REVIEW
147  Treatment options for localised renal cell carcinoma of the transplanted kidney
   Motta G, Ferrarezzo 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
## Contents

### 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

### AIMS AND SCOPE

The primary aim of *World Journal of Transplantation (WJT, World J Transplant)* is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJT* mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone marrow transplantation, bone transplantation, bone-patellar tendon-bone grafting, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, transplantation immunology, and vascularized composite allotransplantation.

### INDEXING/ABSTRACTING

The *WJT* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

### RESPONSIBLE EDITORS FOR THIS ISSUE

| Role                                      | Name                      |
|-------------------------------------------|---------------------------|
| Responsible Electronic Editor             | Yun-Xiaojian Wu           |
| Proofing Production Department Director   | Xiang Li                  |
| Responsible Editorial Office Director     | Jia-Ping Yan              |

### NAME OF JOURNAL

*World Journal of Transplantation*

### ISSN

ISSN 2220-3230 (online)

### LAUNCH DATE

December 24, 2011

### FREQUENCY

Irregular

### EDITORS-IN-CHIEF

Sami Akbulut, Vassilios Papalois, Maurizio Salvadori

### EDITORIAL BOARD MEMBERS

[https://www.wjgnet.com/2220-3230/editorialboard.htm](https://www.wjgnet.com/2220-3230/editorialboard.htm)

### PUBLICATION DATE

June 29, 2020

### COPYRIGHT

© 2020 Baishideng Publishing Group Inc

### INSTRUCTIONS TO AUTHORS

[https://www.wjgnet.com/bpg/getinfo/204](https://www.wjgnet.com/bpg/getinfo/204)

### GUIDELINES FOR ETHICS DOCUMENTS

[https://www.wjgnet.com/bpg/GetInfo/287](https://www.wjgnet.com/bpg/GetInfo/287)

### GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

[https://www.wjgnet.com/bpg/GetInfo/240](https://www.wjgnet.com/bpg/GetInfo/240)

### PUBLICATION ETHICS

[https://www.wjgnet.com/bpg/GetInfo/288](https://www.wjgnet.com/bpg/GetInfo/288)

### PUBLICATION MISCONDUCT

[https://www.wjgnet.com/bpg/GetInfo/208](https://www.wjgnet.com/bpg/GetInfo/208)

### ARTICLE PROCESSING CHARGE

[https://www.wjgnet.com/bpg/GetInfo/242](https://www.wjgnet.com/bpg/GetInfo/242)

### STEPS FOR SUBMITTING MANUSCRIPTS

[https://www.wjgnet.com/bpg/GetInfo/239](https://www.wjgnet.com/bpg/GetInfo/239)

### ONLINE SUBMISSION

[https://www.f6publishing.com](https://www.f6publishing.com)

© 2020 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

E-mail: bpgoffice@wjgnet.com [https://www.wjgnet.com](https://www.wjgnet.com)
Treatment options for localised renal cell carcinoma of the transplanted kidney

Gloria Motta, Mariano Ferraresso, Luca Lamperti, Dhanai Di Paolo, Nicholas Raison, Marta Perego, Evaldo Favi

ORCID number: Gloria Motta (0000-0002-6945-6853); Mariano Ferraresso (0000-0003-3410-9090); Luca Lamperti (0000-0002-6903-532X); Dhanai Di Paolo (0000-0002-2706-4173); Nicholas Raison (0000-0003-0496-4985); Marta Perego (0000-0002-1981-4122); Evaldo Favi (0000-0001-6465-428X).

Author contributions: Motta G contributed to literature review, data collection, data analysis, data interpretation, drafting the article, final approval; Ferraresso M, literature review, critical revision, and final approval; Lamperti L and Di Paolo D contributed to literature review, data collection, and final approval; Raison N contributed to drafting the article, language revision, and final approval; Perego M contributed to data collection, data analysis, editing the article, and final approval; Favi E contributed to literature review, data interpretation, drafting the article, critical revision, and final approval.

Conflict-of-interest statement: The authors do not have any conflicting interests.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution-NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, and build upon this work non-commercially.

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 and 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
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

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

INTRODUCTION

Kidney transplant (KTx) recipients have a survival advantage compared to patients on chronic dialysis or remaining on the transplant waiting list (TWL)\cite{1,2}. 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\cite{3-6}. 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\cite{7-9}. 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\cite{8,10}.

For many years, transplantectomy has been universally considered the golden standard, regardless of the characteristics of the lesion\cite{11}. More recently, widespread and successful application of nephron-sparing surgery (NSS) and ablative therapy (AT) for the treatment of solid neoplasms in native kidneys\cite{12} has favoured the use of conservative approaches in renal allografts\cite{13}. 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\cite{13,14}. 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\cite{13,14}. 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 and 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, Ferraresso 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[7,15-18]. However, taking into account the progressive aging of the patients on the TWL[19], the increased utilization of expanded-criteria donors[20], and the significant amelioration of long-term recipient survival[21], 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[21]. Compared to the general population, the risk of developing RCC is 10-fold higher[22]. 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[13,17,18,23,24].

Higher incidences of allograft RCC have been shown among patients receiving a kidney from a deceased donor compared to living donor recipients[7,13,14]. As pointed out by Griffith et al[7], 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[14,25]. 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[13].

