of systemic therapy to reduce tumors is experimental and cannot be recommended outside of clinical trials.7.2.4.Managing RCC with thrombus thrombus venous tumorTumur in patients with RCC is a significant harmful prognostic factor. Traditionally, patients with thrombus venous tumor thrombuses underwent surgery to remove renal and tumor thrombus. Aggressive surgical was widely accepted as the default management option for patients with tumour vein thrombus [336-344]. However, uncertainties remain regarding the best approach to surgical treatment for these patients.7.2.4.1.The evidence base for surgery in patients with venous tumour thrombodata regardless of whether patients with veined tumour thrombus should undergo surgery is derived only from a series of cases. In one of the largest published studies, higher trombone levels were not associated with increased tumour spread to LN, perinephical fats or distant metastases [341]. Therefore, all patients with non-mematic disease and venous tumour thrombuses and acceptable PS should be considered for surgical intervention, regardless of the extent of the tumour thrombus at the presentation. Surgical technique and case-by-case approach should be chosen based on the extent of tumour thrombus.7.2.4.2.2.Evidence was carried out for various surgical strategiesA systematic examination included only comparative studies on the management of thrombus venous tumour thrombosis in the non-mctatic RCC [345,346]. Only 5 studies were eligible for final inclusion, with a high risk of bias in all studies. Minimum access techniques resulted in significantly shorter working hours compared to the traditional median sternotomy [347,348]. Pre-operative embolism was associated with increased work time, blood loss, hospital stay and peri operative mortality in patients with T3 RCC [349]. No significant differences in oncology and process outcomes were observed between cardiopulmonary bypass with deep hypothermic circulation delay or partial bypass under normothermia or one cariferous clamp without circulation support [350]. It has not been shown that the surgical method is superior to the excision of venous tumor thrombuses. The chosen surgical method depended on the level of tumour thrombus and the degree of IVC occlusion [345,347,348,350]. The relative benefits and harms of other strategies and approaches regarding access to IVC and the role of IVC filters and circumvention procedures remain uncertain.7.2.4.3.Summary of evidence and recommendations for managing the RCC with venous tumour thrombobuss summaries of evidenceleu patients with locally advanced disease due to clinically enlarged lymph nodes (LN), the benefit of surviving LN dissection is unproven, but disseasion of LN adds staging.3An quality data suggest that the excision of tumor thrombus into non-metastatic diseases may be beneficial.3Tumour Embolization or inferior vein cava filter does not offer no benefits.3RecommendationsStrength rating In patients with clinically enlarged lymph nodes (LN), perform LN disseasion for staging or local control purposes. WeakRem renal tumor and thrombus in case of venous involvement in non-metastatic diseases. Strong7.2.5.Adjuvant therapy There is currently no evidence from randomized Phase III trials that adjuvant therapy offers a survival benefit. Impact of adjuvant tumour on OS in selected patients undergoing nonfretomy for renal cancer T3 remains unconfirmed [351-355] (LE: 1b). Results from previous adjuvant studies studying interferon-alpha (IFN-α) and interleukin-2 (IL-2) showed no survival benefit [356]. The heat shock-96 protein-peptide complex (vitespen) may benefit a subset of patients, but the overall data from the Phase III study were negative [357]. A similar observation was made in an adjuvant study of girentuximab, a monoclonal antibody against carboanhydrase IX (CAIX) (ARISER Study) [358]. No difference in DFS was observed in the overall study analysis, but the assessment of a subset of patients with the high term CAIX suggests a potential benefit from girentuximmab in this population. Several studies investigating adjuvant sunitinib, sorafenib or pazopanib reported that studies investigating sorafenib, axitinib and everolimus have completed the standoff and are expected to report in the coming years. Currently, there are no OS data supporting the use of adjuvant VEGFR or mTOR inhibitors. So far, three NCTs have been published comparing VEGFR-TKI versus placebo. One of the largest adjuvant studies compared sunitinib versus sorafenib versus placebo (ASSURE). Its interim results published in 2015 showed no significant differences in DFS or OS between experimental groups and placebo [359]. The study published an updated analysis of a subset of high-risk patients in 2018, which showed 5-year DFS rates of 47.7%, 49.9%, and 50.0%, respectively, for sunitinib, sorafenib and placebo (HR: 0.94 for sunitinib versus placebo; and HR: 0.90, 97.5% CI: 0.71-1.14 for sorafenib vs. placebo) and 5-year OS of 75.2%, 80.2%, and 76.5% (HR: 1.06, 97.5% CI: 0.78-1.45, p = 0.66, sunitinib vs. placebo; and HR : 0.80; 97.5% CI: 0.58-1.11, p = 0.12 for sorafenib vs. placebo). The results showed that adjuvant sunitinib or sorafenib therapy should not be given [360]. The PROTECT study included 1,135 patients between pazopanib (n = 571) and placebo (n = 564) in randomization 1:1 [361]. The primary endpoint was altered after 403 patients were enrolled in pazopanib 800 mg vs. placebo, in DFS with pazopanib of 600 mg. The results of the primary analysis of DFS in the intention of treatment (ITT) pazopanib 600 mg hands were not significant (HR: 0.86; 95% CI: 0.7-1.06, p = 0.16). Disease-free survival in the ITT pazopaniba population of 800 mg (HR: 0.69; 95% CI: 0.61 0.94, 1.06, p = 0.02) was improved. There were no OS uses in the 600 mg ITT pazopanib population (HR: 0.79 [0.57-1.09, p = 0.16]). A subset analysis of these studies suggests that full-dose therapy is associated with improved DFS. Furthermore, there was no strong link between DFS and OS [362,363] for the RCC. In contrast, the S-TRAC study included 615 patients randomised to sunitinib or placebo [364]. Results showed the benefit of sunitinib over placebo for DFS (HR: 0.76; 95% CI: p = 0.03), but the OS data remained immature. Grade 3/4 toxicity in was 60.5% for patients receiving sunitinib, which turned into significant differences in QoL due to loss of appetite and diarrhoea. The study published updated results in 2018; results for DFS did not change significantly (HR: 0.74; 95% CI: 0.55-0.99, p = 0.04), and the median OS was not achieved in any hand (HR: 0.92, 95% CI: 0.66-1.28, p = 0.6). In short, there is conflicting data in three available adjuvant therapy studies. A recent systematic review and meta-analysis combined the results of all three CTTs [365]. A pooled analysis of VEGFR-TKI versus placebo showed that VEGFR-focused therapy was not statistically significantly associated with improved DFS (HR: 0.92, 