



Pathological features and outcomes of incidental renal cell carcinoma in candidate solid organ donors

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Background: We report the findings of a single Italian center in the evaluation of renal lesions in deceased donors from 2001 to 2017. In risk evaluation, we applied the current Italian guidelines, which include donors with small (< 4 cm, stage pT1a) renal carcinomas in the category of non-standard donors with a negligible risk of cancer transmission.

Methods: From the revision of our registries, 2,406 donors were considered in the Emilia Romagna region of Italy; organs were accepted from 1,321 individuals for a total of 3,406 organs.

Results: The evaluation of donor safety required frozen section analysis for 51 donors, in which a renal suspicious lesion was detected by ultrasound. Thirty-two primary renal tumors were finally diagnosed: 26 identified by frozen sections and 6 in discarded kidneys. The 32 tumors included 13 clear cell renal cell carcinomas (RCCs), 6 papillary RCCs, 6 angiomyolipomas, 5 oncocytomas, 1 chromophobe RCC, and 1 papillary adenoma. No cases of tumor transmission were recorded in follow-up of the recipients.

Conclusion: Donors with small RCCs can be accepted to increase the donor pool. Collaboration in a multidisciplinary setting is fundamental to accurately evaluate donor candidate risk assessment and to improve standardized protocols for surgeons and pathologists.

Keywords: Cancer transmission, Donor evaluation, Kidney transplantation, Renal cell carcinoma, Risk assessment

Introduction

The number of patients with end-stage renal disease (ESRD) increases every year; in 2015, nearly 500,000 patients received dialytic treatment, and, in the USA, over 200,000 people live with a transplanted kidney [1]. Kidney transplantation (KT) represents the gold standard of care for ESRD patients. The introduction of expanded criteria donors (ECD) changed the history of the KT waiting list and the kidney allocation system. Kidney ECD are defined as ≥ 60-year-old donors or 50- to 59-year-old donors with vascular comorbidities or long-standing hypertension or diabetes mellitus, or a non-heart beating deceased donor with prolonged cold ischemia time [2].

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Regardless of whether standard or ECD are used, transplantation carries a risk of infectious or neoplastic disease transmission [3–5]. For this reason, risk categories were established, which have standardized the clinical outlook for recipients. Specifically, risk of death on the waiting list versus risk of death from using a non-standard risk donor should be taken into account. Intermediate-risk organs (defined as 1% to 10% risk of neoplastic transmission according to the Disease Transmission Advisory Committee) should be considered for life-saving transplants with patients where the life expectancy without transplant is short [6].

Recently, the European guidelines for organ safety in matters of organ transplantation suggested adding donors with low-grade renal cell carcinomas (RCC) less than 4 cm, limited to the kidney [7] (stage pT1a according to the American Joint Committee on Cancer, AJCC) [8]. pT1a, a low grade RCC, also falls into the category of non-standard/negligible risk for cancer transmission according to Italian guidelines. More than 50% of RCCs are incidentally detected in the general population [9], and the likelihood of tumor diagnoses in donor candidates is increased using ECD.

The gold standard treatment for small renal tumors that are located in the polar site is partial nephrectomy, which has proven to achieve the same oncologic results as radical nephrectomy, even for tumors larger than 4 cm. This evidence has been supported by several retrospective studies and a prospective randomized controlled trial [10,11].

Suspicious primary neoplastic lesions of the kidney less than 4 cm, which could fall into the low risk of non-standard/negligible risk for cancer transmission, have to be considered on a case-by-case basis [12]. In this setting, intraoperative pathological analysis (i.e., frozen section) is required during the evaluation of the donor candidate in cases with suspicious kidney lesions/masses [13].

The original paper by Penn [14] reported 270 donors with a history of malignancy but free from cancer at the time of transplantation; in their study, 117 recipients (43%) developed malignancies from heart, lung, liver, or kidney grafts. In 2013, Xiao et al [15] reported a series of 91 kidney donors with a prior history of malignancy with a frequency of transmission similar to Penn [14]. According to Friberg and Nyström [16], RCC and melanoma represent the malignancies with the highest risk of late re-

currence (more than 10 years). Currently, the overall risk of neoplastic transmission is very small (0.01% to 0.05%) compared with the risk of dying during the first year on the waiting list (2%) [17].

The present study reports a single-center experience of KT from deceased donors with possible or proven RCC from 2001 to 2017 at S. Orsola-Malpighi Hospital of Bologna, in collaboration with Centro Nazionale Trapianti (CNT). In this study, the pathologists played a key role in determining suitability for transplantation. During this complex and multidisciplinary process, which often required intraoperative pathological analysis, frozen section diagnosis was used to determine the specific risk assessment for the recipient. Furthermore, in addition to the adequacy of the sample received, it is fundamental to achieve higher levels of safety in donor evaluation before transplantation.

