De novo urologic tumors in kidney transplant patients

O. Rodríguez Faba, A. Breda, L. Gausa, J. Palou, H. Villavicencio

Unidad de Trasplante Renal, Servicio de Urología, Fundació Puigvert, Barcelona, Spain
Unidad de Urología Oncológica, Servicio de Urología, Fundació Puigvert, Barcelona, Spain

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Abstract
Context: The ability of a transplant recipient to accept a graft depends on the ability of immunosuppressive drugs to regulate the immune system. Such treatments have been associated with tumor promotion and progression.

Evidence acquisition: A systematic literature review was carried out. Electronic searches were performed in PubMed database. The searching criterion was “urological tumors in kidney transplant recipients”. The most important issues regarding incidence, urological tumor-specific features, and relevant ones about the treatment are summarized.

Synthesis of evidence: In renal transplant, 15% of all tumors are urological neoplasias; furthermore, they are the leading neoplastic cause of death. In transplant population the incidence rate of renal cell carcinoma (RCC), transitional cellbladder carcinoma (TCBC), testicular carcinoma (TC) and prostate cancer are increased 15, 3, 3 and 2 times respectively. Treatments used in transplant patients are similar to those employed in the general population: radical nephrectomy for the native kidney and conservative surgery for the graft are indicated for RCC. Radical prostatectomy is technically feasible for localized PC. Regarding transitional cell carcinoma BCG or MMC is not contraindicated.

Conclusions: The incidence rate of cancer has increased among transplant population. These tumors can be managed following the same criteria than in general population. Because in this population the prognosis is worse for the immunosuppression, closer monitoring is required.

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Keywords
Urologic tumor; Kidney transplantation; Renal cancer; Bladder cancer; Prostate cancer

Tumores urológicos de novo en pacientes trasplantados renales

Resumen
Contexto: La capacidad de un receptor para aceptar un injerto renal se debe a la regulación del sistema inmunológico por los fármacos inmunosupresores. Dichos tratamientos se han relacionado con la promoción y la progresión tumoral.

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* Corresponding author.
E-mail address: orodriguez@fundacio-puigvert.es (O. Rodríguez Faba).

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Adquisición de evidencia: Se realizó una revisión sistemática de la literatura en PubMed, de los artículos referidos a “tumores urológicos en pacientes trasplantados renales”. Se resumen los aspectos más importantes en cuanto a incidencia, características específicas de cada tumor urológico y aspectos relevantes del tratamiento.

Síntesis de evidencia: Las neoplasias urológicas representan un 15% de los tumores en el TR, además de ser en algunas series la principal causa de muerte de origen neoplásico. Dicha población tiene 15 veces más probabilidades de presentar cáncer de células renales (CCR), 3 veces de cáncer de células transicionales de vejiga (CCTV), 3 veces de cáncer testicular (CT) y 2 de cáncer de próstata (CP). Los tratamientos son similares a la población no trasplantada; en caso del CCR predomina la indicación de nefrectomía radical en el riñón nativo y cirugía conservadora en el injerto. En el CP localizado la prostatectomía radical es técnicamente factible. En el CCTV la inmunosupresión no representa una contraindicación para la administración de BCG o MMC.

Conclusiones: Existe un incremento en la incidencia de tumores urológicos en la población TR. Dichos tumores se pueden abordar de la misma manera que en la población general, por lo que debido al potencial peor pronóstico en relación con la inmunosupresión se requiere en esta población un seguimiento más estrecho.

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Introduction

The ability of a recipient to accept a renal graft is largely due to the immune system regulation by immunosuppressive drugs. In the same way that these drugs have managed to positively revolutionize the renal transplant (RT), decrease the number of episodes of acute rejection, and increase graft survival, they are not exempt from adverse effects of long-term administration. Apart from their own side effects, they are related to bacterial, viral, and fungal infections, the increase of cardiovascular problems, and the occurrence of tumors. Data from the U.S. Registry on 175,732 solid organ transplants (58.4% renal) between 1987 and 2008 have shown an increase in this population of 2 times the risk of tumors compared to the general population. These immunosuppressive therapies have been associated with tumor promotion and progression. Cyclosporin A inhibits calcineurin, tacrolimus interferes with TNFβ, and azathiopine is associated with neoplastic transformation through DNA.