95% CI: 0.82-1.03, p = 0.16) nor OS (HR: 0.98.95% CI: 0.84-1.15, p = 0.84) compared to placebo. The adjuvant therapy group had significantly higher odds of Grade 3-4 side effects (OR: 5.89.95% CI: 4.85-7.15, p< 0.001). In short, there is currently a lack of proven benefits from adjuvant VEGFR-TKI therapy for patients with high-risk RCC after nonfretomy. The European Medicines Agency (EMA) did not approve sunitinib for adjuvant treatment of high-risk RCC in adult patients after nonfretomy.7.2.5.1.Summary of evidence and recommendations for adjuvant therapySuvant evidenceSumity of evidence daily cytokines do not improve survival after nonfretomy.1bMeal nefrecytomy in selected high-risk patients, adjuvant sunitinib improved disease-free survival (DFS) in one of the two available studies, but not overall survival (OS).1bAdjuvant sorafenib, pazopanib or axitinib does not improve DFS or OS after nephrectomy.1bRecommendationsStrength ratingDo do not offer adjuvant therapy with sorafenib, pazopanib or axitinib. StrongDo do not offer adjuvant sunitinib after surgically resected high-risk clear cancer renal cell cells. Weak7.3.Advanced/metastatic RCC7.3.1.Local advanced/metastatic RCC7 therapy.3.1.1.Cytoreductive nephrectomyTumour resection is potentially curative only if all tumor deposits are cut. This includes patients with primary tumour on site and single or oligometetic resect disease. For most patients with metastatic disease, cytoeductive nonfretomy (CN) is palliative and systemic treatments are required. In a meta-analysis comparing CN+ INF-based immunotherapy versus INF-based immunotherapy, increased long-term survival was found in patients treated with CN+ INF. However, INF-based immunotherapy is no longer relevant in modern clinical practice. In order to investigate the role and sequence of CNs in the era of targeted therapy, a structured literature assessment was carried out to identify relevant CRCT and systematic reviews published between 1 July and 30 June 2019. Two CTTs [367,368] and narrative systematic review [369] were identified. Narrative systematic review included both RCT and 10 NRSS. CARMENA, Phase III non-inferiority RCT investigates immediate CN follows vs. same sunitinib, equal, that sunitinib itself was not worse than CN, followed by sunitinib with respect to OS [370]. The study included 450 patients with medium- and low-risk metastatic CCRCC of which 226 were randomized to immediate CN and then sunitinib, and 224 to sunitinib only. Patients in both groups had a median of two metastatic sites. Patients in both groups had a median/mean tumour load of 140 00 cm of measurable disease according to the Solid Tumour Response Assessment Criteria (RECIST) 1.1, of which the primary tumour accounted for 80 00 000 H. The study did not reach a full estimate of 576 patients and the Independent Data Monitoring Commission (IDMC) advised the trial steering committee to close the study. In the ITT analysis after a median follow-up of 50.9 months, the median OS with CN was 13.9 months versus 18.4 months with sunitinib only (HR: 0.89; 95% CI: 0.71-1.10). This was found in both risk groups. For mid-risk mskcc patients (n = 256), the median OS was 19.0 months with CN and 23.4 months with sunitinib only (HR: 0.92; 95% CI: 0.60-1.24) and for MSKCC bad risk (n = 193) 10.2 months and 13.3 months (HR: 0.86; 95% CI: 0.62-1.17). Non-inferiority was also found in two protocol analyses that accounted for patients in the CN group who either did not undergo surgery (n = 16) or did not receive sunitinib (n = 40), and patients in the sunitinib-only group (n = 11). The median PFS in the ITT population was 7.2 months with CN and 8.3 months with sunitinib only (HR: 0.82; 95% CI: 0.67-1.00). The clinical benefit rate, defined as disease control after 12 weeks, was 36.6% with CN and 47.9% with sunitinib only (p = 0.022). For example, 38 patients in sunitinib only need secondary CN due to acute symptoms or for a complete or almost complete response. The median time from randomization to secondary CN was 11.1 months. A randomized study by EORTC SURTIME showed that the sequence of CN and sunitinib did not affect PFS (HR: [95% CI: 0.88 [0.59-1.37], p = 0.569). The study has come up poorly and therefore the results are mainly research-based. However, a secondary endpoint analysis showed a strong benefit from OS in favor of delayed cn access in the ITT population with a median OS of 32.4 (range 14.5-65.3) months in the delayed CN arm versus. 15.0 (9.3-29.5) months in the immediate CN hand (HR: [95% CI] 0.57 [0.34-0.95], p = 0.032). The delayed CN approach appears to select patients with inherent resistance to systemic therapy. This is confirmed by previous findings from the Phase II one-handed study [371]. Moreover, delayed CN and surgery makes it safe after sunitinib that supports findings, with some caution, of the only available RCT. In patients at poor risk of PS or metastatic consortium for renal cancer databases (IMDC), small pre-elections and high metastatic volume and/or sarcomatoid tumour, CN is not recommended [372]. data is confirmed by CARMENA [370].7.3.1.1.1.1.1.Embolisation of primary tumour In patients who are incapable of surgery or with a disease that cannot be cut, Embolism may control symptoms including visible haematuria or pain on the side [242,243,335] (see recommendations Section 7.1.2.2.4).7.3.1.1.2.Summary of evidence and recommendations for local population therapies advanced the metastatic RCCSu summary of evidenceLEDefered CN with pre-surgical sunitinib in medium-risk patients with cc-mRCC shows the survival benefit in secondary endpoint analyses and selects patients with inherent resistance to systemic therapy.2bSunitinib itself is not inferior compared to immediate CN followed by sunitinib in patients with MSKCC intermediate and poor risk requiring systemic VEGFR-TKI therapy.1aCytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligomet May improve survival and delay systemic therapy.3 Patients with MSKCC or IMDC low risk (≥ 4 risk factors) do not benefit from local therapy.1aRecommendationsStrength ratingDo do not perform cytolectomy (CN) in patients at poor risk of MSKCC. StrongDo does not perform immediate cn in MSKCC medium-risk patients who have an asymptomatic syncrotomatic primary tumor and require systemic therapy with vascular endothelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI). Weak health systemic therapy without CN in medium risk patients of MSKCC who have an asymptomatic syncrotometic primary tumour and require systemic VEGFR-TKI therapy. WeakDiscuss postponed CN in medium risk patients of MSKCC under VEGFR-TKI therapy who benefit from long-term lasting benefit and/or minimal residual metastatic load. WeakPerform direct CN in patients with good performance who do not require systemic therapy. WeakPerform direct CN in patients with oligometastases when complete local treatment of metastases can be achieved. Weak7.3.2.Local metastases