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**REVIEW**

- 147 Treatment options for localised renal cell carcinoma of the transplanted kidney  
*Motta G, Ferraresso M, Lamperti L, Di Paolo D, Raison N, Perego M, Favi E*
- 162 Interrelationship between Toll-like receptors and infection after orthotopic liver transplantation  
*El-Bendary M, Naemattalah M, Yassen A, Mousa N, Elhammady D, Sultan AM, Abdel-Wahab M*

**ORIGINAL ARTICLE****Prospective Study**

- 173 Living kidney donor assessment: Kidney length *vs* differential function  
*Akoh JA, Schumacher KJ*

**ABOUT COVER**

Editorial Board Member of *World Journal of Transplantation*, Luca Toti, MD, PhD, Assistant Professor, Lecturer, Transplant Unit, Policlinico Tor Vergata, Rome 00133, Italy

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## Treatment options for localised renal cell carcinoma of the transplanted kidney

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### Abstract

Currently, there is no consensus among the transplant community about the treatment of renal cell carcinoma (RCC) of the transplanted kidney. Until recently, graftectomy was universally considered the golden standard, regardless of the characteristics of the neoplasm. Due to the encouraging results observed in native kidneys, conservative options such as nephron-sparing surgery (NSS) (enucleation and partial nephrectomy) and ablative therapy (radiofrequency ablation, cryoablation, microwave ablation, high-intensity focused ultrasound, and irreversible electroporation) have been progressively used in carefully selected recipients with early-stage allograft RCC. Available reports show excellent patient survival, optimal oncological outcome, and preserved renal function with acceptable complication rates. Nevertheless, the rarity and the heterogeneity of the disease, the number of options available, and the lack of long-term follow-up data do not allow to adequately define treatment-specific advantages and limitations. The role of active surveillance and immunosuppression management remain also debated. In order to offer a better insight into this difficult topic and to help clinicians choose the best therapy for their patients, we performed an extensive review of the literature. We focused on epidemiology, clinical presentation, diagnostic work up, staging strategies, tumour characteristics, treatment modalities, and follow-up protocols. Our research confirms that both NSS and focal ablation represent a valuable alternative to graftectomy for kidney transplant recipients with American Joint

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Committee on Cancer stage T1aN0M0 RCC. Data on T1bN0M0 lesions are scarce but suggest extra caution. Properly designed multi-centre prospective clinical trials are warranted.

**Key words:** Renal cell carcinoma; Kidney transplant; Graftectomy; Nephron-sparing surgery; Focal ablation; Review

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**Core tip:** Nephron-sparing surgery and ablative therapy have been increasingly recognised as a valuable alternative to transplantectomy in carefully selected kidney recipients with allograft renal cell carcinoma (RCC). The complexity of the disease, the numerosity of the treatments available, the lack of long-term follow-up data, and the relatively poor quality of the studies addressing this topic do not allow to properly define specific advantages and limitations of these conservative strategies. We performed an extensive review of the literature focusing on epidemiology, clinical presentation, diagnostic work up, staging strategies, tumour characteristics, treatment modalities, and follow-up protocols of localised RCC of the transplanted kidney.

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## INTRODUCTION

Kidney transplant (KTx) recipients have a survival advantage compared to patients on chronic dialysis or remaining on the transplant waiting list (TWL)<sup>[1,2]</sup>. Nevertheless, due to the synergistic effect of end-stage renal disease (ESRD) and prolonged exposure to powerful immunosuppressive agents, higher incidences of malignancies and inferior cancer-specific survivals than the general population have been reported<sup>[3-6]</sup>. Among neoplastic complications, renal cell carcinoma (RCC) of the transplanted kidney has been increasingly recognised as an important cause of morbidity and premature allograft loss<sup>[7-9]</sup>. Management can be exceptionally challenging because in this complex subset of patients the theoretical benefit of optimal oncological control must be carefully weighed against the substantial risk of death arising from technically demanding surgical procedures, peri-operative complications, and return to dialysis<sup>[8,10]</sup>.

