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FEATURES OF THE ETIOLOGY, PATHOGENESIS AND EPIDEMIOLOGY OF RENAL CELL CARCINOMA IN KIDNEY TRANSPLANT RECIPIENTS

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Renal cell carcinoma (RCC) in a kidney transplant is a rare condition as it occurs in the donor kidney of a recipient undergoing immunosuppressive therapy and differs exceptionally from a similar cancer that develops in the native kidney. Given the relative rarity, characteristic specificity of RCC in transplant recipients, and the difficulty in diagnosis and treatment, this type of tumor is less thoroughly studied than the "standard" RCC. However, as more transplants are performed and recipients are being detected with this pathology more frequently, the study of this tumor becomes significantly relevant.

Keywords: kidney graft, renal cell carcinoma, etiology, pathogenesis, epidemiology.

INTRODUCTION

Kidney transplantation (KT) is widely recognized as the most effective treatment for end-stage chronic kidney disease (CKD). Compared to dialysis, KT significantly improves overall survival and enhances quality of life for patients [1]. In the Russian Federation, according to the most recent report from the Nationwide Registry of Renal Replacement Therapy by the Russian Dialysis Society, there are 9,984 kidney transplant recipients, representing 16.5% of all patients requiring renal replacement therapy (RRT) [2]. Annually, over 1,000 kidney transplants are performed in Russia, and this number continues to rise [3].

Despite the clear benefits of KT, a major ongoing challenge remains even with advances in surgical techniques and immunosuppressive therapies, graft longevity remains a critical issue in the field of transplantation [4].

Graft and recipient survival rates after KT vary significantly – not only between countries, but also among transplant centers within the same country. For instance, a single-center cohort study conducted by E. Van Loon et al. (2020), which examined long-term graft and recipient survival, reported that 42.2% of recipients had graft failure within ten years, necessitating either a return to dialysis or a re-transplantation [5].

Similarly, a 2013 report by the American Society of Transplant Surgeons, based on data from the Scientific Registry of Transplant Recipients (SRTR), noted marked improvements in graft survival rates over time. According to this review, the 10-year overall survival rate for kidney transplants from both living and deceased donors had increased from 35–40% to 55–60% compared to the previous decade. Five-year graft survival was highest in living donor recipients under the age of 11 (89%) and lowest in deceased donor recipients aged 11–17 years (68%) [6].

Taken together, a synthesis of global literature suggests that, on average, approximately 40–42% of kidney grafts fail within ten years of transplantation, regardless of donor type or recipient characteristics [4].

One of the contributing factors to graft loss in KT recipients is the development of malignant tumors, particularly renal cell carcinoma (RCC) within the graft. This paper focuses on the etiology, pathogenesis, and epidemiology of RCC in the context of KT.

Multiple studies have demonstrated that KT recipients face a significantly increased risk of RCC compared to the general, non-transplanted population [7–9]. For instance, according to the 2023 Clinical Guidelines – Renal Parenchyma Cancer, RCC incidence in Russia was reported to be 16.9 cases per 100,000 population (0.016%) in 2017 [10].

Various single-center studies suggest a much higher incidence of RCC among KT recipients. For example, a study by Guillaume Ploussard et al. (2012) estimated the incidence at approximately 0.5% [7]. However, the statistical robustness of such studies is limited due to small sample sizes, typically encompassing only a few dozen RCC cases.

More comprehensive data comes from a large meta-analysis conducted by Griffith et al. (2017), which reviewed 56 studies published between 1988 and 2015.

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This analysis found the incidence of RCC in transplant recipients to range from 0.19% to 0.5%, representing a more than 10-fold increase compared to the general population (0.017%) [11]. In total, the analysis documented 174 cases of solid renal tumors among 163 KT recipients worldwide as of 2017.

Over time, as the number of kidney transplants and the duration of recipient follow-up have increased, a growing body of research has emerged investigating variations in RCC incidence among transplant recipients, with studies now examining differences across geographic regions and racial populations.