therapy in metastatic RCCA SR local treatment of metastases from RCC in any organ was undertaken [373]. Interventions included metastasectomy, various radiotherapy modalities and no local treatment. The estimated outcomes were OS, CSS and PFS, local symptom control and adverse events. A bias risk assessment [374] was carried out. Of the 2,235 trials, only sixteen non-randomized comparative studies were identified. Eight studies reported local RCC-metastases therapies in different organs [375-382]. This included metastases on any organ or multiple organs. Three studies reported local RCC metastasis therapies in the bones, including the spine [383-385], two in the brain [386,387] and one each in the lungs [388] [389] and pancreas [390]. Three studies were published only as summaries [378,380,389]. The data was too heterogeneous for meta-analysis. There were significant variations in the type and distribution of systemic therapies (cytokines and VEGF inhibitors) and in the reporting of results.7.3.2.1.Complete no/incomplete metastasectomyAn systematic review, including only 8 studies, compared to not and/or incomplete metastasectomy of RCC metastases in different organs [375-382]. In one study, complete resection was achieved in only 45% of metastasectomy cohorts, which was compared without metastasectomy [382]. No non-surgical modalities were applied. Six studies [376-378,380-382] reported a significantly longer median OS or CSS after complete metastasectomy (median value for OS or CSS was 40.75 months, range 23-122 months) compared to incomplete and/or no metastasectomy (median value for OS or CSS was 14.8 months, range 8.4-55.5 months). Of the two remaining studies, one [375] showed no significant difference in CSS between complete and no metastasectomy, and one [379] reported a longer median OS for metastasectomy, although no p-value was provided. Three studies reported treatment for RCC metastases in the lungs [389], liver [388], pancreas [390]. The lung study showed a significantly higher median OS for metastasectomy versus medical therapy only for targeted therapy and immunotherapy. Similarly, a liver and pancreas study showed a significantly higher median OS and 5-year OS for metastasectomy versus. No metastasectomy.7.3.2.2.Local therapies for RCC bone metastases Out of three studies identified, one compared single-breasted image-guided radiotherapy (IGRT) with hypofractional IGRT in patients with RCC bone metastases [385]. Single-day IGRT (≥ 24 Gy) had a significantly better three-year actuary rate of local PFS, as cox's regression analysis also showed. The second study compared metastasectomy/curettage and local stabilization without lone RCC bone metastases surgery at various locations [383]. A much higher five-year CSS rate was observed in the intervention. After adjusting for prior nephrectomy, gender and age, multi-variate analysis continued to favor metastasectomy/curettage and stabilization. The third study compared the efficacy and durability of pain relief between single-dose stereotactic body radiotherapy (SBRT) and conventional radiotherapy in patients with RCC bone metastases with spine [384]. Pain, objective response rate (ORR), time relief to pain and duration of pain relief were similar.7.3.2.Local therapies for RCC brain metastasesTwo studies on RCC brain metastases were included. The three-armed study [386] compared stereotactic radio surgery (SRS) versus whole brain radiotherapy (WBRT) versus SRS and WBRT. Each group is further divided into recursive class I to III partition analysis (RPA) (I favorable, II moderate and III poor patient status). Two-year OS and intra-cerebral control were equivalent in patients treated only with SRS and SRS plus WBRT. Both treatments were superior only to WBRT in the general study population and in RPA subgroup analyses. Comparing SRS vs. SRS and WBRT in RPA class subgroup analysis showed significantly better 2-year OS and control for SRS plus WBRT based on only three participants. Second study compared to stereotactic radiotherapy (FSRT) with metastasectomy and conventional radiotherapy or conventional radiotherapy only [387]. Several patients in all groups underwent alternative surgical and no-surgical treatments after initial treatment. One-, 2-year and three-year survivals were higher, but not significant for FSRT as for metastasectomy and conventional radiotherapy or conventional radiotherapy only. Fractional stereotactic radiotherapy did not result in a significantly better two-year local control rate compared to metastasectomy plus conventional radiotherapy.7.3.2.4.Embolism of metastasesEmbolization before hypervascular bone or spinal metastasis resection may reduce intraperative blood loss [391]. U odabranih bolesnika s bolnim koštanim ili paravertebralnim metastazama, Embolija može ublažiti simptome [392] (vidi preporuku Odjeljka 7.1.2.2.4).7.3.2.5.Sažetak dokaza i preporuka za lokalnu terapiju metastazama u metastatskom RCCSu sažetku dokazaLESve studije uključene u sustavni pregled Panela bile su retrospektivne ne-randomizirane komparativne studije, što je rezultiralo visokim rizikom od pristranosti povezane s ne-randomizacijom, attrition, i selektivno izvještavanje.3Uz iznimku metastaza u mozgu i eventualno koštanim metastazama, metastasektomija ostaje prema zadanim postavkama jedini lokalni tretman za većinu mjesta.3Retrospektivna komparativna ispitivanja dosljedno ukazuju na korist potpune metastasektomije u bolesnika s mRCC-om u pojmovi ukupnog preživljenja, preživljenje specifično za rak i odgoda sistemske terapije.3Radioterapija metastazama kostiju i mozga iz RCC-a može izazvati značajno olakšanje od lokalnih simptoma (npr. bol).3RecommendationsStrength ratingTo kontrolirati lokalne simptome , offer ablation therapy, including metastasectomy, to patients with metastatic disease and favourable disease factors and for whom complete resection is achievable. WeakOffer stereotactic radiotherapy for clinically relevant bone or brain metastases for local control and symptom relief. Weak7.4.Systemic treatment for advanced/metastatic RCC7.4.1.Chemotherapy has proven generally ineffective in the treatment of RCC, but can be offered in rare patients, with the exception of canal collection and medullary carcinoma [393].7.4.1.1.1.Recommendation for systemic therapy in advanced/metastatic RCCRecommendationStrength ratingDo does not offer chemotherapy to patients with metastatic renal cell carcinoma. Strong7.4.2.Immunotherapy7.4.2.1.IFN-α monotherapy and combined with bevacizumabAll studies comparing targeted drugs with IFN α monotherapy showed superiority for sunitinib, bevacizumab plus IFN-α and temsirolimus [394-397]. Interferon-α was maimed by targeted therapy in clear-cell-mRCC (cc-mRCC). Table 7.1: Metastatic Risk Model consortium for Kidney Cancer Databases (IMDC) [398]*Risk Factors**Point of Benefit Cutting Off 80%Time from diagnosis to treatment< 12 monthsHaemoglobin< Lower limit of laboratory reference rangeIspid serum serum 10.0 mg/dl (2.4 mmol/L)Absolute number of neutrophils (neutrophilia)> upper limit of normal payment (plateletosis)> upper limit of normal*MSKCC(Motzer) criteria are also widely used in this environment [204].