Allograft RCC are predominantly of donor origin[25]. However, lesions arising from recipient-derived cells have been reported[26]. 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[7]. 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[7,13,14,18,27]. According to the largest studies available[7,13,14,18], 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[27]. Reported time intervals between transplantation and diagnosis are extremely variable[7,13,14,28]. Colour-Doppler ultrasound (US) is widely considered the first line modality for the evaluation of solid masses of the transplant[16,27,28]. 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\textsuperscript{[14,15]}. More recently, excellent results have been demonstrated using contrast-enhanced US (CEUS)\textsuperscript{[19]}. 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\textsuperscript{[20]}. 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\textsuperscript{[7,14,18]}. Histology not only allows to assess type, grading, and origin of the neoplasm but also provides fundamental information for epidemiological and clinical purposes.

**STAGING**

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\textsuperscript{[32,33]}. 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\textsuperscript{[18]}. According to Tillou \textit{et al}\textsuperscript{[18]}, 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\textsuperscript{[7,14,18,34]}. Albeit recommended by the American Urology Association (AUA) guidelines\textsuperscript{[32]} and the European Association of Urology (EAU) guidelines\textsuperscript{[33]}, contrast-enhanced chest CT scan is seldom included in KTx RCC staging protocols.

**CANCER CHARACTERISTICS**

Similarly to native kidneys, three main variants of RCC have been identified in renal allografts: Clear cell, papillary, and chromophobe\textsuperscript{[7,14,18]}. Compared to the general population, a significantly higher prevalence of papillary type over clear cell type has been observed among KTx patients\textsuperscript{[7,14,18]}. 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\textsuperscript{[14,18-20]}. More recently, results achieved with AT\textsuperscript{[14]} 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\textsuperscript{[14]}. 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\textsuperscript{[14,18,34]}. Conservative management of T1bN0M0 RCC remains anecdotal and seems to offer mixed outcomes\textsuperscript{[14,36,40]}.  

**TREATMENT OPTIONS AND TREATMENT-SPECIFIC OUTCOMES**

**Graftectomy**

For many years, graftectomy has represented the only acceptable option for RCC of the transplanted kidney\textsuperscript{[14,15]}. 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\textsuperscript{[15]}. Studies comparing NNS and AT to graftectomy, especially in recipients with T1aN0M0 lesions, have shown comparable oncological outcomes with fewer complications\textsuperscript{[7,14,15]}. For these reasons, transplanteectomy 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\(^6\) whereas 5-year survival rate after allograft removal and return to dialysis is only 34\(^6\). Analyses of non-cancer specific mortality after KTxs failure also confirm the long-term survival benefit of maintained renal function\(^6\).

**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\(^{32,39}\). Albeit encouraging, experience in recipients with allograft RCC is limited\(^{32,39,54,57}\). 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 transplantection. 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\(^{54,56}\). Main limitations of NSS compared to AT are invasiveness, higher technical difficulty, and increased risk of peri-operative complications\(^{54,56,58}\). Most cases of NSS in transplant setting have been performed using an open technique but minimally invasive approaches have been also described\(^{59,60}\). 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\(^{59}\). In case of lesions very close to the vessels, renal pedicle control is advised\(^{59}\).

**RFA**

RFA is the preferred AT for KTxs neoplasms (approximately, 80\% of all the procedures reported in the literature\(^{14,69}\)). Excellent oncological and functional outcomes in the treatment of solid masses in native kidneys have undoubtedly favoured its application in the transplant setting\(^{14,48}\). 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\(^{11}\). Relatively wide thermal dispersion and subsequent risk of thermal damage to critical peri-lesional structures represent the main limitations of the technique\(^{11}\). RFA has been mostly utilized to treat small exophytic lesions distant from the renal hilum\(^{53}\). However, experience in allograft RCC demonstrates that it can be effectively used for both exophytic and endophytic masses\(^{14}\). According to a recent systematic review\(^{14}\), 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\(^{11}\). 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\(^{13}\). Minimal impact on renal function represents another important feature\(^{44}\). Possible limitations, at least as shown in native kidneys, are higher risk of intra-operative bleeding\(^{11}\), higher rate of primary treatment failure in case of neoplasms greater than 3 cm in maximal diameter\(^{46,58}\) and higher recurrence rate for tumours with an endophytic growth pattern\(^{59}\). 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\(^{46,49,50}\). 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\(^{40}\).

**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\textsuperscript{[94]}. 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\textsuperscript{[70,71,73-75]}. There are several studies supporting the application of MWA for malignant tumours in native kidneys\textsuperscript{[67,68]} 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\textsuperscript{[70]}. 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\textsuperscript{[95]}. 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.

\textbf{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)\textsuperscript{[71]}. Potential benefits of HIFU are fast action, minimal thermal dispersion, and reduced invasiveness as it does not require direct contact with the target-lesion\textsuperscript{[71,72,73]}. 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\textsuperscript{[71,72]}. Excellent results have been reported in native kidneys\textsuperscript{[73-75]} 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\textsuperscript{[95]} 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\textsuperscript{[76]}.

\textbf{IRE}

IRE is a non-thermal AT with extraordinary connective tissue-sparing properties that has been successfully used to treat renal\textsuperscript{[77]} and extra-renal neoplasms\textsuperscript{[78]}. This novel treatment modality utilizes an electrical field to generate nanopores into target-cells and induce permanent membrane permeability, disruption of homeostasis, and apoptosis\textsuperscript{[79]}. 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\textsuperscript{[69]}. 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.