For many years, transplantectomy has been universally considered the golden standard, regardless of the characteristics of the lesion<sup>[11]</sup>. More recently, widespread and successful application of nephron-sparing surgery (NSS) and ablative therapy (AT) for the treatment of solid neoplasms in native kidneys<sup>[12]</sup> has favoured the use of conservative approaches in renal allografts<sup>[13]</sup>. Enucleation, partial nephrectomy (PN), radiofrequency ablation (RFA), cryoablation, microwave ablation (MWA), high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE) have been proposed as valuable alternatives to graftectomy in carefully selected recipients with localised RCC but evidence remain weak<sup>[13,14]</sup>. The rarity of the disease, the numerosity of the techniques, and the quality of the studies (mostly case reports or small retrospective case series) do not allow to adequately assess treatment-specific outcomes and to clearly define indications and limitations<sup>[13,14]</sup>. In particular, no clinical guidelines or comprehensive meta-analyses have been published and there is still concern in the transplant community regarding long-term efficacy and safety. In order to offer a better insight into this difficult topic and to help clinicians choose the best therapy for their patients, we performed an extensive review of the literature focusing on conservative treatments of localised RCC.

## LITERATURE RESEARCH

PubMed was searched for manuscripts reporting on RCC of the transplanted kidney.



No time limits were applied. The following key words combinations were used: “kidney transplant neoplasm”, “kidney transplant tumour”, “kidney transplant mass”, “kidney transplant cancer”, “kidney transplant renal cell carcinoma”, “renal transplant neoplasm”, “renal transplant tumour”, “renal transplant mass”, “renal transplant cancer”, “renal transplant renal cell carcinoma”, “kidney allograft neoplasm”, “kidney allograft tumour”, “kidney allograft mass”, “kidney allograft cancer”, “kidney allograft renal cell carcinoma”, “renal allograft neoplasm”, “renal allograft tumour”, “renal allograft mass”, “renal allograft cancer”, “renal allograft renal cell carcinoma”, “nephrectomy”, “transplantectomy”, “graftectomy”, “nephron-sparing surgery”, “ablation”, “radiofrequency ablation”, “cryoablation”, “microwave ablation”, “high-intensity focused ultrasound”, “irreversible electroporation”, “surveillance”, and “watchful waiting”. Preliminary screening was performed by Motta G, Ferrareso M, Lamperti L, Di Paolo D, and Favi E. Manuscripts reporting on localised kidney allograft RCC were further evaluated by Motta G and Favi E as a potential source of information for the review. Considered sub-topics were: Epidemiology, clinical presentation, diagnosis, staging, neoplasms’ characteristics, treatment options, and follow-up strategies.

## EPIDEMIOLOGY

Reported incidence of primary RCC in kidney allografts varies between 0.2% and 0.5%, depending on the series<sup>[7,15-18]</sup>. However, taking into account the progressive aging of the patients on the TWL<sup>[19]</sup>, the increased utilization of expanded-criteria donors<sup>[20]</sup>, and the significant amelioration of long-term recipient survival<sup>[2]</sup>, it is reasonable to expect that the cumulative incidence of the disease will rise considerably in the next few years. KTx patients are approximately at 2-fold increased risk of developing malignancies than healthy controls<sup>[21]</sup>. Compared to the general population, the risk of developing RCC is 10-fold higher<sup>[22]</sup>. Even though, several studies have demonstrated an association between specific primary renal diseases, ESRD, long-term dialysis, immunosuppressive therapy and post-transplant RCC, the reason behind this increased susceptibility remains unknown<sup>[13,17,18,23,24]</sup>.

Higher incidences of allograft RCC have been shown among patients receiving a kidney from a deceased donor compared to living donor recipients<sup>[7,13,14]</sup>. As pointed out by Griffith *et al*<sup>[7]</sup>, this trend probably mirrors the disparity between the number of deceased and living donor transplants performed in most countries. Age differences and disparities in cancer screening protocols between donor types may also play a role<sup>[14,25]</sup>. Other possible variables such as deceased donor category, ethnicity, gender or age have not been extensively investigated. Regarding recipient’s characteristics, a disproportion of male patients with RCC of the transplanted kidney was observed by Tillou *et al*<sup>[13]</sup>.