*Favorable (low) risk, no risk factors; medium risk, one or two risk factors; poor (high) risk, three to six risk factors.7.4.2.2.Interleukin-2Interleukin-2 has been used to treat mRCC since 1985. However, complete and sustained responses were achieved with a high dose of bolus IL-2, however, this can be achieved at less toxicity with combination therapy of immune checkpoint inhibitors and IL-2 is no longer widely used.7.4.2.3.Blockage of the immune system checkpoint7.4.2.3.1.Immuno-oncology monotherapyImu blockage of the checkpoint with monoclonal antibody targets and blocks the inhibitory PD-1 receptor of the T-1 receptor or cytotoxic antigen associated with T-lymphocyte 4 (CTLA-4)to restore tumor-specific T-cell immunity [401]. Monotherapy with an immune checkpoint inhibitor has been investigated as second and third line therapy. A Phase III study of nivolumab versus everolimus after one or two lines of VEGF-focused therapy (CheckMate 025, NCT01668784) reported a longer OS, better QoL and fewer grade 3 or 4 adverse events with nivolumab than in everolimus [182]. Nivolumab has superior everolimus OS (HR: 0.73, 95% CI: 0.57-0.93, p < 0.002) in VEGF-refractory RCC with a median OS of 25 months for nivolumab and 19.6 months for everolimus (LE: 1b). Patients who failed in multiple LINES of VEGF-focused therapy were enrolled in this study, making the results widely applicable. The study involved 15% of patients at poor risk of MSKCC. There was no PFS advantage with nivolumab despite the OS advantage. Progression-free survival does not appear to be a reliable surrogate of outcomes for PD-1 therapy in the RCC. Currently, PD-L1 biomarkers are not used to select patients for this therapy. There are no ERTs that support the use of single-agent immune checkpoint blockage in patients who are naïve to treatment. Randomized Phase II data for atezolizumab vs. sunitinib showed hr of 1.19 (95% CI: 0.82-1.71) which did not justify further assessment of atezolizumab as an individual means as a first-line treatment in this group of patients, despite high rates of complete response in the biomarker-positive population [402]. Phase II data from the Keynote-427 pembrolizumab study show high response rates of 38% (up to 50% in PD-L1+ patients), but PFS of 8.7 months (95% CI: 6.7-12.2) [403]. Based on these results and in the absence of randomized Phase III data, single-agent checkpoint inhibitor therapy is not recommended as an alternative primarily to therapy.7.4.2.4.Immunotherapy/combination therapy A Phase III CheckMate 214 study (NCT 02231749) showed superiority of nivolumab and ipilimumab over sunitinib. endpoint populations focused on the medium and bad IMDC risk populations where the combination showed OS OS (HR 0.63 95% CI: 0.44-0.89) which led to regulatory approval [404] and paradigm shifts in the treatment of mRCC [1]. Checkmate 214 results further found that the combination of ipilimumab and nivolumab was associated with higher response rates (RR) (39% in the ITT population), complete response rates (8% in the ITT population [central radiology review]) and duration of response compared to sunitinib. Progression-free survival did not achieve a predefined outcome. Research analysis of OS data in the PD-L1 positive population was 0.45 (95% CI: 0.29-0.41). The frequency of grade 3-4 adverse events and QoL data favored the immune combination. Nivolumab plus ipilimumab was associated with 3-5 degrees 15% toxicity including 1.5% of treatment-related deaths. Therefore it should be used in centers with experience of immune combination therapy and

appropriate supportive care in the context of a multidisciplinary team (LE: 4). The frequency of steroid use has caused controversy and further analysis, as well as real world data, are required. A recent update with 32-month data shows lasting benefits for immune combination with CR rates of 11% assessed by investigators and OS HR in the MID- and bad-risk IMDC group of 0.66 (95% CI 0.54-0.80) [406]. The IMDC Good Risk Group continues to perform well with sunitinib, although this seems less marked than in previous analyses (HR for OS 1.22 [95% CI: 0.73-2.04]). For these reasons, the Guidelines Commission continues to recommend ipilimumab and nivolumab in the middle and poor populations. The Keynote-426 study (NCT02853331) recently reported results from a combination of axitinib plus pembrolizumab versus sunitinib in 861 patients with CC-mRCC [407]. Total survival and PFS assessed by the central independent review in the ITT population were co-primary endpoints. Response and assessment rates in the PD-L1 positive patient population were secondary endpoints. With a median follow-up of 12.8 months, At the first interim analysis, both primary outcomes were achieved, median PFS in the pembrolizumab plus axitinib group was 15.1 months versus 11.1 in the sunitinib group (HR 0.69; 95% CI: 0.57-0.84, p < 0.001). The median OS was not achieved in either hand, but the risk of death was 47% lower in the hand of axitinib plus pembrolizumab compared to sunitinib (OS HR: 0.53; 95% CI: 0.38–0.74, p < 0.0001). Response rates were also higher in experimental arms (59.3% vs. 35.7%). Efficacy occurred regardless of imdc group and PD-L1 status. Treatment-related ace (≥ Grade 3) occurred in 63% of patients receiving axitinib and pembrolizumab versus 58% of patients receiving sunitinib. Treatment-related deaths occurred in approximately 1% in both hands. The JAVELIN study looked at 886 patients in Phase III RCT avelumab plus axitinib versus sunitinib [408]. He fulfilled one of his endpoint (PFS in PD-L1 positive population at first interim analysis [median follow-up 11.5 months]). Progression-free survival and OS in the ITT population were HR 0.69 (95% CI: 0.56-0.84) and 0.78 respectively (95% CI: 0.55-1.08). The same applies to the combination of atezolizumab/bevacizumab which also achieved a PFS advantage over sunitinib in the PD-L1 positive population at interim analysis and ITT (HR: 0.74 [95 % CI: 0.57-0.96]), but has not yet shown a significant OS advantage (HR: 0.81 [95% CI: 0.63-1.03]) [409]. The results are pending and the combination cannot be recommended at this time. Table 7.2: Cross trial comparison is not recommended and should occur with cautionStudyNExperimental armPrimary endpointRisk groupsPFSMedian (95% CI)HRKEYNOTE-426NCT02853331[407]861Pembrolizumab 200 mg. IV Q3W plus axitinib 5 mg. PO BIDvs.sunitinib 50 mg PO QD 4/2 weeksPFS and OS in the ITT by BICRIMDCFAV 31%IMD 56%POOR 13%MSKCCNot determined(ITT)PEMBRO + AXI 15.1 (12.6-17.7)SUN 11.1 (8.7-12.5)HR: 0.69 (95% CI: 0.57, 0.84)p = < 0.0001JAVELIN 101 NCT02684006[408]886Avelumab 10 mg/kg IV Q2W plus axitinib, 5 mg PO BIDvs.sunitinib 50 mg PO QD 4/2 weeksPFS in the PD-L1+ population