\textbf{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\textsuperscript{[80,81,83-85]}. 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\textsuperscript{[82]} and to consider both patient-related and tumour-related characteristics. As pointed out by Griffith et al\textsuperscript{[94]}, given the higher incidence of papillary RCC observed in recipients with allograft neoplasms\textsuperscript{[14,83,84]}, a lower threshold for renal mass biopsy is advised.

\textbf{Immunosuppression modification}

Immunosuppression is a well-recognised risk factor for the development of malignancies, particularly infectious-related ones and non-melanoma skin cancers (NMSC)\textsuperscript{[83]}. 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\textsuperscript{[21,84,85]}. Associations between specific immunosuppressive drugs and risk of cancer after solid organ transplantation have been extensively investigated. Considering the role of NK\textsuperscript{[86]}, CD4+, and CD8+ T cells\textsuperscript{[87]} in virus-specific immunity and in eliminating neoplastic cells, lymphocyte-
depleting agents such as anti-thymocyte polyclonal antibodies\textsuperscript{[88]} or anti-CD52 monoclonal antibody alemtuzumab\textsuperscript{[85,89]} and calcineurin inhibitors (CNI) cyclosporine and tacrolimus\textsuperscript{[89]} 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-b\textsuperscript{[88,92]}. A significant link between chronic azathioprine exposure and squamous cell carcinoma of the skin has been also demonstrated\textsuperscript{[93]}. 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)\textsuperscript{[85-88]} and results of the studies addressing the role of steroids in cancer development\textsuperscript{[88,89]} 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\textsuperscript{[86]}. 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\textsuperscript{[90,91]}. As such, mTOR signalling is also primarily involved in cancer growth, angiogenesis, and metastasis formation\textsuperscript{[92]}. Outside the transplant setting, PSI have been successfully used for the treatment of neuro-endocrine tumours\textsuperscript{[93]} and advanced RCC\textsuperscript{[94]}. Encouraging results have been also obtained in KTx recipients with NMSC\textsuperscript{[95]} and Kaposi’s sarcoma\textsuperscript{[96]}. 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\textsuperscript{[96]}. 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\textsuperscript{[7,9,13,18]}. Increased risk of rejection\textsuperscript{[102]} and severe drug-related side effects\textsuperscript{[103]} are the main drawbacks of the strategy and therefore a tailored approach based on specific patient’s and cancer’s characteristics should be preferred.

**FOLLOW-UP STRATEGIES**

In our review, we found minimal information regarding follow-up protocols. Proposed strategies were also quite heterogeneous in terms of timing and techniques\textsuperscript{[7,14,18]}. Overall, the risk of local recurrence and metastatic disease after successful treatment of T1aN0M0 and T1bN0M0 RCC in native kidneys is extremely low\textsuperscript{[18]}. Albeit limited, experience in KTx suggests that cancer-specific outcomes are not significantly different\textsuperscript{[7,14,18]}. As such, it seems reasonably safe to adopt what recommended by current AUA\textsuperscript{[104]} or EAU guidelines\textsuperscript{[104]}. 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\textsuperscript{[105]}. After AT, discriminating between necrosis, inflammation, neoplastic tissue and normal parenchyma can be challenging\textsuperscript{[15]}. In this context, protocol ablation-site biopsy may help promptly detect persistent or recurrent neoplasms\textsuperscript{[104]}.

**CONCLUSION**

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 purpose and proper treatment planning. Ideally, RCC should be assessed using the Fuhrman grading score and the modified AJCC staging system. Compared to the...
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

| RFA | CA | MWA | HIFU | IRE | NSS |
|-----|----|-----|------|-----|-----|
| Ref. | Charbonneau et al[107] | Shingleton et al[60] | Gul et al[63] | Chakera et al[77] | Gul[63] | Chambade et al[11] |
| | Baughman et al[108] | Cornelis et al[61] | Ploussard et al[69] | Di Candio et al[76] | | Varotti et al[39] |
| | Roy et al[61] | Goeman et al[63] | Guleryuz et al[34] | | | Tillou et al[42] |
| | Goeman et al[63] | Aron et al[77] | Gul et al[60] | | | Barana et al[47] |
| | Matevossian et al[110] | Veltre et al[111] | | | | Kaouk et al[41] |
| | Sánchez et al[112] | Sánchez et al[112] | | | | Mundel et al[122] |
| | Elkentouli et al[115] | Olivari et al[118] | | | | Ribal et al[123] |
| | Cornelis et al[113] | Cornelis et al[113] | | | | Lamb et al[124] |
| | Leveridge et al[113] | Tillou et al[109] | | | | |
| | Swords et al[114] | Su et al[114] | | | | |
| | Végó et al[115] | Christensen et al[115] | | | | |
| | Su et al[116] | Hernández-Socorro et al[117] | | | | |
| | Guleryuz et al[34] | Guleryuz et al[34] | | | | |
| | Cool et al[118] | Lezzi et al[118] | | | | |
| | Di Candio et al[76] | | | | | |
| Patients (n) | 70 | 11 | 5 | 3 | 1 | 61 |
| Lesions (n) | 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 (n) | 10 | 7 | 2 | 1 | 1 | 24 |
| PA (n) | 41 | 3 | 3 | 2 | 0 | 33 |
| Other (n) | 5 | 1 | 0 | 0 | 0 | 2 |
| NA (n) | 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 | | | | | | |
| T1aN0M0 (n) | 78 | 10 | 5 | 2 | 1 | 60 |
| T1bN0M0 (n) | 0 | 1 | 0 | 1 | 0 | 3 |
| PTF (n) | 2 | 0 | 0 | 1 | 0 | 0 |
| Relapse (n) | 1 | 0 | 0 | 0 | 0 | 0 |
| DSM (n) | 0 | 0 | 0 | 0 | 0 | 0 |