Thus, Chun-Chieh Yeh, et al. in 2020 published a large study based on the Taiwan's National Health Institute Research Database for the period from 1997 to 2011, which included 5038 kidney transplant recipients (50% living related-donor, 50% deceased-donor transplants). This study found that in the Taiwanese population, the likelihood of developing RCC occurring in a recipient was 37.3 times higher than in the general world population. Based on this, the authors concluded that "regional endemic epidemiologic factors play significant roles in the development of RCC in kidney transplant recipients and that each regional organ transplant program should tailor and establish its surveillance protocol based on epidemiologic data [12].

It should be noted that about 90% of RCC cases in transplant recipients are found in the native kidneys, and only about 10% are detected in the transplanted organ itself [13].

It is reasonable to anticipate that the rising number of transplants, combined with the increasing average age of both donors and recipients, may contribute to a future increase in RCC incidence within graft kidneys [14].

This trend is supported by comparative meta-analyses: the number of RCC cases in kidney transplant recipients reported worldwide has increased significantly – from 163 cases as of 2017 (according to a meta-analysis by Griffith et al.) to 357 cases by 2023 (as reported in a more recent meta-analysis by Fabio et al.) [11, 13]. This reflects a more than twofold increase in detected cases over a six-year period [11, 13].

CURRENT TRENDS IN THE SELECTION OF DONOR ORGANS FOR KIDNEY TRANSPLANTATION

In response to the growing global shortage of donor organs, there is a discernible shift in transplant practices toward relaxing the selection criteria for donor kidneys. A notable trend involves the increased use of extended criteria donor kidneys, including those from elderly individuals and even reconstituted kidneys with previously undiagnosed or historical RCC [15–16].

The aforementioned risks, combined with the growing number of kidney transplants and prolonged survival of transplant recipients, are likely to result in a progressive increase in the detection of RCC within graft kidneys – both in absolute numbers and as a percentage relative to RCC in native kidneys. It is important to note that the previously cited estimate – where only 10% of RCC cases in transplant recipients occurred in graft kidneys – was reported during a period when strict donor selection criteria were consistently applied [17–18].

Supporting this trend, Hendrik Eggers et al. (2019) published the results of a retrospective study involving 5,250 KT recipients at Hannover Medical School (Germany), revealing a significantly higher incidence of RCC in graft kidneys – 2.36%, compared to the previously estimated 0.5% [19].

In line with these findings, several authors, including Warren H. and Olsburgh J., emphasize that with the growing use of organs from elderly donors and the increasing longevity of graft survival, the development of neoplasia within the renal graft is likely to become a more prevalent clinical challenge for both urologists and transplant surgeons [20].

ETIOLOGY AND PATHOGENESIS

RCC in a transplanted kidney presents a unique pathological entity. On one hand, the tumor originates in the donor kidney, whose tissues are genetically distinct from the recipient. On the other hand, the graft functions long-term within the recipient's physiological environment, becoming integrated into the homeostatic system, yet remains subject to ongoing immune surveillance due to its allogeneic nature. Importantly, tumor development and progression occur under the influence of chronic immunosuppressive therapy [21–22].

Immunosuppression is a risk factor for malignant tumors in transplant recipients. It compromises the immune system's ability to recognize and destroy emerging cancer cells [23]. This increased risk is largely attributed to prolonged viral infections with oncogenic potential and a partial loss of immune surveillance mechanisms [24–25].

A number of studies have investigated the impact of specific immunosuppressants on the risk of cancer development in KT recipients. These studies emphasize the crucial role of natural killer (NK) cells, CD4+, and CD8+ T-cells in virus-specific immunity and the elimination of tumor cells [26]. Notably, lymphocyte-depleting agents such as polyclonal anti-T-lymphocyte antibodies (e.g., ATG-Fresenius S) [27], monoclonal anti-CD52 antibody alemtuzumab [28], and calcineurin inhibitors (CNIs) like cyclosporine and tacrolimus [29] have been shown to modulate these immune responses. In particular, calcineurin inhibitors (CNIs) act by inhibiting T-

cell activation and proliferation through suppression of interleukin-2 (IL-2) production. In addition, CNIs have been associated with a direct upregulation of vascular endothelial growth factor (VEGF) and transforming growth factor beta-1 (TGF-β1) [29]. A study by Engels et al. demonstrated that CNIs significantly increase circulating levels of VEGF and TGF-β1, potentially promoting the proliferation and survival of malignant cells in transplant recipients [30]. A dose-dependent elevation of TGF-β1 levels has been documented both *in vitro* and *in vivo* [29].