and OS in the ITT by BICRIMDCFAV 22%IMD 62%POOR 16%MSKCCFAV 23%IMD 66%POOR 12%(PD-L1+)AVE + AXI 13.8 (11.1-NE)SUN 7.2 (5.7-9.7)HR: 0.61 (95% CI : 0.475, 0.790)p < .0001Immotion 151NCT02420821[409]915Atezolizumab 1200 mg fixed dose IV plus bevacizumab 15 mg/kg IV on days 1 and 22 of each 42-day cyclevs.sunitinib 50 mg. BY QD 4/2 weeksPFS in the PD-L1+ population and OS in the ITT by IRIMDCNot determinedMSKCCFAV 20%IMD 70%POOR 10%(PD-L 1+)ATEZO + BEV 11.2 (8.9-15.0)SUN 7.7 (6.8-9.7)HR: 0.74 (9 5% CI: 0.57, 0.96)p = 0.02Checkmate 214NCT02231749[405,410]1096Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2Wvs.sunitinib 50 mg. BY QD 4/2 weeksPFS and OS in the IMDC intermediate and poor population by BICRIMDCFAV 23%IMD 61%POOR 17%MSKCCNot determined(IMDC intermediate/poor)NIVO + IPI 11.8 (8.7-15 .5)SUN 8.4 (7.0-10.8)HR : 0.82 (99.1% CI: 0.64, 1.05)p = 0.03ATEZO = atezolizumab; AVE = avelumab; AXI = axitinib; BEV = bevacizumab; BICR = blinded independent central audit; CI = confidence interval; FAV = favorable; HR = hazard ratio; IPI = ipilimumab; IMD = medium; IMDC = Metastatic Consortium for Kidney Cancer Databases; IR = investigator review; ITT = intended treatment; IV = intravenous; NO = fixed; NR = not achieved; NIVO = nivolumab; OS = total survival; PEMBRO = pembrolizumab; PFS = survival without a profession; PO QD = by mouth, once a day; SUN = sunitinib. While this table provides a broad overview of the available ones, direct comparisons of cross-examinations of data should be avoided. Patients who stop nivolumab plus ipilimumab due to toxicity require expert guidance and support from a multidisciplinary team before a re-challenge occurs (LE: 1). (LE: 4). Treatment of progression of nivolumab disease and ipilimumab can be justified, but requires close examination and support from the expert multidisciplinary team [405,410] (LE: 1). Patients who stop axitinib and pembrolizumab due to immune system-related toxicity may receive single-agent axitinib after the adverse event has been resolved (LE: 1). Managing adverse events, including transaminitis and diarrhoea, requires particular attention, as both agents may be causal. Expert advice should be sought on re-contesting immune checkpoint inhibitors after significant toxicity (LE: 4). Treatment of disease progression on axitinibu and pembrolizumab requires careful consideration as it differs biologically from the treatment of past progression on ipilimumab and nivolumab. In general, The Panel is of the opinion that nivolumab plus ipilimumab and pembrolizumab plus axitinib should be used in centres with experience in immunological combination therapy and appropriate supportive care in the context of a multidisciplinary team (LE: 4).7.4.2.5.Summary of evidence and recommendations for immunotherapy in metastatic RCCSu summary provenLEInterferon-α monotherapy is inferior to VEGF-focused therapy or mTOR inhibition in mRCC.1bNivolumab leads to superior OS compared to everolimus in patients who fail one or two lines of VEGF.1bThebThe combination nivolumab and ipilimumab in patients who were naïve in treatment with clear cell mRCC (cc-mRCC) of medium and poor risk showed overall survival (OS) and objective response rate (ORR) compared to sunitinib.1 a combination of pembrolizumab and axitinib in treatment-naïve patients with cc-mRCC in all IMDC risk groups showed benefits from OS and ORR compared to sunitinib.1bCurrently, PD-L1 term is not used to select patients.2bAxitinib may continue if immune-related adverse events result in discontinuation of axitinib and pembrolizumaba. The re-challenge with immunotherapy requires expert support.4 Patients who do not receive full 4 doses of ipilimumab due to toxicity should continue to single-agent nivolumab, where safe and feasible. The re-challenge with combination therapy requires professional support.4Treatment past progression may be warranted, but requires close examination and support from the expert multidisciplinary team.1bNivolumab plus ipilimumab and pembrolizumab plus axitinib should be administered in centres with experience of immune combination therapy and appropriate supportive care in the context of multidisciplinary combination of nivolumab and ipilimumab in the ITT population of unelected patients with CC-mRCC leads to superior survival compared to sunitinib.2bDue to the research nature of PD-L1 tumour expression , small sample sizes, lack of OS data and premature results in this subpopulation, no definitive conclusions can be drawn in relation to the usefulness of PD-L1 plus ipilimumab was associated with 15% of the class toxicity and 1.5% treatment-related deaths.1bRecommendationsStrength ratingOffer pembrolizumab plus axitinib for patients who were naïve in treatment with any metastatic renal cell carcinoma (cc-mRCC) StrongOffer ipilimumab plus nivolumab for patients with medium- and bad-risk IMDC cc-mRCC.StrongAdminister nivolumab plus ipilimumab and pembrolizumab plus axitinib in centers with experience in immune combination therapy and appropriate supportive care in the context of a multidisciplinary team. WeakPatients who do not receive full 4 doses of ipilimumab due to toxicity should continue to single-agent nivolumab, where safe and feasible. WeakOffer axitinib as a follow-up treatment for patients who experience adverse immune-related events after treatment that limit treatment with a combination of axitinib and pembrolizumab. The feeant progression of the past can be justified, but it requires close examination and support from an expert multidisciplinary team. WeakDo does not reassess patients who have stopped immune checkpoint inhibitors due to toxicity without the expert guidance and support of a multidisciplinary team. StrongOffer nivolumab after one or two lines of vascular endothelial therapy focused on growth factor in mRCC.StrongOffer sunitinib or pazopanib for the treatment of naïve patients with IMDC favorable, medium and poor cc-mRCC risk who cannot receive or tolerate inhibition of the immune checkpoint. StrongOffer cabozantinib for the treatment of naïve patients with medium- and bad-risk CC-mRCC imDC who cannot receive or tolerate inhibition of an immune checkpoint. Strongaa While this is based on a randomized Phase II trial, cabozantinib (weak) looks at least as good as the sunitinib in this population. This justified the same recommendation in exceptional circumstances.7.4.3.Targeted therapies In sporadic CCRCC, the accumulation of hypoxia inducibar (HIF) due to VHL inactivation results in excessive expression of VEGF and platelet-derived growth factor (PDGF), which promote neoangiogenesis [411-413]. This process contributes significantly to the development and progress of the RCC. Several targeted medicines for the treatment of mRCC have been approved in both the US and Europe.Most of the published trials have been selected for clear cell cancer sub types, therefore no firm evidence-based recommendations can be made for non-CCRCC sub-types. In