Allograft RCC are predominantly of donor origin<sup>[25]</sup>. However, lesions arising from recipient-derived cells have been reported<sup>[26]</sup>. Albeit generally neglected by current diagnostic and staging protocols, discriminating between transmitted and acquired allograft neoplasms might have relevant therapeutic and prognostic consequences that should encourage further investigation.

## CLINICAL PRESENTATION

Overall, no more than 20% of the patients exhibit clinical manifestations of the disease<sup>[7]</sup>. The vast majority of lesions are asymptomatic and incidentally discovered during imaging studies performed as a part of the routine post-transplant follow-up or to rule out other conditions<sup>[7,13,14,18,27]</sup>. According to the largest studies available<sup>[7,13,14,18]</sup>, most frequently reported symptoms eventually leading to the diagnosis of allograft RCC are haematuria, abdominal pain, asthenia, weight loss, fever, flu-like syndrome, hypertension, recurrent urinary tract infections, and allograft dysfunction.

## DIAGNOSIS

Localised allograft RCC often represents an incidental finding<sup>[27]</sup>. Reported time intervals between transplantation and diagnosis are extremely variable<sup>[9,14,15,28]</sup>. Colour-Doppler ultrasound (US) is widely considered the first line modality for the evaluation of solid masses of the transplant<sup>[16,27,29]</sup>. In case of indeterminate lesions, contrast-enhanced computed tomography (CT) scan and magnetic resonance imaging

(MRI) with or without contrast dye are the preferred options<sup>[14,18]</sup>. More recently, excellent results have been demonstrated using contrast-enhanced US (CEUS)<sup>[30]</sup>. Main advantages of CEUS over contrast-enhanced CT scan and MRI are lack of radiation exposure, avoidance of contrast-induced nephropathy (CIN) or nephrogenic systemic sclerosis, and cost savings<sup>[31]</sup>. In order to avoid diagnostic delays that may compromise the chance of conservative treatment or unnecessary interventions that may irreversibly damage the transplanted kidney, an allograft biopsy should be obtained whenever possible<sup>[7,14,18]</sup>. Histology not only allows to assess type, grading, and origin of the neoplasm but also provides fundamental information for epidemiological and clinical purposes.

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## STAGING

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Since accepted indication for conservative treatment of allograft RCC is restricted to localised neoplasms, careful staging is mandatory. The staging system proposed by the American Joint Committee on Cancer (AJCC) for RCC in native kidneys is currently the most used tool in combination with the Fuhrman grading score<sup>[32,33]</sup>. However, the transplanted kidney has peculiar anatomical characteristics that may limit the use of standard staging tools. In this regard, the modified version of the AJCC staging system proposed by the Comité de Transplantation de l'Association Française d'Urologie seems a better option<sup>[18]</sup>. According to Tillou *et al*<sup>[18]</sup>, T3 tumours extend into major veins or invade renal sinus fat or peritoneum whereas T4 lesions invade perinephric organs such as psoas muscle, iliac vessels wall, bladder, small intestine or colon. There is no consensus among the transplant community on the optimal staging work up. Contrast-enhanced abdomen CT scan and MRI with or without contrast material are the preferred imaging techniques in most centres<sup>[7,14,18,34]</sup>. Albeit recommended by the American Urology Association (AUA) guidelines<sup>[32]</sup> and the European Association of Urology (EAU) guidelines<sup>[33]</sup>, contrast-enhanced chest CT scan is seldom included in KTx RCC staging protocols.

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## CANCER CHARACTERISTICS

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Similarly to native kidneys, three main variants of RCC have been identified in renal allografts: Clear cell, papillary, and chromophobe<sup>[7,14,18]</sup>. Compared to the general population, a significantly higher prevalence of papillary type over clear cell type has been observed among KTx patients<sup>[7,14,18]</sup>. The reason behind this difference is obscure. Even though, papillary RCC is generally less aggressive than clear cell RCC, its multifocality has been often considered a relative contraindication to conservative treatments<sup>[18,35-37]</sup>. More recently, results achieved with AT<sup>[14]</sup> have demonstrated that patients with papillary type RCC can be excellent candidate for allograft preservation strategies. Another interesting data is the high proportion of endophytic lesions successfully treated with AT<sup>[14]</sup>. Endophytic masses have been generally considered less suitable for AT than exophytic ones. The outcomes reported in renal allografts seem to contradict this opinion and suggest that tumour growth pattern may not be a relevant prognostic factor of primary treatment failure. According to the literature, the vast majority of localised allograft RCC successfully treated with NNS or AT is less than 4 cm in maximal diameter, Fuhrman grade 1-2, and staged T1aN0M0<sup>[14,18,34]</sup>. Conservative management of T1bN0M0 RCC remains anecdotal and seems to offer mixed outcomes<sup>[14,38-41]</sup>.

