TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

INVITED COMMENTARY

Incidental carcinoma of native kidneys in dialyzed and renal transplant patients: do we need new guidelines?

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Conflicts of interest
The authors have declared no conflicts of interest.

Received: 5 April 2015
Accepted: 7 April 2015

doi:10.1111/tri.12581

Cancer is one of the main causes of death in transplant patients, and young renal transplant recipients have the greatest risk of cancer death [1,2]. The risk of renal cell carcinoma (RCC) in renal transplant patients is 15-fold greater than in the general population [3], and RCC is categorized among the cancers showing the highest standardized incidence ratio [2]. The immunosuppressive therapy could increase the risk for RCC and accelerate its progression, disrupting the immune antitumor surveillance and displaying direct carcinogenetic effects [1,4]. Nevertheless, in renal transplant patients, immunosuppression has not been shown to have any additive effect on the development of RCC, and RCC arising in native kidney seems to have a good prognosis [5,6].

In patients on long-term dialysis, the duration of dialysis and the acquired cystic disease (ACDK) is established risk factors for RCC development. Nevertheless, incidental RCC arising in these patients has been shown to exhibit favourable histology and outcome [7].

The European Association of Urology (EAU) guidelines on renal transplantation do not indicate a defined disease-free waiting period after removal of RCC in dialyzed patients, and consider incidentally discovered RCC after transplant at low risk of recurrence [8]. In addition, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the care of kidney transplant recipients do not advise screening for RCC after transplant [2]. More recently, the European Renal Best Practice Transplantation Guidelines (ERBP) suggest to screen renal transplant candidates for the presence of kidney cancer by ultrasound, while patients with incidentally discovered and successfully removed kidney cancer are allowed to be immediately registered on the waiting list [9].

Goh *et al.* [10] reasonably propose that the frequency of screening of native kidneys after transplant should be decided considering the presence of renal cysts and the duration of the dialysis.

The management of patients in waiting list for renal transplant and that of patients following renal transplant markedly vary in different excellent Institutions in Italy. At the Unit of Kidney and Pancreas Transplantation,

Department of Surgical Sciences and Gastroenterology, University of Padua, in transplanted patients, after nephrectomy for incidental RCC, the immunosuppressive therapy is not modified, reduced, or converted to mTOR inhibitors based on a case-per-case analysis. All transplanted patients are yearly screened for RCC, while dialyzed patients in waiting list every 2 years (Dr Cristina Silvestre, personal communication). For dialyzed patients undergoing nephrectomy for incidental RCC, no disease-free period is prescribed before re-entering the waiting list [11].

At the Department of Gastroenterology and Transplantation, Marche Polytechnic University, Ancona, in transplanted patients, after nephrectomy for incidental RCC, the immunosuppressive therapy is converted to mTOR inhibitors. All transplanted patients are screened for RCC yearly. Dialyzed patients follow the screening recommendations that apply to the general population, and for dialyzed patients undergoing nephrectomy for incidental RCC a disease-free period of 2–5 years is established before re-entering the waiting list, considering the tumor histology and grading (Dr Andrea Vecchi, personal communication).

At the Renal Transplant Center, SCU Nephrology, Dialysis and Transplantation, University of Torino, in transplanted patients, after nephrectomy for incidental RCC, the immunosuppressive therapy is moderately reduced or converted to mTOR inhibitors. Both transplanted patients and dialyzed patients are screened for RCC yearly. For dialyzed patients undergoing nephrectomy for incidental RCC, a disease-free period of 5 years before re-entering the waiting list is prescribed (Dr Massimo Gai, personal communication).

Ryosaka *et al.* in this issue of Transplant International demonstrate in a retrospective study in 212 patients that incidental solid RCC arisen in renal transplant patients was more aggressive than that developed in dialyzed patients, in terms of recurrence, cancer-specific survival, and 5-year nonrecurrence rate [11]. The RCC in the two groups had comparable staging and grading. Moreover, no difference in the histological subtypes was observed; thus, the different behaviour of RCC in dialyzed patients was not attributable to a higher number of papillary tumors, having better prognosis than clear cell RCC, and usually arising in the context of ACDK. Thus, the authors hypothesize that in transplant patients the immunosuppression is the important factor influencing the progression of solid RCC.

Interestingly, no differences, in terms of recurrence, cancer-specific survival, and 5-year nonrecurrence rate, were observed between cystic RCC of transplanted and dialyzed patients. In this case, a significantly higher number of papillary tumors was present in dialyzed patients. Therefore, an unfavourable effect of the immunosuppression would affect solid but not cystic tumors. This conclusion was supported by preliminary observations that in transplant patients, cancer-specific survival and nonrecurrence rate were worse in solid RCC than in cystic RCC.

Why solid tumors should be more sensitive than cystic tumors to immunosuppression? One possible explanation could be that in solid tumors the number of cells submitted to deleterious immunosuppressive effects would be higher than in cystic tumors. Alternatively, cystic tumors may be biologically less aggressive and less sensitive to immunosuppression.

Interestingly, very recent studies have shown that, regardless of the histological subtype, renal malignant tumors presenting as cystic masses, following nephrectomy did not develop local or metastatic recurrence [12,13]. Taken together, the latter studies [12,13] and the results shown by Ryosaka *et al.* in this issue of Transplant Inernational suggest that changes in the management of both dialyzed and transplant patients could be taken into consideration.

The therapy received by renal transplant patients in the study by Ryosaka *et al.* was a triple immunosuppressive protocol including the calcineurin inhibitor Tacrolimus. Calcineurin inhibitors disrupt the immune antitumor surveillance and display direct carcinogenetic effects [reviewed in 1]. Tacrolimus induces production of TGF-β, promoting angiogenesis and tumor progression in murine models of lung metastasis by renal cell tumors [1]. Moreover, it activates the oncogene RAS in normal and in cancer renal epithelial cells [4]. In contrast, mTOR inhibitors in murine models have been shown to decrease angiogenesis by inhibiting both the production and the response to vascular endothelial growth factor (VEGF). Moreover, in renal transplant patients treated with an mTOR inhibitor the risk of developing any malignancy was decreases by 60% compared with patients on regimens without mTOR inhibitors [1]. These findings have been subsequently supported by several other studies [1]; thus, when possible, mTOR inhibitors should be considered in the treatment of patients undergoing renal transplant at high risk for cancer development and of those who develop RCC in the post-transplant course.

Funding

The authors have declared no funding.

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