Methods

This was a retrospective monocentric study on archival tissue. Therefore ethics approval was deemed unnecessary according to national regulations and was not required for the study according to the general authorization to process personal data for scientific research purposes from “The Italian Data Protection Authority” (<http://www.garanteprivacy.it/web>), which regulates the privacy of deceased organ donors. All donors and recipients were treated anonymously according to Declaration of Helsinki (2013).

Data from archives of the pathology department (from 2001 to 2005) and the registries of CNT (National Transplant Reference Centre of Emilia-Romagna region, from 2006 to 2017) were reviewed.

All deceased donors with suspected renal tumors were selected together with all cases in which renal masses were found at the time of organ retrieval. The pre-transplant risk of neoplastic transmission was assessed according to the Italian guidelines [18]. Before 2015, risk category was assessed according to the European Best Practice Guidelines and the Kidney Disease Improving Global Outcomes (KDIGO) organization [19,20].

Neoplastic transmission risk categories according to the old and new Italian guidelines compared with the European and UK guidelines are shown in Table 1 [7,18,21]. Renal lesions suspected as primary malignancy were

Table 1. Comparison among the old and recent Italian guidelines and the currently used European and UK guidelines

CNT/Italy 2008 [21]	CNT/Italy 2015 [18]	Council of Europe [7]	SaBTO/UK 2014
Standard risk	Standard	Standard risk	Standard
Calculated risk	Non-standard: negligible	Minimal risk: donor acceptable for all organs and recipients	Minimal risk (< 0.1%)
Increased but acceptable risk	Non-standard: acceptable	Low to intermediate risk: donor acceptable, justified by specific situation of emergency	Low risk (0.1% to 2%)
Unacceptable risk	Unacceptable	High risk: may be discussed in exceptional cases and for some life-saving transplantation procedures Unacceptable risk: absolute contraindication due to active malignancy and/or metastatic disease.	High risk (> 10%) Absolute contraindication

CNT, Centro Nazionale Trapianti.

evaluated in our Transplant Pathology Unit with intraoperative pathological diagnosis (frozen sections) during the routine consultation for donor safety. Lesions were sent to the pathology unit for evaluation of size; macroscopic appearance; and histological diagnosis of histotype, nuclear grade, and margins of resection.

After frozen section analysis, samples were formalin-fixed, paraffin-embedded, and routinely processed. Routine pathological analysis was carried out on 2- μ m-thick hematoxylin-eosin (H&E) sections, with eventual immunohistochemistry (IHC) when required.

IHC was performed with Benchmark ULTRA[®] Immunostainer (Ventana/Roche, Ventana Medical Systems, Tucson, AZ, USA) following the manufacturer's instructions. Required IHC included cytokeratin 7, CD10, PAX-8, RCC, Alpha-Methylacyl-CoA Racemase, HMB45, and CD117 [22].

Results

Over 17 years, 2,406 deceased donor candidates were considered, of which 1,321 became effective, for a total of 3,406 available organs (1,607 kidneys, 1,433 livers, 296 hearts, 52 lungs, 17 bowels, and 1 pancreas).

Intraoperative pathological evaluation with frozen-section analysis was required for suspicious renal lesions in 51 donors (3.9% of effective donors). These lesions were detected by ultrasound (US) during donor safety evaluation or at the back-table directly by the surgeon. Of the 51 lesions submitted, 26 were found to be neoplastic at frozen sections evaluation; 25 were negative. Moreover, 6 additional renal lesions were found at routine pathological evaluation of kidneys not used for donation (after the donation of other organs) due to specific graft disease or lack of recipients. Ultimately, 32 donors with kidney neo-

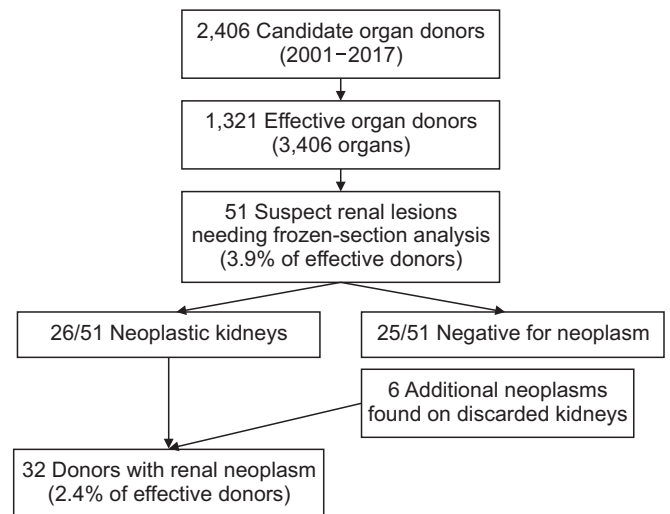


Figure 1. Flow-chart illustrating the study population.

plastic lesions were identified in the present study.