1Summaries based on individual cases should not be considered as an estimate of the “real world”.
2American 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.
| Advantages | Limitations |
|------------|------------|
| Complete tumour removal | Technically demanding |
| Definitive histology | Invasive |
| Easy imaging-based follow-up | Higher peri-operative complication rate |
| Good preliminary results with T1bN0M0 | Higher risk of allograft dysfunction |
| Minimally invasive | Higher risk of primary treatment failure |
| Highly selective | Lack of definitive histology |
| Can treat centrally located lesions | Difficult imaging-based follow-up |
| Lower peri-operative complication rate | Dubious results with T1bN0M0 |
| Better allograft function preservation | |

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

**REFERENCES**

We thank Paolo San for logistic support.

**ACKNOWLEDGEMENTS**

**REFERENCES**

1. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; 341: 1725-1730. [PMID: 10580071 DOI: 10.1056/NEJM19991223142303]

2. Favi E, Salerno MP, Romagnoli J, Castagneto M, Citterio F. Significant improvement in patient survival after renal transplantation in the last decade. *Transplant Proc* 2011; 43: 285-287. [PMID: 21335207 DOI: 10.1016/j.transproceed.2010.09.105]

3. Birkeland SA, Lokkegaard H, Storm HH. Cancer risk in patients on dialysis and after renal transplantation. *Lancet* 2000; 355: 1886-1887. [PMID: 10866440 DOI: 10.1016/S0140-6736(00)02298-4]

4. Mazzucchelli V, Piselli P, Verdiramo D, Cimaglia C, Cancarini G, Serraino D, Sandrini S. De novo cancer in patients on dialysis and after renal transplantation: north-western Italy, 1997-2012. *J Nephrol* 2017; 30: 851-857. [PMID: 28317077 DOI: 10.1007/s40620-017-0585-x]

5. Taborelli M, Toffolulli F, Del Zotto S, Clagnan E, Furian L, Piselli P, Citterio F, Zanier L, Boscotti G, Serraino D. Italian Transplant Cancer Cohort Study. Increased cancer risk in patients undergoing dialysis: a population-based cohort study in North-Eastern Italy. *BMC Nephrol* 2019; 20: 107. [PMID: 30922926 DOI: 10.1186/s12882-019-1283-4]

6. Au EH, Chapman JR, Craig JC, Lim WH, Teixeira-Pinto A, Ullah S, McDonald S, Wong G. Overall and Site-Specific Cancer Mortality in Patients on Dialysis and after Kidney Transplant. *J Am Soc Nephrol* 2019; 30: 471-480. [PMID: 30765426 DOI: 10.1681/ASN.2018090906]

7. Griffith JJ, Amin KA, Wangankur N, Lerner SM, Delaney V, Ames SA, Badani K, Palese MA, Mehran R. Solid Renal Masses in Transplanted Allograft Kidneys: A Closer Look at the Epidemiology and Management. *Am J Transplant* 2017; 17: 2775-2781. [PMID: 28544435 DOI: 10.1111/ajt.14366]

8. Rao PS, Schaubel DE, Jia X, Li S, Port FK, Saran R. Survival on dialysis post-kidney transplant failure: results from the Scientific Registry of Transplant Recipients. *Am J Kidney Dis* 2007; 49: 294-300 [PMID: 17264422 DOI: 10.1053/j.ajkd.2006.11.022]

9. Diller R, Senninger N. Treatment options and outcome for renal cell tumors in the transplanted kidney. *Int J Artif Organs* 2008; 31: 867-874. [PMID: 19009504 DOI: 10.1177/03913988083101002]

10. de’Angelis N, Espósito F, Memeo R, Lizi V, Martínez-Pérez A, Landi F, Genova P, Campri P, Brunetti F. Acutn D. Emergency abdominal surgery after solid organ transplantation: a systematic review. *World J Emerg Surg* 2016; 11: 43. [PMID: 27532783 DOI: 10.1186/s13071-016-0101-6]

11. Chambade D, Meria P, Tariel E, Vérine J, De Kerviler E, Peraldi MN, Glotz D, Desgrandchamps F, Mazzucotelli V. Nephron sparing surgery is a feasible and efficient treatment of T1a renal cell carcinoma in kidney transplant: a prospective series from a single center. *J Urol* 2008; 180: 2106-2109. [PMID: 18804233 DOI: 10.1016/j.juro.2008.07.015]

12. Van Poppel H, Becker F, Cadeddu JA, Gill IS, Juarez A, Peraldi MN, Glotz D, Desgrandchamps F, Gabriele G, Delbue S, Clementi MC, Lamperti M, Perego M, Bischeri M, Ferraresso M. Solid Renal Masses in Transplanted Allograft Kidneys: A Feasible and Efficient Treatment of T1a Renal Cell Carcinoma in Kidney Transplant: A Prospective Series from a Single Center. *J Urol* 2011; 185: 1886-1887. [PMID: 10866449 DOI: 10.1016/S0021-973X(00)02298-4]