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## TREATMENT OPTIONS AND TREATMENT-SPECIFIC OUTCOMES

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### Graftectomy

For many years, graftectomy has represented the only acceptable option for RCC of the transplanted kidney<sup>[14,42]</sup>. However, death rates as high as 3% with up to 50% of the patients experiencing severe post-operative complications have been reported following this aggressive surgical procedure<sup>[43]</sup>. Studies comparing NNS and AT to graftectomy, especially in recipients with T1aN0M0 lesions, have shown comparable oncological outcomes with fewer complications<sup>[7,14,42]</sup>. For these reasons, transplantectomy should be currently restricted to patients with irreversible allograft dysfunction, sarcomatoid type RCC, multi-focal papillary type RCC, RCC greater than 7 cm in maximal diameter (AJCC stage II), locally-invasive or metastatic RCC (AJCC

stage III or IV), and RCC infiltrating critical structures. Recent data support this position and demonstrate that for T1aN0M0 RCC a 5-year survival rate of 95% can be expected<sup>[9,44]</sup> whereas 5-year survival rate after allograft removal and return to dialysis is only 34%<sup>[8]</sup>. Analyses of non-cancer specific mortality after KTx failure also confirm the long-term survival benefit of maintained renal function<sup>[45,46]</sup>.

### **NSS**

NSS techniques such as enucleation, wedge resection, and PN are now considered the treatment of choice for patients with T1aN0M0 RCC in native kidneys<sup>[32,33]</sup>. Albeit encouraging, experience in recipients with allograft RCC is limited<sup>[7,9,11,39,42,47]</sup>. Available studies demonstrate that with NSS excellent oncological outcomes can be obtained in patients with T1aN0M0 lesions. Local recurrence rates of less than 5%, lower post-operative complication rates (between 15% and 21%, depending on the series), marginal impact on allograft function, and the possibility to treat residual or relapsing neoplasms with further conservative strategies support NSS over transplantectomy. Successful resection of localised RCC greater than 4 cm in maximal diameter remains anecdotal and therefore should not favour the use of NSS over graftectomy<sup>[39,41]</sup>. Main limitations of NSS compared to AT are invasiveness, higher technical difficulty, and increased risk of peri-operative complications<sup>[7,14,38]</sup>. Most cases of NSS in transplant setting have been performed using an open technique but minimally invasive approaches have been also described<sup>[39,41]</sup>. The tumour can be resected getting access to the allograft *via* a retro- or an intra-peritoneal route depending on the location of the mass<sup>[39]</sup>. In case of lesions very close to the vessels, renal pedicle control is advised<sup>[39]</sup>.

### **RFA**

RFA is the preferred AT for KTx neoplasms (approximately, 80% of all the procedures reported in the literature)<sup>[14,48]</sup>. Excellent oncological and functional outcomes in the treatment of solid masses in native kidneys have undoubtedly favoured its application in the transplant setting<sup>[49-52]</sup>. RFA uses high-frequency alternating electrical current to force extra- and intra-cellular ions to follow the same route as the current thus generating agitation, frictional heat, and coagulative necrosis<sup>[53]</sup>. Relatively wide thermal dispersion and subsequent risk of thermal damage to critical peri-lesional structures represent the main limitations of the technique<sup>[53]</sup>. RFA has been mostly utilized to treat small exophytic lesions distant from the renal hilum<sup>[49,53]</sup>. However, experience in allograft RCC demonstrates that it can be effectively used for both exophytic and endophytic masses<sup>[14]</sup>. According to a recent systematic review<sup>[14]</sup>, among 78 T1aN0M0 RCC treated with percutaneous US- or CT-guided RFA, only two episodes of primary treatment failure and one episode of local recurrence could be identified. Moreover, persistent and relapsing tumours were successfully managed by repeated ablation. Safety profile was also encouraging as no peri-operative deaths were recorded and complication rates did not exceed 15%. The most relevant adverse events were transient lower limb pain due to thermal injury to nerves or muscles and urinary leakage secondary to thermal damage to the renal pelvis. Renal function preservation was obtained in the vast majority of patients included in the analysis.