Frozen-section analysis and National Second Opinion (Fig. 1)

In total, we consulted with the Pathology Unit, of S. Orsola-Malpighi University Hospital of Bologna on 26 intraoperative frozen surgical specimens; the surgical specimens analysis included 17 lumpectomies, 5 nephrectomies, 2 wedge resections, and 2 fragmented nodules. In the latter cases (fragmented nodules), the evaluation of the dimensions and margins status was not possible. The average size of the tumors was 1.7 cm (range, 0.3 to 3.2 cm).

Intraoperative diagnoses and risk assessments are summarized in Table 2. A diagnosis of malignancy, including clear-cell RCC, papillary RCC, RCC not specified, and chromophobe (at the time of donor evaluation), resulted in 20 candidate donors (62.5%) cases. There were 6

Table 2. Clinical data and kidney tumor feature at the moment of donor evaluation suitability from 2001 to 2017

Donor gender, yr	Year	Specimen	Dimension (cm)	Frozen-section	Final diagnosis and WHO tumor grade	Risk assessment	Donated organs	Follow-up
M, 77	2001	Nodulesctomy	2.1	ccRCC	ccRCC G2	Standard	None	
F, 84	2001	Nodulesctomy	0.4	Papillary adenoma	Papillary adenoma	Standard	None	
F, 74	2002	Nodulesctomy	1.5	Oxyphilix neoplasia	Oncocytoma	Standard	Liver	Lost
M, 69	2002	Nodulesctomy	N/A	Suspect angiomyolipoma	Angiomyolipoma	Standard	None	
M, 54	2003	Nodulesctomy	N/A	RCC	ccRCC G3	Standard	Liver	DOAD
F, 83	2004	Nodulesctomy	1.0	Suspect angiomyolipoma	Angiomyolipoma	Standard	None	
M, 80	2005	Nodulesctomy	0.6	Low-grade tubulopapillary neoplasia	Papillary RCC (type 1) G2	Not standard/ acceptable	None	
M, 75	2005	Discarded kidney (incidental)	2.0	Not performed	ccRCC	N/A	None	
M, 77	2005	Discarded kidney (incidental)	N/A	Not performed	Papillary RCC (type 1) G2	N/A	Liver	Alive
F, 52	2005	Nodulesctomy	1.2	Oncocytoma	Oncocytoma	Standard	None	
F, 67	2006	Discarded kidney (incidental)	3.0	Not performed	ccRCC G3	N/A	None	
F, 70	2006	Discarded kidney (incidental)	0.7	Not performed	ccRCC G2	N/A	Liver	Alive
F, 74	2007	Discarded kidney (incidental)	1.8	Not performed	Chromophobe RCC	N/A	Liver	Lost
F, 74	2008	Nodulesctomy	2.0	Cystic ccRCC	Cystic ccRCC G1	Not standard/ acceptable	None	
F, 58	2008	Discarded kidney (incidental)	1.3	Not performed	Angiomyolipoma	N/A	None	
F, 49	2008	Nodulesctomy	0.8	Suspect angiomyolipoma	Angiomyolipoma	Standard	Liver, kidney	Lost (liver), alive (kidney)
M, 79	2008	Nodulesctomy (<i>known tumor</i>)	N/A	ccRCC	ccRCC G2	Not standard/ acceptable	Liver, kidney	Alive
M, 78	2011	Nodulesctomy	2.0	Oncocytoma	Oncocytoma	Standard	Liver	Lost
F, 66	2011	Nodulesctomy	0.3	ccRCC	ccRCC G2	Not standard/ acceptable	Kidney	DOAD
M, 78	2013	Nephrectomy	1.8	ccRCC	ccRCC G2	Standard	Liver, kidney	Alive
M, 53	2013	Nodulesctomy	1.0	Papillary RCC	Papillary RCC (type 1) G2	Not standard/ acceptable	Liver; heart, lung	Alive
M, 58	2013	Nodulesctomy	0.8	ccRCC	Papillary RCC (type 1) G2	Standard	Liver	DOAD
F, 54	2013	Nephrectomy	0.7	Suspect angiomyolipoma	Angiomyolipoma	Standard	Liver, kidney, heart	Alive
M, 51	2014	Wedge resection	1.5	Papillary RCC	Papillary RCC (type 1) G2	Standard	Kidney	Alive
F, 46	2015	Nephrectomy	3.2	ccRCC	ccRCC G2	Not standard/ negligible	Liver	Alive
M, 52	2015	Wedge resection	2.3	RCC	Clear-cell papillary RCC G2	Standard	Liver	DOAD