This creates a clinical dilemma: while low-dose CNI regimens are linked to reduced risk of malignancy, they simultaneously increase the risk of acute rejection [31]. As research progresses, a growing body of evidence supports the antitumor potential of proliferation signal inhibitors, particularly sirolimus and everolimus, which belong to the class of mammalian target of rapamycin (mTOR) inhibitors (mTOR-I) [23, 32–33].

The primary immunosuppressive mechanism of mTOR-Is involves the inhibition of T-cell activation and proliferation, achieved through suppression of IL-2 signaling and cell cycle arrest [25, 27, 34]. Beyond their immunosuppressive role, mTOR pathways also regulate amino acid metabolism, ribosome biosynthesis, transcriptional programming, cell growth, proliferation, senescence, and lifespan in virtually all human cells. Consequently, mTOR signaling is involved in angiogenesis, tumor progression, and metastasis [35–38].

The use of mTOR inhibitors as part of immunosuppressive regimens can reduce the incidence of *de novo* malignancies in transplant recipients. However, this benefit must be weighed against their side effect profile, which can lead to treatment discontinuation in some cases.

In addition to immunosuppressive therapy, other established risk factors for RCC in the graft include prolonged end-stage CKD, extended dialysis duration, advanced recipient age, and a personal history of RCC in the native kidneys [39–40].

FEATURES OF MORPHOLOGICAL FORMS OF RCC IN KIDNEY TRANSPLANT RECIPIENTS

In terms of morphological characteristics, the largest meta-analysis to date – encompassing 129 studies conducted between 1980 and 2020 and published by Fabio et al. in 2023 – revealed that the most frequent histological subtype of RCC arising in graft kidneys is the papillary type, accounting for 42.5% of all cases. This is followed by clear cell carcinoma at 40.2%, and chromophobe carcinoma at 3.5% of cases [13].

By contrast, in the general population of patients without a history of KT or dialysis, the predominant histological subtype is clear cell carcinoma, comprising up to 90% of cases, as documented in earlier epidemiological studies [41–42].

The higher prevalence of papillary RCC over clear forms in a kidney graft may be attributed to the factors described above [39–40, 43].

Further insight into the morphological spectrum of RCC in renal transplant recipients is provided by a large retrospective study by Billis et al., which analyzed RCC cases in patients undergoing dialysis or KT between 2003 and 2016 [44]. This study revealed an increased incidence of rare histological subtypes, specifically acquired cystic disease-associated RCC (11.8%) and clear cell papillary RCC (5.9%), which are exceedingly uncommon in patients not receiving dialysis or transplantation. Notably, both of these subtypes were only recently recognized and were officially included in the World Health Organization (WHO) Classification of Renal Tumors in 2016 [45–46].

Of particular significance, papillary RCC was the most frequently identified subtype in this patient group, accounting for 64.7% of all tumors [44]. It has been proposed that papillary RCC in transplant or dialysis patients may be associated with c-MET oncogene activation, trisomy of chromosomes 7 or 17, and loss of the Y chromosome, although these genetic mechanisms remain under investigation [11].

In addition, current research is examining the potential role of ischemic injury – both warm and cold ischemia – during donor kidney procurement and transplantation as a contributing factor to the increased risk of developing papillary RCC in the graft [11].

The third most common histological subtype of RCC identified in renal grafts is chromophobe carcinoma (3.5%) [13, 47–48]. One particularly noteworthy case involved the detection of chromophobe RCC in a transplanted kidney following the onset of macrohematuria nearly three decades post-transplant in a patient with a history of three prior kidney transplants [49].