large studies leading to the registration of approved targeted funds, patients were stratified according to the IMDC risk model (Table 7.1) [205]. Table 7.3: Median OS and Percentage of Patients Who Survived Two Years of Treatment in The Age of Targeted Therapy per IMDC Risk Group*,**IMDC ModelPatients**Median OS* (Months)2-yr OS (95% CI)*n%Favorably1571843 .275% (65-82%)Intermediate4405222.553% (46-59%)Poor252307.87% (2-16%)* Based on [205]; ** based on [398]. CI = confidence interval; IMDC = Metastatic Consortium for Databases on kidneys; n = number of patients; OS = total survival; yr = year.7.4.3.1.Tyrosine kinase kinases oral inhibitor of multi-kinase. The study compared sorafenib and placebo after failure of prior systemic immunotherapy or in patients unsuitable for immunotherapy. Sorafenib Enhanced PFS (HR: 0.44; 95% CI: 0.35-0.55, p< 0.01) [414]. Overall survival improved in patients initially assigned placebos who were censored on crossover [415]. In patients with previously untreated mRCC sorafenib, it was not superior to IFN α (Phase II study). Numerous studies have used sorafenib as a control group in sunitinib-refractory disease versus axitinib, dovitinib and temsirolimus. None showed superior survival for the drug for the study compared to sorafenib.7.4.3.1.2.SunitinibSunitinib is an oral inhibitor of TKI and has anti-tumor and antiangiogenic activity. The first line of sunitinib monotherapy showed significantly longer PFS compared to IFN-α. Overall survival was higher in patients treated with sunitinib (26.4 months) α versus INF (21.8 months) despite crossover [417]. In effect, sunitinib 50 mg/day (4 weeks per/2 weeks off) was compared with continuous continuous sunitinib of 37.5 mg/day in patients with cc-mRCC [418]. No significant differences were seen in the OS (23.1 vs. 23.5 months, p = 0.615). Toxicity was comparable in both hands. Due to a non-significant but numerical long time to progression with a standard dosing of 50 mg, the authors recommended the use of this regimen. Alternative sunitinib scheduling (2 weeks per/one week off) is used to manage toxicity, but robust data are missing to support its use [419,420].7.4.3.1.3.PazopanibPazopanib is an oral angiogenesis inhibitor. A significant improvement in PFS and tumour response [421] was observed in the pazopanib versus placebo study in patients with naïve mRCC therapy and cytokine-treated patients. A non-inferior study comparing pazopanib with sunitinib (COMPARZ) established pazopanib as an alternative to sunitinib. Pazopanib has been shown not to be associated with significantly worse PFS or OS compared to sunitinib. The two drugs had different toxicity profiles and QoL was better with pazopanib [422]. In another study preferred to the patient (PISCES), patients preferred pazopanib to sunitinib (70% vs. 22%, p< 0.05) due to symptomatic toxicity [423]. Both studies were limited in this intermittent therapy (sunitinib) compared to continuous therapy (pazopanib).7,4,3,1,4,axitinibAxitinib is an oral selective inhibitor of the second generation VEGFR-1, -2 and -3. Axitinib was first evaluated as a second line of treatment. In the AXIS study, axitinib was compared with sorafenib in patients who had previously failed to treat cytokine or targeted agents (mainly sunitinib) [424]. The total median pfs was higher for axitinib than sorafenib. Axitinib was associated with higher PFS than sorafenib (4.8 vs. 3.4 months) after progression Axitinib showed grade 3 diarrhoea at 11%, hypertension in 16%, and fatigue in 11% of patients. The final OS analysis showed no significant differences between the or sorafenib [425,426]. The randomised Phase III study of axitinib versus sorafenib in frontline treatment with naïve CCRCC showed no significant difference in the median PFS between treatment groups, although the study was insufficient, which increased the possibility of type II error [427]. As a result of this study, axitinib was not approved for first-line therapy.7.4.3.1.5.CabozantinibCabozantinib is an oral inhibitor of tyrosine kinase, including MET, VEGF and AXL. Cabozantinib was investigated in a Phase I study in patients resistant to VEGFR and mTOR inhibitors showing objective responses and disease control [180]. Based on these results, RCT investigated cabozantinib versus everolimus in patients with CCRCC who had one or more VEGF(METEOR)-focused therapies [181,428]. Cabozantinib delayed PFS compared to everolimus in vegf-focused refractory disease therapy (HR: 0.58 95% CI: 0.45-0.75) [181] (LE: 1b). The median OS was 21.4 months (95% CI: 18.7 to cannot be estimibilly) with cabozantinib and 16.5 months (95% CI: 14.7-18.8) with everolimus in VEGF-resistant RCC. HR for death was 0.66 (95% CI: 0.53-0.83, p = 0.0003) [428]. Grade 3 or 4 side effects were reported in 74% with cabozantinib and 65% with everolimus. Side effects were managed by dose reduction; doses were reduced in 60% of patients receiving cabozantinib. A randomised Phase II study of The A031203 CABOSUN Alliance comparing cabozatinib and frontline sunitinib in 157 medium and bad risk patients preferred cabozantinib for RR and PFS but not OS [429,430]. Cabozantinib significantly increased the median PFS (8.2 vs. 5.6 months, adjusted HR: 0.66; 95% CI: 0.46 to 0.95; one-sided p = 0.012). The objective response rate was 46% (95% CI: 34-57) for cabozantinib versus 18% (95% CI: 10-28) for sunninib. Grade 3 or 4 side effects were similar for cabozantinib and sunitinib. No difference was seen in the OS. Due to the limitations of statistical analyses in this study, the evidence is inferior to the existing choices.7.4.3.1.6.LenvatinibLenvatinib is the oral multi-target TKI VEGFR1, VEGFR2 and VEGFR3, with inhibitory activity against fibroblast growth factor receptors (FGFR1, FGFR2, FGFR3 and FGFR4), platelet growth factor receptors [(PDGFR- α), re-deployed during transfection (RET) and stem cell factor receptors (KIT). It was recently investigated in a randomized Phase II study in combination with everolimus versus lenvatinib or everolimus (see section 7.4.6.1.1.5 for discussion of results) [431].7.4.3.1.7.TivozanibTivozanib is a powerful and selective TKI VEGFR1, VEGFR2 and VEGFR3 and was compared in two Phase III studies with sorafenib in patients with mRCC [432,433]. Tivozanib is approved by the EMA in the first place of the MRCC. Although it is associated with PFS advantage in both studies, it has not seen an OS advantage. Given the choice of sorafenib as a control arm in the frontline study, the Commission considers that there is too much uncertainty and alternatives, to support its use in this environment.7.4.4.Monoclon antibody against circulating VEGF7.4.4.1.Bevacizumab monotherapy and bevacizumab plus IFN-αBevacizumab is a humanized monoclonal antibody. The double blind AVOREN study compared bevacizumab plus IFN-α with inf-α monotherapy in mRCC. The overall response was higher in the group that was in the α issuing group. Median PFS increased