### **Cryoablation**

Cryoablation uses a cryogenic freezing unit connected with special hollow needles to deliver a cooled fluid into the target-tissue and to simultaneously remove heat from it. At a cellular level, such a technique promotes ice crystal formation, irreversible membrane damage, cell lysis, and apoptosis whereas at a supra-cellular level, it causes ischemic necrosis secondary to intra-vascular coagulation<sup>[53]</sup>. Compared to RFA and MWA, cryoablation entails a lower risk of thermal damage to surrounding structures. For this reason, it is widely considered the most selective AT and it is particularly indicated for centrally located lesions<sup>[53]</sup>. Minimal impact on renal function represents another important feature<sup>[54]</sup>. Possible limitations, at least as shown in native kidneys, are higher risk of intra-operative bleeding<sup>[55]</sup>, higher rate of primary treatment failure in case of neoplasms greater than 3 cm in maximal diameter<sup>[56-58]</sup>, and higher recurrence rate for tumours with an endophytic growth pattern<sup>[59]</sup>. To date, only 10 cases of biopsy-proven T1aN0M0 and 1 case of biopsy-proven T1bN0M0 RCC of the transplanted kidney treated by cryoablation have been documented<sup>[34,60-63]</sup>. The procedures were mostly performed percutaneously under US- or CT-guidance with no persisting disease, no local relapse (post-ablation follow-up ranging from 1 to 59 mo), and excellent allograft function. Overall, there were 2 episodes of peri-operative bleeding<sup>[14]</sup>.

### **MWA**

MWA is a thermal ablation modality that uses microwaves to cause oscillation of polar molecules into the target-lesion thus generating frictional heat and coagulative



necrosis<sup>[53]</sup>. Major advantages compared to other AT are the ability to deliver higher intra-lesion temperatures, a marginal dependency on tissue-specific electrical conductivity, simultaneous treatment of multiple neoplasms, and the possibility to ablate the puncture tract<sup>[53,64-66]</sup>. There are several studies supporting the application of MWA for malignant tumours in native kidneys<sup>[67,68]</sup> but experience in renal allografts is limited to a couple of small case series. Successful ablation of one Fuhrman grade 1-2, T1aN0M0 clear cell RCC and two Fuhrman grade 1-2, T1aN0M0 papillary RCC was first reported by Gul *et al*<sup>[63]</sup>. The procedures were performed under CT-guidance *via* a percutaneous or a trans-osseous approach with no serious complications, no allograft dysfunction, and no recurrence after a follow-up ranging from 8 to 61 mo. Other two cases of MWA of RCC of the transplanted kidney were more recently described by our group<sup>[69]</sup>. More in details, we treated one Fuhrman grade 2, T1aN0M0 papillary RCC and one Fuhrman grade 1, T1aN0M0 clear cell RCC. Ablations were carried out under US-guidance using an open retro-peritoneal route for the first patient and a percutaneous approach for the other one. Complete tumour destruction was achieved in both the operations without complications, loss of allograft function or recurrence after 3 and 5 years of follow-up, respectively.

### **HIFU**

HIFU incorporates multiple US beams directed into a three-dimensional focal point to produce tissue destruction by combined effects of thermal and mechanical energies (more precisely, cavitation, micro-streaming, and radiation forces)<sup>[70]</sup>. Potential benefits of HIFU are fast action, minimal thermal dispersion, and reduced invasiveness as it does not require direct contact with the target-lesion<sup>[71,72]</sup>. On the contrary, recognised limitations of the technique are the need for an optimal acoustic window, the inability to reach deep organs or tissues due to US penetration, and complex pre-operative planning<sup>[71,72]</sup>. Excellent results have been reported in native kidneys<sup>[73-75]</sup> but in KTx setting data are scarce. Searching the literature, we could find only three cases of allograft RCC treated by HIFU. US-guided percutaneous ablation of two T1aN0M0 papillary RCC was described by Di Candio *et al*<sup>[76]</sup> with excellent short-term oncological outcomes (6-mo follow-up) and no peri-operative adverse events whereas multiple unsuccessful attempts in a patient with a 55 mm T1bN0M0 clear cell RCC were reported by Chakera *et al*<sup>[77]</sup>.