13. Montorsi F, Polascik TJ, Ukimura O, Zhu G. Treatment of localised renal cell carcinoma. *Eur Urol* 2011; 60: 662-672. [PMID: 21726933 DOI: 10.1016/j.eururo.2011.06.040]

14. Tilou X, Guleruya Y, Collon S, Doerfler A. Renal cell carcinoma in functional renal graft: Toward ablative treatments. *Transplant Rev (Orlando)* 2016; 30: 20-26. [PMID: 26318289 DOI: 10.1016/j.trrev.2015.07.001]

15. Favi E, Raison N, Ambroggi F, Delbue S, Clementi MC, Lamperti M, Perego M, Bischeri M, Ferreira M. Systematic review of ablative therapy for the treatment of renal allograft neoplasms. *World J Clin Cases* 2019; 7: 2487-2504. [PMID: 31559284 DOI: 10.1098/1007-989X-199588490-00006]

16. Poupin P, Peraldi MN, Thunat O, Chrétién Y, Thiounn N, Dufour B, Kreis H, Mejean A. Renal cell carcinoma of the grafted kidney: how to improve screening and graft tracking. *Transplantation* 2004; 77: 146-148. [PMID: 14724485 DOI: 10.1097/01.TP.0000071787.78160.F2]

17. Buel JF, Gross TG, Woodie ES. Malignancy after transplantation. *Transplantation* 2005; 80: S254-S264. [PMID: 16251858 DOI: 10.1097/01.TP.0000186382.81130.bx]
Tillou X, Doerfler A, Collon S, Kleinclauss F, Patard JJ, Badet L, Barrou B, Audet M, Bensadoun H, Berthoux E, Bigot P, Boutilin JM, Bougueney Y, Chambade D, Codas R, Danial J, Deturmeny J, Devonec M, Dagurdain F, Ferrière JM, Erassu A, Feuillu B, Gigante M, Guy L, Karam G, Lebret T, Neuzillet Y, Legendre C, Perez T, Rerolle JP, Salomon L, Sallusto F, Sénchal C, Terrier N, Thuret R, Verhoest G, Petit J; “Comité de Transplantation de l’Association Française d’Urologie (CTAFU)” De novo kidney graft tumors: results from a multicentric retrospective national study. *Am J Transplant* 2012; 12: 3308-3315 [PMID: 22959208 DOI: 10.1111/1600-6143.2012.04248.x]

Roodnat JJ, Zietse R, Mulder PG, Risken-Vos J, van Gelder T, JZerrmans JN, Weimar W. The vanishing importance of age in renal transplantation. *Transplantation* 1999; 67: 570-580 [PMID: 10701030 DOI: 10.1097/00007890-199902270-00015]

Pérez-Sáez MJ, Montero N, Redondo-Pachón D, Crespo M, Pascual J. Strategies for an Expanded Use of Kidneys From Elderly Donors. *Transplantation* 2017; 101: 727-745 [PMID: 28072755 DOI: 10.1097/TP.0000000000001635]

Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Greenberg ER, Wang Z, Yaffe MJ, Petroni GR, Atkinson SJ, Parkin DM, Gail MH. Mortality among heart, lung, liver, kidney, pancreas, and bone marrow transplant recipients: a collaborative study of 13 transplant centers in North America. *J Natl Cancer Inst* 2006; 98: 1731-1739 [PMID: 16847197 DOI: 10.1093/jnci/dji006]

Sassa N, Hattori R, Tsuzuki T, Watarai Y, Fukatsu A, Katsuno S, Nishikimi T, Fujita T, Ohnaka K, Gotoh M. Renal cell carcinoma in haemodialysis patients: does haemodialysis duration influence pathological cell types and prognosis? *Nephrol Dial Transplant* 2011; 26: 1677-1682 [PMID: 21436283 DOI: 10.1093/ndt/gfr674]

Nepple KG, Yang L, Grubb RL, Stope A. Population based analysis of the increasing incidence of kidney cancer in the United States: evaluation of age specific trends from 1975 to 2006. *J Urol* 2012; 187: 32-38 [PMID: 22088338 DOI: 10.1016/j.juro.2011.09.028]

Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 2010; 7: 245-257 [PMID: 20446558 DOI: 10.1038/nrurol.2010.46]

Sassa N, Hattori R, Tsuzuki T, Watarai Y, Fukatsu A, Katsuno S, Nishikimi T, Fujita T, Ohnaka K, Gotoh M. Renal cell carcinoma in haemodialysis patients: does haemodialysis duration influence pathological cell types and prognosis? *Nephrol Dial Transplant* 2011; 26: 1677-1682 [PMID: 21436283 DOI: 10.1093/ndt/gfr674]

Desai R, Collart D, Watson CJ, Johnson P, Evans T, Neuberger J. Cancer transmission from organ donors-unavoidable but low risk. *Transplantation* 2012; 94: 1200-1207 [PMID: 23269448 DOI: 10.1097/TP.0b013e318272df41]

Boix R, Sanz C, Mora M, Quer A, Beyer K, Musulen E, González C, Bayona S, Saladí ME, Ariza A. Primary renal cell carcinoma in a transplanted kidney: genetic evidence of recipient origin. *Transplantation* 2009; 87: 1057-1061 [PMID: 19353128 DOI: 10.1097/01.TP.0000358194.02215.1e]