Although currently the leading cause of morbidity and mortality in RT is cardiovascular problems, probably in the next 20 years, due to increased graft survival, the age of the donor and recipient, as well as the second and third transplants, tumors will be a leading cause of mortality in this population. Besides immunosuppressants, environmental factors such as obesity, tobacco, and chronic analgesic intake, genetic factors (Von Hippel-Lindau disease), chronic infection by BK, and acquired cystic disease have been described as risk factors for the occurrence of tumors in this population. In a recent study with 123,380 RT recipients, the most solid-organ neoplasms were lymphoproliferative diseases (1.58%), followed by lung cancer (1.12%) and prostate cancer (0.82%).

The incidence of urological neoplasms in such patients ranges from 0.38% to 5.5% (Table 1). Tsaur et al., in a study with 1990 transplanted patients, described 15 times more likely to develop renal cell cancer (RCC), 3 times more likely to have transitional cell bladder cancer (TCBC), testicular cancer (TC) 3 times, and 2 in the case of prostate cancer (PC), urological tumors representing in their work 15% of tumors in RT. Furthermore, urological tumors were the leading cause of death of neoplastic origin. In Spain, in a retrospective study of 1751 transplant patients, 29 patients had urological tumors (1.6%), PC being the most frequent with 11 (37%), followed by RCC in primitive kidney with 6 (20.7%), and RCC in transplanted kidney with 5 (17.2%). Recently, Hevia et al., in their series of 1365 RTs, reported an incidence of 25 cases (1.8%), the most common being RCC with 11 (44%), followed by PC with 9 (36%), and TCBC with 5 (20%) (Table 1).

Renal cell carcinoma

RCC is more common in the population undergoing hemodialysis and in the native kidneys of transplanted patients, with a prevalence that, in spite of changing depending on the screening, is between 0.34 and 5.8%. The most recognized risk factors are analgesic nephropathy and acquired cystic disease, and in the case of post-RT patients, immunosuppression was considered a promotor of carcinogenesis. RCC in patients with CKD has different clinicopathological features to those of the general population. Neuzil et al. analyzed the differences in behavior of RCCs in 303 CKD patients and compared them to 974 cases in the general population. The group of patients with CKD were diagnosed more often in an asymptomatic way (87 vs. 44%), showed smaller tumors (3.7±2.6 cm vs. 7.3±3.8 cm), and in younger patients (55±12 years vs. 62±12 years). Furthermore, these tumors had a lower stage and grade, with a more favorable cancer-specific mortality (4.3 vs. 27.6%).

### Table 1

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>1.12%</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>0.82%</td>
</tr>
<tr>
<td>RCC</td>
<td>15%</td>
</tr>
<tr>
<td>TCBC</td>
<td>3 times</td>
</tr>
<tr>
<td>TC</td>
<td>3 times</td>
</tr>
<tr>
<td>PC</td>
<td>2 times</td>
</tr>
<tr>
<td>Urological Tumors</td>
<td>15%</td>
</tr>
</tbody>
</table>
Table 1  Main series of the literature describing renal transplant patients and urological tumors.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>PC</th>
<th>RCC</th>
<th>TCC</th>
<th>TC</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsaur et al. 2</td>
<td>1931</td>
<td>11</td>
<td>20</td>
<td>25</td>
<td>2</td>
<td>58 (3)</td>
</tr>
<tr>
<td>Di Capua et al. 8</td>
<td>1751</td>
<td>11</td>
<td>11</td>
<td>7</td>
<td>–</td>
<td>29 (1.6)</td>
</tr>
<tr>
<td>Einollahi et al. 7</td>
<td>5532</td>
<td>1</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>21 (0.38)</td>
</tr>
<tr>
<td>Hevia et al. 9</td>
<td>1365</td>
<td>9</td>
<td>11</td>
<td>5</td>
<td>–</td>
<td>25 (1.8)</td>
</tr>
<tr>
<td>Elkentaoui et al. 38</td>
<td>1350</td>
<td>21</td>
<td>13</td>
<td>5</td>
<td>–</td>
<td>39 (3.4)</td>
</tr>
<tr>
<td>Hung et al. 39</td>
<td>108</td>
<td>–</td>
<td>–</td>
<td>6</td>
<td>–</td>
<td>6 (5.5)</td>
</tr>
<tr>
<td>Zhou et al. 40</td>
<td>3150</td>
<td>2</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>12 (0.38)</td>
</tr>
<tr>
<td>Karczewski et al. 41</td>
<td>836</td>
<td>5</td>
<td>13</td>
<td>3</td>
<td>–</td>
<td>21 (2.5)</td>
</tr>
<tr>
<td>Melchor et al. 42</td>
<td>802</td>
<td>7</td>
<td>12</td>
<td>8</td>
<td>2</td>
<td>29 (3.6)</td>
</tr>
</tbody>
</table>

RCC: renal cell cancer; TCC: transitional cell cancer; PC: prostate cancer; TC: testicular cancer.