### **IRE**

IRE is a non-thermal AT with extraordinary connective tissue-sparing properties that has been successfully used to treat renal<sup>[78]</sup> and extra-renal neoplasms<sup>[79]</sup>. This novel treatment modality utilizes an electrical field to generate nanopores into target-cells and induce permanent membrane permeability, disruption of homeostasis, and apoptosis<sup>[80,81]</sup>. It is particularly indicated in case of neoplastic lesions close to important vessels or structures. There is only one study describing the use of IRE in KTx tumours<sup>[63]</sup>. The procedure was performed percutaneously under CT-guidance to ablate a Fuhrman grade 3, T1aN0M0 clear cell RCC. The post-operative course was uneventful with preserved allograft function and no recurrence after 3 years of follow-up.

### **Active surveillance**

There are no reports describing active surveillance (AS) in KTx recipients with RCC of the allograft. A major concern is that chronic immunosuppression may increase the risk of cancer spreading compared to the general population. Actually, such an assumption has never been confirmed. Recent studies have shown that growth rate and metastatic potential of transplant neoplasms are overall similar to those observed in native kidneys and in healthy controls<sup>[7,9,13,14,18,34]</sup>. As such, no hard recommendations can be made against the use of AS in the transplant setting. A reasonable approach would be to follow the principles stated by the AUA guidelines<sup>[32]</sup> and to consider both patient-related and tumour-related characteristics. As pointed out by Griffith *et al*<sup>[7]</sup>, given the higher incidence of papillary RCC observed in recipients with allograft neoplasms<sup>[14,18,82]</sup>, a lower threshold for renal mass biopsy is advised.

### **Immunosuppression modification**

Immunosuppression is a well-recognised risk factor for the development of malignancies, particularly infectious-related ones and non-melanoma skin cancers (NMSC)<sup>[83]</sup>. Increased susceptibility to long-lasting viral infections with oncogenic potential and partial loss of immune-surveillance processes are considered the main reasons behind this phenomenon<sup>[21,84,85]</sup>. Associations between specific immunosuppressive drugs and risk of cancer after solid organ transplantation have been extensively investigated. Considering the role of NK<sup>[86]</sup>, CD4+, and CD8+ T cells<sup>[87]</sup> in virus-specific immunity and in eliminating neoplastic cells, lymphocyte-

depleting agents such as anti-thymocyte polyclonal antibodies<sup>[88]</sup> or anti-CD52 monoclonal antibody alemtuzumab<sup>[83,89]</sup> and calcineurin inhibitors (CNI) cyclosporine and tacrolimus<sup>[90]</sup> seem to play a major role. In particular, CNI have been shown to exert their action through indirect inhibition of T cells activation/proliferation (*via* decreased IL-2 production) and direct up-regulation of VEGF and TGF- $\beta$ 1<sup>[91,92]</sup>. A significant link between chronic azathioprine exposure and squamous cell carcinoma of the skin has been also demonstrated<sup>[93]</sup>. An accepted explanation is that azathioprine inhibits T cells proliferation and alters DNA repair mechanisms thus leading to impaired immune-surveillance and cell transformation. Data on cancer-related side effects of mycophenolic acid (MPA)<sup>[83,94,95]</sup> and results of the studies addressing the role of steroids in cancer development<sup>[83,87]</sup> remain unclear. There is mounting evidence that proliferation signal inhibitors (PSI)/mammalian target of rapamycin inhibitors (mTOR-I) sirolimus and everolimus may have important anti-neoplastic properties<sup>[83]</sup>. Main immunosuppressive action of mTOR-I is inhibition of T cells activation/proliferation through down-regulation of IL-2 and cell-cycle block. Nevertheless, the mTOR pathway regulates amino acid biosynthesis, glucose homeostasis, adipogenesis, actin cytoskeleton polarization, nutrient-response transcription programs, ribosome biosynthesis, size, growth, proliferation, aging, survival, and life-span of every human cell<sup>[96,97]</sup>. As such, mTOR signalling is also primarily involved in cancer growth, angiogenesis, and metastasis formation<sup>[96]</sup>. Outside the transplant setting, PSI have been successfully used for the treatment of neuro-endocrine tumours<sup>[98]</sup> and advanced RCC<sup>[99]</sup>. Encouraging results have been also obtained in KTx recipients with NMSC<sup>[100]</sup> and Kaposi's sarcoma<sup>[101]</sup>. Currently, there are no formal recommendations on how to manage immunosuppression in patients with post-transplant malignancies but common trend is to reduce CNI and switch from MPA to mTOR-I whenever possible<sup>[83]</sup>. Recent reports suggest that using mTOR-I may be a valid option also in recipients with localised allograft RCC but larger populations and long-term outcomes are needed to confirm this hypothesis<sup>[7,9,13,18]</sup>. Increased risk of rejection<sup>[102]</sup> and severe drug-related side effects<sup>[103]</sup> are the main drawbacks of the strategy and therefore a tailored approach based on specific patient's and cancer's characteristics should be preferred.