Viart L, Sarga N, Collon S, Jauregui M, Elalouf V, Tillou X. The high rate of de novo graft carcinomas in renal transplant recipients. *Am J Nephrol* 2013; 37: 91-96 [PMID: 23363786 DOI: 10.1519/MRN.0b013e3182466242]

Walton TM, McCulloch TA, Bishop MC. Aggressive renal cell carcinoma in a 27-year-old kidney transplant. *Nephrol Dial Transplant* 2005; 20: 1018-1021 [PMID: 15785278 DOI: 10.1093/ndt/gfh748]

Rodgers SK, Sorensen CA, Porro MM. Ultrasonographic evaluation of the renal transplant. *Radiol Clin North Am* 2014; 52: 1307-1324 [PMID: 25444108 DOI: 10.1016/j.rcl.2014.07.009]

Harvey CJ, Alsafi A, Kuzmich S, Ngo A, Papadopoulou I, Lakhani A, Berkowitz Y, Moser S, Sidhu PS, Cosgrove DO. Role of US Contrast Agents in the Assessment of Indeterminate Solid and Cystic Lesions in Native and Transplant Kidneys. *Radiographics* 2015; 35: 1419-1430 [PMID: 26273994 DOI: 10.1148/rg.2015140222]

Streb JW, Tchelepi H, Malhi H, Deurulian C, Grant EG. Retrospective Analysis of Contrast-enhanced Ultrasonography Effectiveness in Reducing Time to Diagnosis and Imaging-related Expenditures at a Single Large United States County Hospital. *Ultrason Q* 2019; 35: 99-102 [PMID: 30169489 DOI: 10.1097/RUQ.0000000000000375]

Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, Clark PE, Davis BJ, Derweesh IH, Giambareci L, Gervais DA, Hu SL, Lane BR, Leibovich BC, Pierrozato PM. Renal Mass and Localized Renal Cancer: AUA Guideline. *J Urol* 2017; 198: 520-529 [PMID: 28479239 DOI: 10.1016/j.juro.2017.04.100]

Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, Giles RH, Hofmann F, Hora M, Kuczyk MA, Kruse V, Lam T, McEvoy ME, Menke A, Metzger J, Mihatsch MJ, Röcken MA, Roche C, Schmidbauer B, Schöder H, Schuler F, Schuster S, Sebaldt R, Waller J, Winkler J, Wirth T, Winter E, Zimmer B, Zwingmann H, Zyczek M, Zechmann CM, Zechmann CM. EAU Guidelines on Renal Cancer: AUA Guideline. *J Urol* 2017; 198: 550-554 [PMID: 28195407 DOI: 10.1016/j.juro.2016.01.022]

Roy C, El Ghali S, Buy X, Lindner Y, Gangi A. Papillary renal cell carcinoma in allograft kidney. *Eur Urol* 2005; 48: 661-665 [PMID: 15378336 DOI: 10.1016/j.eururo.2004.10.011]

Delahunt B, Ebbe JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. *Virchows Arch* 1997; 431: 237-245 [PMID: 9304420]

Motta G et al. Kidney allograft renal cell carcinoma June 29, 2020 Volume 10 Issue 6
Motta G et al. Kidney allograft renal cell carcinoma

43 Chowaniec Y, Layeck F, Karam G, Glenmain P, Danial J, Rigaud J, Branchereau J. Transplant nephrectomy after graft failure: is it so risky? Impact on morbidity, mortality and allogimmunization. *Int Urol Nephrol* 2018; 50: 1787-1793 [PMID: 30126697 DOI: 10.1007/s11255-018-1960-4]

44 Zini L, Patard JJ, Capitanio U, Crepel M, de La Taille A, Tostain J, Ficarra V, Bernhard JC, Ferrière JM, Pfister C, Villers A, Montorsi F, Karakiewicz PI. Cancer-specific and non-cancer-related mortality rates in European patients with T1a and T1b renal cell carcinoma. *BJU Int* 2009; 103: 894-898 [PMID: 19076131 DOI: 10.1111/j.1444-4110.2008.08252.x]

45 Brar A, Markell M, Stefanov DG, Timpo E, Jindal RM, Nee R, Sumrani N, John D, Tedla F, Salifu MO. Mortality after Renal Allograft Failure and Return to Dialysis. *Am J Nephrol* 2017; 45: 180-186 [PMID: 28110327 DOI: 10.1159/000466505]

46 Gill JS, Abichandani R, Kaus AT, Pereira BJ. Mortality after kidney transplant failure: the impact of non-immunologic factors. *Kidney Int* 2002; 62: 1875-1883 [PMID: 12371992 DOI: 10.1046/j.1523-1755.2002.00640.x]

47 Barama A, St-Louis G, Nicolet V, Hadjeres R, Daloue P. Renal cell carcinoma in kidney allografts: a case series from a single center. *Am J Transplant 2005; 5: 3015-3018* [PMID: 1630018 DOI: 10.1111.j.1600-6143.2005.01099.x]

48 Iezzi R, Posa A, Romagnoli J, Salerno MP, Carecchio F, Vehbi G, Spagnolotti G, Citterio F, Manfredi R. Radiofrequency thermal ablation of renal graft neoplasms: Case report and literature review. *Clin Transplant* 2018; 32: e13432 [PMID: 30357920 DOI: 10.1111/ctr.13432]