Among other histological forms of tumor in a transplanted kidney, it is worth mentioning the single, at this time of observation, cases of mucinous tubular and spindle cell variant of RCC [50], oncocytoma [51], and benign anastomosing hemangioma that mimicked RCC [52].

In summary, the predominance of papillary RCC over clear cell RCC in kidney grafts represents a distinctive histopathological profile that differentiates transplant-associated renal tumors from those typically arising in the native kidneys of patients without a history of transplantation or dialysis.

ORIGIN OF RENAL TRANSPLANT TUMORS

For a long time, the origin of tumors developing in transplanted kidneys remained a subject of uncertainty. It was traditionally believed that RCC in the graft origi-

nated exclusively from donor-derived cells, a view supported by several genetic analyses of newly diagnosed cases [53].

However, a pivotal study published in 2009 by Boix et al. challenged this notion. Using microsatellite analysis, the authors provided the first evidence of RCC in a renal transplant arising from recipient-derived cells [54–55].

The accumulation of renal cancer cases in KT recipients enabled a landmark scientific study in 2023 at Municipal Clinical Hospital No. 52 in Moscow, aimed at elucidating the etiology of RCC in graft kidneys. The researchers analyzed chromosomal DNA from both tumor and surrounding normal tissue of the transplanted kidneys. Using short tandem repeat (STR) markers, they confirmed that in 100% of cases, the tumor originated from donor-derived tissue.

Notably, this study was the first in the world to assess Von Hippel–Lindau (VHL) gene expression in a cohort of KT recipients. The findings provided compelling evidence of genetic determinism in the development of clear cell RCC in graft kidneys. The authors concluded that this tumor type most likely arises from an inherent genetic predisposition in the donor renal parenchyma, which is exacerbated by long-term immunosuppressive therapy in the recipient [56].

FEATURES OF RENAL TUMORS IN KIDNEY RECIPIENTS

In a comprehensive study by Fabio et al. examining the quantitative characteristics of renal tumors in kidney grafts, it was found that the majority of RCC cases (84.5%) presented as solitary tumors, with most falling into the cT1a stage category (83.6%). In contrast, among patients with multifocal lesions, the proportion of cT1a tumors was notably lower at 67.9%.

Histologically, clear cell RCC was more prevalent in multifocal tumors (39.6%), whereas papillary RCC predominated in solitary lesions (42.7%), with clear cell tumors accounting for 40.2% in this group.

When classified by Fuhrman nuclear grading, the majority of solitary tumors were grade 2 (60.1%), while multifocal tumors were more frequently high-grade, with 41.7% classified as grade 3 [13].

It is important to note that, in contrast to the extensively studied "classical" RCC observed in non-transplanted patients, RCC in KT recipients remains poorly understood and is currently the subject of active investigation [57–58].

For instance, the aforementioned comprehensive meta-analysis by Fabio et al., published in 2023, emphasized the limited volume of literature on this topic. According to their findings, the majority of publications (73%) were clinical case reports, 21% were retrospective single-center studies, and only 4% comprised retrospective multicenter analyses. Notably, as of 2023, only 357 cases of RCC in transplanted kidneys had been documented worldwide [13].

This relative scarcity of data can be attributed to the narrow scope and highly specialized nature of the subject, as well as the limited number of transplant centers with the capacity and expertise to study such cases in detail – typically no more than one or two per country.

CONCLUSION

RCCs arising in the native kidneys of renal transplant recipients differ from those occurring in the native kidneys of individuals without transplantation or dialysis in several key aspects. These tumors exhibit a complex interplay of genetic factors, a tendency for multifocal growth, and a potential connection to chronic immunosuppressive therapy. Furthermore, there is a potential for increased incidence of this tumor in the future, as transplant numbers rise and recipient follow-up periods continue to lengthen under current clinical conditions.

The authors declare no conflict of interest.

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