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## FOLLOW-UP STRATEGIES

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In our review, we found minimal information regarding follow-up protocols. Proposed strategies were also quite heterogeneous in terms of timing and techniques<sup>[7,14,18]</sup>. Overall, the risk of local recurrence and metastatic disease after successful treatment of T1aN0M0 and T1bN0M0 RCC in native kidneys is extremely low<sup>[32]</sup>. Albeit limited, experience in KTx suggests that cancer-specific outcomes are not significantly different<sup>[7,14,18,34]</sup>. As such, it seems reasonably safe to adopt what recommended by current AUA<sup>[32]</sup> or EAU guidelines<sup>[104]</sup>. Considering the risk and the burden of CIN in KTx recipients, colour-Doppler US, CEUS or MRI should be preferred over CT scan with contrast media<sup>[105]</sup>. After AT, discriminating between necrosis, inflammation, neoplastic tissue and normal parenchyma can be challenging<sup>[14]</sup>. In this context, protocol ablation-site biopsy may help promptly detect persistent or recurrent neoplasms<sup>[106]</sup>.

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## CONCLUSION

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Kidney allograft RCC represents a difficult challenge for the transplant community. Maximal renal function preservation is paramount to achieve the best outcome. In this regards, post-transplant routine follow-up colour-Doppler US may help detect lesions amenable of conservative treatment. Renal mass biopsy is advised for diagnostic purpose and proper treatment planning. Ideally, RCC should be assessed using the Fuhrman grading score and the modified AJCC staging system. Compared to the general population, higher incidences of papillary type RCC have been demonstrated among recipients with allograft neoplasms. Over years, improved surgical techniques and technological advances have favoured the use of NSS and AT over graftectomy. Available data on T1aN0M0 RCC are reassuring as they show excellent cancer-related outcomes, acceptable complication rates, and optimal allograft function whereas experience with T1bN0M0 remains mostly anecdotal (Table 1). RCC type and growth pattern do not seem to affect primary treatment efficacy and relapse rates. Due to the rarity of the disease and the lack of properly designed studies, no hard recommendation can be made (Table 2). A reasonable approach would be to choose a tailored strategy considering both patient's and tumour's characteristics. Individual

surgical risk and local expertise are also important. Multi-centre prospective comparative trials are warranted.

Table 1 Summary of conservative treatments of localised allograft renal cell carcinoma<sup>1</sup>