49 Lui KW, Gervais DA, Arellano RA, Mueller PR. Radiofrequency ablation of renal cell carcinoma. *Clin Radiol* 2003; 58: 905-913 [PMID: 14654022 DOI: 10.1016/S0009-9260(03)00222-8]

50 Wagstaff P, Inghels A, Zondervan P, de la Rosette JJ, Laguna MP. Thermal ablation in renal cell carcinoma management: a comprehensive review. *Curr Opin Urol* 2014; 24: 472-482 [PMID: 25051022 DOI: 10.1097/MOU.0000000000000081]

51 Pries FM, Kerkermeijer LGW, Pronk AA, Vonken EPA, Meijer RP, Bex A, Barendrecht MM. Renal Cell Carcinoma: Alternative Nephron-Sparing Treatment Options for Small Renal Masses, a Systematic Review. *J Endourol* 2017; 31: 963-975 [PMID: 28743377 DOI: 10.1089/end.2017.0382]

52 Uhlig J, Strauss A, Rückert G, Seif Amir Hosseini L, Lote J, Trojan K. Partial nephrectomy versus ablative techniques for small renal masses: a systematic review and network meta-analysis. *Eur Radiol* 2019; 29: 1293-1307 [PMID: 30255245 DOI: 10.1007/s00330-018-6560-3]

53 Hinshaw JF, Lubben MG, Ziemlewicz TJ, Lee FT Jr, Brace CL. Percutaneous tumor ablation tools: microwave, radiofrequency, or cryoablation—what should you use and why? *Radiographics* 2014; 34: 1344-1362 [PMID: 25208294 DOI: 10.1148/rg.341400509]

54 Aoun M, Kamis K, Remer E, Berger A, Desai M, Gill I. Laparoscopic renal cryoablation: 8-year, single surgeon outcomes. *J Urol* 2010; 183: 889-895 [PMID: 20088263 DOI: 10.1016/j.juro.2009.11.041]

55 Gervais DA. Cryoablation versus radiofrequency ablation for renal tumor ablation: time to reassess? *J Vasc Interv Radiol* 2013; 24: 1135-1138 [PMID: 23838912 DOI: 10.1016/j.jvir.2013.05.030]

56 Finley DS, Beck S, Box G, Chu W, Deane L, Vajgrt DJ, McDougall EM, Clayman RV. Percutaneous and laparoscopic cryoablation of small renal masses. *J Urol* 2008; 180: 492-498 [PMID: 18550687 DOI: 10.1016/j.juro.2008.04.019]

57 Laguna MP, Bocemster P, Nkone K, Klingler HC, Wyler S, Anderson C, Keelley FX, Bachmann A, Rioja J, Mamoulakis C, Wijkstra H, de la Rosette JJ, Laguna MP. Laparoscopic radiofrequency cryoablation using 17- gauge cryoprobes: mid-term oncological and functional results. *BJU Int* 2011; 108: 577-582 [PMID: 21044339 DOI: 10.1111/j.1464-410X.2010.08076.x]

58 Tsivian M, Lyne JC, Mayes JM, Mouraviev V, Kimura M, Polascik TJ. Tumor size and endophytic growth pattern affect recurrence rates after laparoscopic renal cryoablation using ultrathin 17-gauge cryoprobes: mid-term oncological and functional results. *BJU Int* 2014; 114: 963-975 [PMID: 25459369 DOI: 10.1111/bju.12421]

59 De Souza W, Mattos P, Gervais DA, Arellano RA, Mueller PR. Radiofrequency ablation of renal cell carcinoma: Technical considerations and clinical results. *Diagn Interv Imaging* 2017; 98: 287-297 [PMID: 28611048 DOI: 10.1016/j.dii.2016.12.002]

60 Hernandez JI, Cepeda MF, Valdez F, Guerreos GD. Microwave ablation: state-of-the-art review. *Onco Targets Ther* 2015; 8: 1627-1632 [PMID: 26185452 DOI: 10.2147/OTT.S88734]

61 Choi SH, Kim JW, Kim JH, Kim KW. Efficacy and Safety of Microwave Ablation for Malignant Renal Tumors: An Updated Systematic Review and Meta-Analysis of the Literature Since 2012. *Korean J Radiol* 2018; 19: 938-949 [PMID: 30178448 DOI: 10.3348/kjr.2018.19.9.938]

62 Shakery S, Afzaliri Mirak S, Mohammadian Bagiran A, Parnack T, Sisk A, Aljub J, Pa DS, Raman SS. The effect of tumor size and location on efficacy and safety of US- and CT-guided percutaneous microwave ablation in renal cell carcinomas. *Abdom Radiol* (NY) 2019; 44: 2308-2315 [PMID: 30847565 DOI: 10.1007/s00261-019-01967-8]

63 Favi E, Raiteri M, Paone G, Alfieri CM, Ferarese M. Microwave Ablation of Renal Cell Carcinoma of the Transplanted Kidney: Two Cases. *Cardiovasc Intervent Radiol* 2019; 42: 1653-1657 [PMID: 31388701 DOI: 10.1007/s00270-019-02302-w]
The Role of mTOR in Neuroendocrine Tumors: Future Cornerstone of a Winning Strategy? 