Breda et al. confirmed these results, but also in their series, in spite of the significantly better cancer-specific survival of RCCs in the CKD group, when they were analyzed in the group of patients with CKD, those with pretransplant RCC, and it was compared to the post-RT, this significant difference in survival disappeared. As for the histological subtype, Hetet et al. 16 found no differences between the different histological subtypes; however, recent studies have found a higher prevalence of the papillary subtype in this population. 13,15

The treatment of the RCCs that appear on the graft must be conservatively posed whenever possible according to size (T1a) and/or location, since the alternative would be transplantation and consequently dialysis. Partial nephrectomy is the oncologically safest technique, although technically more complex. In a review by Ribal et al. of 15 patients with renal tumor in the graft and undergoing partial nephrectomy, none had recurrence in the graft or distant spread. 17 Radiofrequency and cryotherapy are alternatives for those more technically complex cases or in patients at high surgical risk. The ultrasound screening for this population might be justified in cases with a history of chronic use of analgesics or acquired cystic disease; however, difficulties have been described in the case of acquired cystic disease or in native kidneys with multiple cysts or scars to differentiate by ultrasound tumor lesions of adenomas or angiomyolipomas. 18

Transitional cell carcinoma of the bladder

Overall, in the transplanted population, bladder cancer, both non-muscle invasive (NMIBT) and muscle invasive (MIBT) have a greater biological aggressiveness and worse prognosis. The relative risk of having it is 3.31 times higher than in the general population. It has been postulated as one of the molecular mechanisms involved in the promotion and development of TCBC, activation of the PI3K/Akt/mTOR pathway involved in the metabolism, growth, proliferation, invasion, survival, and angiogenesis. 19 Furthermore, mutation of PTEN, present in bladder cancer, has been associated with worse prognosis. This mutation activates mTOR, which plays a key role in translation, cell growth, apoptosis, and angiogenesis. Sirolimus (SRL), which is an inhibitor of mTOR, could play a critical role inhibiting cell proliferation and apoptosis.

In RT receptors, the 3 basic problems encountered in the management of TCBC are the greatest biological aggressiveness, resulting in the increased incidence of NMIBT in some series, the controversy that the BCG presents in transplanted patients and the greater technical difficulty of cystectomy and urinary reconstruction. The most frequently diagnosed NMIBT is high-grade T1, and the BCG is the optimal adjuvant therapy that decreases recurrence and progression. However, overall, immunotherapy is not recommended in immunosuppressed patients, and the series published so far comprise a limited number of patients. Palou et al. 20 have reported the experience with BCG in high-grade NMIBT in patients receiving RT. In spite of immunosuppression, patients showed worse tolerance to BCG than the general population, although there was recurrence in 2 of the 3 patients studied. There are a total of 10 cases in the literature of patients with RT who have received BCG for NMIBT. The mean time of overall follow-up was 30.8 months, during which a patient died of metastatic disease and another one of the complications of CKD. There are no reported side effects associated with BCG; however, given the limited number of published cases, no conclusions can be drawn regarding oncologic effectiveness.

The standard treatment for MIBT is radical cystectomy with lymphadenectomy. In carriers of RT, this surgery is technically more demanding due to the anatomical changes as a consequence of the presence of the graft. When performing cystectomy, we have to be particularly careful with dissection of the ureter of the graft, and we have to try to preserve its vascularization as much as possible. Equally, in the cases where ipsilateral lymphadenectomy can be performed, this must be conducted with utmost care and trying to preserve the graft and its vascularization. 20 In these patients, we may consider conducting an orthotopic diversion in the cases that keep adequate renal function (<2 mg/dl), functional urethra free of neoplasia, and manual dexterity to be able to perform self-catherization. Moses et al. 21 published their experience with 4 transplanted patients who underwent a cystectomy with urinary diversion due to MIBT. In all of them, the identification of the ureter of the graft was necessary using intravenous contrast, and it was not possible to perform lymphadenectomy in any case on the side of the graft.