	RFA	CA	MWA	HIFU	IRE	NSS
Ref.	Charboneau <i>et al</i> <sup>[107]</sup> Baughman <i>et al</i> <sup>[108]</sup> Roy <i>et al</i> <sup>[35]</sup> Goeman <i>et al</i> <sup>[109]</sup> Aron <i>et al</i> <sup>[106]</sup> Matevossian <i>et al</i> <sup>[110]</sup> Veltri <i>et al</i> <sup>[111]</sup> Sanchez <i>et al</i> <sup>[112]</sup> Elkentaoui <i>et al</i> <sup>[113]</sup> Olivani <i>et al</i> <sup>[114]</sup> Cornelis <i>et al</i> <sup>[61]</sup> Leveridge <i>et al</i> <sup>[115]</sup> Tillou <i>et al</i> <sup>[18]</sup> Swords <i>et al</i> <sup>[116]</sup> Végső <i>et al</i> <sup>[117]</sup> Su <i>et al</i> <sup>[118]</sup> Christensen <i>et al</i> <sup>[119]</sup> Hernández-Socorro <i>et al</i> <sup>[120]</sup> Guleryuz <i>et al</i> <sup>[34]</sup> Cool <i>et al</i> <sup>[121]</sup> Iezzi <i>et al</i> <sup>[48]</sup> Di Candio <i>et al</i> <sup>[76]</sup>	Shingleton <i>et al</i> <sup>[60]</sup> Cornelis <i>et al</i> <sup>[61]</sup> Ploussard <i>et al</i> <sup>[62]</sup> Guleryuz <i>et al</i> <sup>[34]</sup> Gul <i>et al</i> <sup>[63]</sup>	Gul <i>et al</i> <sup>[63]</sup> Favi <i>et al</i> <sup>[69]</sup>	Chakera <i>et al</i> <sup>[77]</sup> Di Candio <i>et al</i> <sup>[76]</sup>	Gul <sup>[63]</sup>	Chambade <i>et al</i> <sup>[111]</sup> Varotti <i>et al</i> <sup>[39]</sup> Tillou <i>et al</i> <sup>[42]</sup> Barama <i>et al</i> <sup>[47]</sup> Kaouk <i>et al</i> <sup>[41]</sup> Mundel <i>et al</i> <sup>[122]</sup> Ribal <i>et al</i> <sup>[123]</sup> Lamb <i>et al</i> <sup>[124]</sup>
Patients ( <i>n</i> )	70	11	5	3	1	61
Lesions ( <i>n</i> )	78	11	5	3	1	63
FU (range)	3-71 mo	1-59 mo	8-61 mo	73-81 mo	34 mo	5-109 mo
RCC type						
CC ( <i>n</i> )	10	7	2	1	1	24
PA ( <i>n</i> )	41	3	3	2	0	33
Other ( <i>n</i> )	5	1	0	0	0	2
NA ( <i>n</i> )	22	0	0	0	0	4
Size (range)	0.5-4.0 cm	1-4.1 cm	2.2-3.1 cm	0.8-5.5 cm	1.6 cm	0.9-7.0 cm
TNM <sup>2</sup>						
T1aN0M0 ( <i>n</i> )	78	10	5	2	1	60
T1bN0M0 ( <i>n</i> )	0	1	0	1	0	3
PTF ( <i>n</i> )	2	0	0	1	0	0
Relapse ( <i>n</i> )	1	0	0	0	0	0
DSM ( <i>n</i> )	0	0	0	0	0	0

<sup>1</sup>Summaries based on individual cases should not be considered as an estimate of the "real world".

<sup>2</sup>American Joint Committee on Cancer Tumour Node Metastasis Staging System. RFA: Radiofrequency ablation; CA: Cryoablation; MWA: Microwave ablation; HIFU: High-intensity focused ultrasound; IRE: Irreversible electroporation; NSS: Nephron-sparing surgery; FU: Follow-up; RCC: Renal cell carcinoma; CC: Clear cell; PA: Papillary; NA: Not available; TNM: Tumour node metastasis; PTF: Primary treatment failure; DSM: Disease-specific mortality.

**Table 2 Advantages and limitations of conservative treatments of localised allograft renal cell carcinoma**

	<b>Advantages</b>	<b>Limitations</b>
Nephron-sparing surgery	Complete tumour removal Definitive histology Easy imaging-based follow-up Good preliminary results with T1bN0M0	Technically demanding Invasive Higher peri-operative complication rate Higher risk of allograft dysfunction
Focal ablation	Minimally invasive Highly selective Can treat centrally located lesions Lower peri-operative complication rate Better allograft function preservation	Higher risk of primary treatment failure Lack of definitive histology Difficult imaging-based follow-up Dubious results with T1bN0M0

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