from 5.4 months from IFN to α 10.2 months with bevacizumab plus IFN-α. There was no benefit in patients at poor risk of MSKCC. The median OS in this study, which allowed the transition after progression, was not higher in α the group that was in the vaccination group/IFN (23.3 vs. 21.3 months) [434]. An open label study (CALGB 90206) of bevacizumab plus IFN α versus IFN showed α higher median PFS for the combined group [435,436]. The objective response rate was also higher in the combined group. Overall toxicity was higher for bevacizumab plus IFN-α, with significantly more Grade 3 hypertension, anorexia, fatigue and proteinuria. Bevacizumab, alone or in combinations, is not widely recommended or is used in mRCC due to more attractive alternatives.7.4.5.mTOR inhibitors7.4.5.1.TemsirolimusTemsirolimus is a specific mTOR inhibitor [437]. Its use is supersed as a first-line treatment option.7.4.5.2.EverolimusEverolimus is an oral mTOR inhibitor, which has been established in the treatment of VEGF-refractory disease. The RECORD-1 study compared everolimus plus best supportive care (BSC) versus placebo plus BSC in patients with previously failed VEGFR treatment (or previously intolerant of VEGF-focused therapy) [438]. The data showed a median PFS of 4 vs. 1.9 months for everolimus and placebo, respectively [438]. The RCC Guidelines Committee considers, even in the absence of compelling data, everolimus may be a therapeutic option in patients who have been insinterested in, or previously failed therapies targeting immunological and VEGFR (LE: 4). Recent Phase II data suggest that the addition of levantinib is attractive.7.4.6.Therapeutic strategies7.4.6.1.Treatment for naïve patients with clear cellular metastatic RCC-1. The combination of pembrolizumab and axitinib as well as nivolumab and ipilimumab is the standard of care in all patients at medium and poor risk of IMDC and IMDC (Figure 7.1). Therefore, vegfr-TKI's role alone in the frontline mRCC is superseded. Sunitinib, pazopanib, and cabozantinib (a disease of medium and bad IMDC risk), alternative treatment options remain for patients who cannot receive or tolerate the inhibition of an immune checkpoint in this environment (Figure 7.1).7.4.6.6. 1.1.1.Sequencing systemic therapy in metastatic RCC the biscuit RCC Sequencing of Targeted Therapies was established in the mRCC and maximizes outcomes [181,182,431]. Pembrolizumab plus axitinib and nivolumab plus ipilimumab are the new standard of care for frontline therapy. Impact immune checkpoints to subsequent therapies is unclear. Randomised data on patients with the disease refractory to nivolumab plus plus or pembrolizumab plus axitinib in the first river environment, and the cohorts available are limited [439]. Potential data on cabostinib and axitinib are available to patients advancing immunological therapy, but these studies do not focus only on the frontline setting, include subgroup analysis and are too little for definitive conclusions [181,440]. Retrospective data on VEGFR-TKI therapy after progression on the front line of immune combinations exist, but they have significant limitations. When these data are taken into account in its entirety, there is some activity, but it is still too early to recommend one VEGFR-TKI above the other after immunotherapy-immunotherapy or immunotherapy-VEGFR combinations (Figure 7.2). After a combination of axitinib and pembrolizumab, it is recommended to change VEGFR-TKI in progression, which may be cabozantinib or any other TKI that has not previously been used. The Panel does not favour the use of mTOR inhibitors unless vegf-focused therapy is contraindicated because they are mapped by other VEGF-focused therapies in mRCC [441]. The choice of the drug in a third-line environment, following combinations of immune checkpoint inhibitors and subsequent VEGF-focused therapy, is unknown. The commission recommends a subsequent agent approved in vegf-refractory diseases, with the exception of a renewed challenge with the blocking of the immune checkpoint. Cabozantinib is the only agent in VEGF-refractory disease with survival advantage in RCT and should be used preferentially [424]. Axitinib has positive PFS data in VEGF-refractory disease. Both sorafenib and everolimus were surpassed by other agents in VEGF-refractory diseases and are therefore less attractive [441]. The combination of Lenvatinib and everolimus seems superior only to everolimus and has received EMA regulatory approval based on randomized Phase II data. This is an alternative despite the availability of Phase II data only [431]. Tivozinib has pfs superiority in sorafenib in VEGF-refractory disease, as shown in a study involving patients with immune checkpoint inhibitors [442].7.4.6.2.Unclear RCCNo Phase III metastatic studies of patients with non-cc-mRCC have been reported. Extended access programmes and subgroup analysis from the RCC study suggest that the outcome of these targeted therapy patients is worse than for ccRCC. Targeted treatment in non-cc-mRCC focuses on temsirolimus, everolimus, sorafenib, sunitinib and pembrolizomab [396,443-445]. The most common subtypes of obscure cells are papillary type I and non-type I papillary CCACs. There are small one-handed trials for sunitinib and everolimus [445-448]. The study of both types of everolimus treated pRCC (RAPTOR) [448], showed a median PFS of 3.7 months per central review in the ITT population with an OS median of 21.0 months. However, a randomized Phase II study of everolimus versus sunitinib (ESPN) with crossover design in non-cc-mRCC, including 73 patients (27 with pRCC) je nakon analize uzaludnosti za PFS i OS [449]. The The results showed an insatiable trend of favoring sunninib (6.1 vs. 4.1 months). Based on a systematic review, including analysis of a subset of ESPN, RECORD-3, and other Phase II (ASPEN) trials, sunitinib and everolimus remain options in this population, with a preference for sunitinib [7,139,450]. Patients with non-cc-mRCC should be referred for a clinical trial, as appropriate. Pembrolizumab efficacy (n = 165; response rates of 24%, PFS 4.1 months [95% CI: 2.8-5.6 months] 72% one-year OS) were reported, but these results are based on a Phase II one-handed study [403]. Pembrolizumab can be recognized in this environment due to the great unmet need. Subgroup analysis showed impressive results for PD-L1 inhibitors in combination with CTLA4 or VEGF-focused therapy in renal tumors with sarcomatoid features. Bevacizumab/atezolizumab, ipilimumab/nivolumab, axitinib/pembrolizumab and avelumab/axitinib may only be recommended instead of VEFG-focused therapy. These options have impressive OS benefits over sunitinib and supersed VEGF targeted therapies. Canal collection cancers and renal medullary cancers are very resistant to systemic therapy. So far, only case reports have been published for a range of treatment options and no clear recommendations can be made until data from international registers (RARECARE) or clinical trials become available. Figure 7.1: Updated recommendations from the European Association for Urological Guidelines for FirstLine Treatment and Next Line in Metastatic Kidney Cancer U IFDC = International Consortium for Metastatic Renal Cell Databases*pazopanib only for medium-risk diseases. [1b] = based on a single randomised phase III controlled trial. [2a] = based on a single randomised Phase II controlled trial. Figure 7.2: Recommendations of guidelines for later therapy IO = immunotherapy; TKI = tyrosine kinase inhibitors; VEGF = vascular endothelial growth factor. [1b] = based on a single randomised phase III controlled trial. [2b] = analysis of a subset of a randomised Phase III controlled trial. [4] = expert opinion.7.4.7.Summary of evidence and recommendations for targeted therapy in metastatic RCCSu summary of VEGF vegf-focused therapy is surpassed by combination therapy based on immune checkpoint.1bPazopanib is not inferior to sunitinibu in the front line of mRCC.1bCabozantinib in intermediate and poorly risky treatment-naïve RCC clean cells leads to better response rates and PFS, but not OS compared to sunitinib.2bTivozanib is approved by the EMA, but evidence is still considered inferior to existing choices in the frontline environment.3Single-agent VEGF-targeted therapies are recommended preferentially after combinations based on the front line of PD-L1. It is necessary to avoid re-challenging with treatments already used.3Single-agent cabozantinib or nivolumab are superior to everolimus after one or more vegf.1bEverolimus-focused therapy prolongs PFS after VEGF-focused therapy compared to placebo. This One no longer recommended before the third line of therapy.1bBoth mTOR inhibitors and VEGF-focused therapies have limited activity in non-cc-mRCC. There is a non-significant trend for improved oncology outcomes for sunitinib over everolimus.2aLenvatinib combined with everolimus enhanced PFS via everolimus alone in VEGF-refractory disease. Its role after immune checkpoint inhibitors is uncertain. There is a lack of reliable data on this combination which makes its recommendation challenging.2aRecommendationsStrength ratingOffer nivolumab or cabozantinib for immune checkpoint inhibitor-naïve vascular endothelial receptor growth factor (VEGFR)-refractory metastatic renal cell carcinoma (cc-mRCC). It is recommended to strongen the agent not used as a second-class therapy (nivolumab or cabozantinib) for third-line therapy. WeakOffer VEGF-tyrosine kinase inhibitors as a second line of therapy for patients refractory to nivolumab plus ipilimumab or axitinib plus pembrolizumab. WeakOffer cabozantinib after VEGF-focused therapy in cc-mRCC.StrongSequence systemic therapy in the treatment of mRCC.Strong7.5.Recurrent RCCLocally recurrent disease may affect either the kidney carrying the tumor after PN, or the focal ablative therapy such as RFA and cryotherapy, or occur outside the kidneys after PN or RN for RCC. After NSS for pT1 disease, relapses within the remaining kidney occur in about 1.8-2.2% of patients [451,452]. While the impact of positive margins on clinical prognosis is still a non-final [287,452,453] preferred management, when technically feasible, it repeats surgical intervention to avoid the potential risk of tumour recurrence. After thermal ablation or cryotherapy in general intrarethional, but also peri-renal, relapses were recorded in up to 14% of cases [454]. While repeated ablation is still recommended as the preferred therapeutic option after treatment failure, the most effective rescue procedure as an alternative to complete nonfretomy has not yet been defined. Most studies that reported oncological efficacy of surgery for recurrent disease after kidney removal, did not consider the traditional definition of local relapse after RN, PN and thermal ablation, namely: tumor growth exclusively limited to real renal phossu. Instead, repetitions are included in this term within the renal vein, the overbrain glands of the ypsilateral superstitious or regional LPs. Isolated recurrence of tumors within a real renal phossa is only a rare event. Repetitive tumour growth in regional BN or ypsilateral overcooked gland may reflect methacronous metastatic spread (see Section 7.3). Only retroactive and non-comparative data on the frequency and efficacy of available therapeutic options have been reported. One of the largest batches, including 2,945 patients treated with RN, reported 54 patients with recurrent disease localized in the renal fossa, overcood glands or regional RONs as the only metastatic sites [455]. Others The series identified 33 local relapses within a group of 2,502 surgically treated patients, confirming the efficacy of surgical treatment versus conservative approaches (observation, medical therapy). In a series of 1,955 patients with clinical T1 RNACs treated with PN, 95 patients (4.9%) pT3a upstaging, indicating a high risk for local and intrajournalial repetition and reduced survival [456]. This data was further confirmed by an analysis of the SEER database showing that up-up to pT3a with worse CSS occurred in 4.2% of cT1a tumours and in 9.5% of cT1b tumours [457]. In short, limited available evidence suggests that in selected patients, surgical removal of locally recurrent disease may cause permanent tumour control. Since local recurrences develop early, with a median time interval of 10-20 months after treatment for primary tumour [458], a guidance-adjusted early detection monitoring programme is recommended (see Chapter 8 . The data shows that both appropriate predis operational assessment and careful surgical technique are essential in reducing the local risk of recurrence of the disease. Unfavorable prognostic parameters are a short time interval (< 3-12 months) from primary tumor treatment [459], sarcomatoid differentiation of recurrent lesion and incomplete surgical resection [455]. In the event that full surgical removal is unlikely or significant commodities are present (especially in combination with poor prognostic tumour features), palliative therapeutic approaches should be considered, including radiation therapy aimed at controlling symptoms and preventing local complications (see sections 7.3 and 7.4).7.5.1.Summary of evidence and recommendations for advanced/metastatic RCCSu summary of evidenceLEIsolated recurrence in local renal fossa is rare.3In the absence of adverse prognostic factors such as sarcomatoid features or a median time interval of < 12 months after treatment for primary tumour, resection of local relapses may cause permanent tumour local control.3 Most local relapses develop within the first two years after treatment of the primary tumour. For early detection, a guidance-adjusted monitoring system is advised.3RecommendationStrength ratingOffer surgical resection of a locally recurrent disease when complete resection is possible and significant commobidites are absent. Weak absentee. Weak