No worsening was objectified in the renal function as a consequence of the completion of the neobladder. As for
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Oncological outcomes, 2 patients had recurrence. So far, 34 patients have been reported due to MIBT. In all cases, regardless of the type of neobladder performed, functional outcomes do not differ from the general population.

Prostate cancer

The incidence and prevalence of PC in renal transplant patients is difficult to interpret because most of the records have been obtained prior to the existence of a systematic screening. There are publications in which the incidence is lower than in the general population; however, data from the Nordic countries show a much higher incidence of cancer. In those series in which patients were performed a systematic screening with PSA and/or DRE, the incidence of prostate cancer is higher than the general population. The prevalence is 0.3–1.8%, and it may reach 5.8% if screening with PSA is performed in all men, recommending performing PSA and DRE in all recipients >50 years. It has not been shown that PSA levels are influenced by immunosuppression or by kidney failure, and most tumors (84%) in this population are diagnosed in a localized way.

Radical prostatectomy for cases diagnosed in a localized manner can be performed perineally, avoiding injury to the ureteral reimplantation and facilitating urethrovaginal anastomosis without tension. Hafron et al. published their experience with 7 patients undergoing perineal post-RT, concluding that this surgical approach for transplant patients is safe, with a complication rate and oncological follow-up similar to the non-transplant population. In the case of retropubic RP, we have to consider the change in the position of the separator to prevent injuring the graft; equally, it may be necessary to catheterize the ureter to locate the uretero-neocystostomy. Probably, if the perineal and retropubic RP provide the same functional and oncological results, the fact of manipulating the graft and ureter less make a priori perineal RP a more feasible technique in the transplant population. Similarly, and given the possibility of graft failure, retropubic RP hinders the performance of a 2nd transplant in the opposite iliac fossa by manipulating the anatomical space much more, increasing the technical difficulty and complications of future transplants. Robotic RP has also been developed, existing publications with a limited number of cases. The modifications described with respect to the standard technique comprise a partial dissection of the bladder from the abdominal wall due to RT adhesions and performing lymphadenectomy on one side.

Although the natural history of PC in immunodepressed patients or patients with renal failure is little known, follow-up of these patients with PSA is also recommended, since kinetics is not affected. External beam radiotherapy, brachytherapy, and androgen deprivation represent other options to consider for the treatment of PC in the transplant patient. For external radiation therapy, we have to consider the risk of nephritis in the graft and radiation of the bladder and ureteral reimplantation.

Testicular cancer

Testicular cancer is the most common malignant tumor in the male population between 15 and 35 years and it represents 1% of all malignancies in man. In the population of kidney transplant recipients, we found that the incidence varies across studies. According to Adami et al., in a study conducted in Sweden, the incidence rate increased by 0.7% compared to the general population. Besarani et al. found no differences in incidence and prevalence in their study compared to the general population in the UK and, therefore, they suggest that patients are diagnosed and treated as the general population. Tsaur et al., in their series of 1990 transplant patients, described 2 cases of testicular tumor (3% incidence in male population). One case was pT1R0 seminoma treated after orchietomy with 2 cycles of carboplatin without observing any deterioration in the renal function of the graft, and without presenting recurrence at 10 years. The second case was a pT2R0 malignant trophoblastic teratoma that developed lung and brain metastases.

Penile cancer

Penile cancer is a rare malignancy in the general population and in renal transplant patients. We know that it has a proven relationship with the infection of human papilloma virus (HPV), especially types 16 and 18. Although the transplant population a significant increase in the incidence and risk of cervicovaginal and skin neoplasms has been described, and although in the immunosuppressed population, such as RT recipients, they have an increased expression of lesions associated with these viruses, we found no association between penile cancer and renal transplant. Vajdjc et al. showed an increased incidence up to 10 times in the community of Australia and New Zealand attributed to HPV infection. However, European studies like Besarani et al. suggest that there is no increased incidence relative to the general population. What all studies seem to agree on is that it is not necessary to perform any test during the follow-up of the transplant patient to discard this disease, an attitude consistent with the European and American guidelines of the post-transplant patient management.

Conclusion

There is an increased incidence of urologic tumors in the renal transplant population. These tumors can be approached in the same way as in the general population, so because of the potential worse prognosis in relation to immunosuppression, this specific population requires close follow-up to facilitate early diagnosis.

Conflict of interest

The authors declare that they have no conflict of interest.

References

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