Brighi N, Maggio I, Manuzzi L, Peterle C, Ambrosini V, Ricci C, Campana D, Lamberti G

DOI: 10.1111/bph.12749

1. Introduction

mTOR is a cellular serine/threonine protein kinase that integrates diverse extracellular signals into the regulation of cell growth and metabolism. mTOR is activated in a variety of human tumors, including neuroendocrine tumors (NETs). The high mTOR pathway activity in NETs suggests that mTOR is a promising target for therapeutic intervention.

2. mTOR Inhibitors in Leukemias and Lymphomas

Several studies have demonstrated the antitumor effect of mTOR inhibitors in leukemias and lymphomas. For instance, Everolimus, a specific mTOR inhibitor, has been shown to reduce the growth of leukemia and lymphoma cells in vitro and in vivo.

3. mTOR Inhibitors in Solid Tumors

mTOR inhibitors have demonstrated antitumor activity in a variety of solid tumors, including NETs. In a preclinical study, Everolimus treatment led to a significant reduction in tumor size in NET xenografts.

4. Clinical Trials of mTOR Inhibitors

Several clinical trials have been conducted to evaluate the efficacy and safety of mTOR inhibitors in NETs. A phase II trial of everolimus in carcinoid syndrome patients showed a significant improvement in symptoms and quality of life.

5. Future Directions

Despite the promising preclinical and clinical data, further research is needed to fully understand the role of mTOR in NETs and to develop more effective therapeutic strategies. Future studies should focus on identifying the optimal mTOR inhibitors and combination therapies for NETs.

6. Conclusion

mTOR is an attractive target for the treatment of NETs. However, more research is needed to optimize the use of mTOR inhibitors in NETs. Future studies should aim to identify the most effective therapeutic strategies for NETs.
Nephron-sparing surgery of a low grade renal cell carcinoma in a renal allograft 12 years after transplantation. J Urol 2006; 1700-1703 [PMID: 17986871 DOI: 10.4161/cbt.6.11.5165]

Mundel TM, Schaefer KL, Colombo-Benkmann M, Dietl KH, Diallo-Danebrock R, Senninger N. Radiofrequency ablation as an alternative therapy for renal neoplasms in graft recipients. A preliminary report. J Vasc Interv Radiol 2015; 26: 1658-1663 [PMID: 26707334 DOI: 10.1160/jvir.2015.07.023]

Hernández-Socorro CR, Al-Geizawi SM, Farney AC, Rogers J, Burkart JM, Assimos DG, Stratta RJ. Treatment of incidental de novo renal cell carcinoma in the native and allograft kidneys of renal transplant recipients. J Urology 2011; 186: 1262-1263 [PMID: 21575970 DOI: 10.1016/j.juro.2011.03.032]

Goeman L, Joniau S, Oyen R, Van Poppel H. Percutaneous ultrasound-guided radiofrequency ablation of renal cysts and renal cell carcinoma in transplant recipients: a report of 5 cases. J Vasc Interv Radiol 2004; 17: 1262-1263 [PMID: 15371819 DOI: 10.1016/j.jvir.2004.06.003]

Veltri A, Novotny A, Vogelsang B, Mehler J, Stangl M, Thorban S, Dobritz M. Noninvasive imaging of renal masses in renal transplant recipients: a case series from a single institution. Clin Transplant 2013; 27: E199-E205 [PMID: 23419131 DOI: 10.1111/cit.12088]

Végső G, Toronyi É, Deák PÁ, Doros A, Langer RM. Detection and management of renal cell carcinoma in the renal allograft. Int Urol Nephrol 2013; 45: 1229-1237 [PMID: 28952410 DOI: 10.1007/s10343-013-0001-z]

Christensen SF, Hansen JM. Donor Kidney With Renal Cell Carcinoma Successfully Treated With Radiofrequency Ablation: A Case Report. Transplant Proc 2015; 47: 3031-3033 [PMID: 26707334 DOI: 10.1160/jvir.2015.01.039]

Hernández-Socorro CR, Henriquez-Palop F, Santana-Toledo L, Gallego-Sampere R, Rodriguez-Pérez JC. Radiofrequency ablation as an alternative therapy for renal neoplasms in graft recipients. A preliminary study. Nefronlogia 2015; 35: 514-516 [PMID: 26368931 DOI: 10.1016/j.nefr.2015.03.005]

Cool DW, Kachura JR. Radiofrequency Ablation of T1a Renal Cell Carcinomas in Renal Transplant Allergies: Oncologic Outcomes and Graft Viability. J Vasc Interv Radiol 2017; 28: 1658-1663 [PMID: 28916346 DOI: 10.1016/j.jvir.2017.07.023]

Mundel TM, Schaefer KL, Cobolbro-Benkmann M, Dietl KH, Diallo-Danebrock R, Senninger N. Nephron-sparing surgery of a low grade renal cell carcinoma in a renal allograft. Transplantation 2007; 83: 1700-1703 [PMID: 17966717 DOI: 10.1097/01.TP.000041432.11561.5F]

Ribal MJ, Rodriguez F, Musquera M, Segarra J, Guirado L, Villavicencio H, Alarcón A. Nephron-sparing surgery for renal tumor: a choice of treatment in an allograft kidney. Transplant Proc 2006; 38: 1359-1362 [PMID: 16797303 DOI: 10.1016/j.transproceed.2006.03.033]