Table 2. Continued

Donor gender, yr	Year	Specimen	Dimension (cm)	Frozen-section	Final diagnosis and WHO tumor grade	Risk assessment	Donated organs	Follow-up
M, 52	2015	Nephrectomy	1.3	Oxyphilix neoplasia	Oncocytoma	Not standard/negligible	Liver	Alive
F, 52	2016	Fragments	2.4	ccRCC	ccRCC G2	Not standard/negligible	Liver, kidney	Lost (liver), DOAD (kidney)
M, 79	2016	Fragments	1.0	Suspect angiomyolipoma	Angiomyolipoma	Not requested	None	
M, 63	2016	Nephrectomy	2.5	ccRCC	Papillary RCC (type 2) G2	Not standard/negligible	None	
F, 63	2017	Nodulectomy	1.0	ccRCC	ccRCC G2	Not standard/negligible	Liver	Alive
F, 82	2017	Nodulectomy	1.0	Papillary neoplasia	Oncocytoma	Not requested	None	

ccRCC, clear cell renal cell carcinoma; DOAD, died of other diseases; F: female; M: male; N/A, not available; WHO, World Health Organization.

(18.8%) angiomyolipomas and 6 (18.8%) benign tumors.

A consultation with an expert (from National Second Opinion) was requested for 24 of the 26 donors to assess the oncologic risk of neoplastic transmission. According to the guidelines before 2015, 5 cases were assessed as not standard risk/acceptable [23,24], and 13 were assessed as standard risk. Standard risk included the two cases of low-stage and low-grade clear-cell RCC [24]. Furthermore, according to 2015 guidelines [18], 5 cases were assessed as not standard/negligible risk and 1 as standard risk. In 2 cases the small dimensions of the lesions and the pathological diagnosis did not require activation of the National Second Opinion by the Regional Transplant Center.

Definitive diagnosis and tumor histotypes

As shown in Table 2, final histopathological diagnosis confirmed low-grade RCC in all 11 cases. Only 1 case showed clear cell RCC (ccRCC) grade 3 according to World Health Organization (WHO) [22]; in all of these, low-grade malignancy was identified on frozen sections. A major disagreement between the intraoperative and final histological examination was reported in just one case (1/26; 3.8%); initially, the tumor was interpreted as a papillary growth pattern neoplasia, but it turned out to be an oncocytoma. Minor discrepancies have been observed for papillary neoplasias (types 1 and 2). In 2 out of 6 neoplasias, the suspicion was low grade RCC (1 resulted in a discarded kidney). In addition, 5 of 6 angiomyolipomas submitted for intraoperative consultation were con-

firmed.

All final histological slides from the 32 kidneys tumors were reviewed by three pathologists (F.A., F.V., and M.F.) and classified according to the current WHO classification of Renal Tumors-2016 [22]. The 32 suspected neoplastic lesions identified during the intraoperative donor risk assessments were 11 clear-cell RCC (9 grade 2 and 2 grade 3), 6 papillary RCC (5 types 1 and 1 type 2), 6 angiomyolipomas, 5 oncocytomas, 1 chromophobe RCC, 1 cystic clear-cell RCC, 1 clear-cell papillary RCC, and 1 papillary adenoma.

After donor risk assessment, 17 livers, 7 kidneys (contralateral to the neoplastic ones), 2 hearts, and 2 lungs became effective grafts from these 32 deceased donors. In all donors, the kidney with the suspected neoplastic lesion was used for the donation pool after surgical resection of the lesion with reliable free margins.

Recipients were periodically screened with US and/or computed tomography imaging and blood tests according to the protocols of the single centers to monitor any disease relapse. After a mean follow-up time of 87.8 ± 40.4 months (range, 32 to 164 months), no cases of neoplastic transmission or *de novo* RCC were recorded. Five recipients (3 liver and 2 kidney recipients) died of other diseases. Five additional liver recipients were lost in follow-up (Table 2).

Discussion

The progressive increase of ESRD has led to the need to expand the kidney donor pool including ECD and do-

nors with neoplasms with low to no risk of transmission (pT1a ccRCC, pRCC grade 1 to 2). Small RCC are often detected during the process of donor suitability. In the last 16 years, the Bologna Team for Transplantation (surgeons, nephrologists, and pathologists) identified 32 renal tumors in 2,406 donor candidates (1.3%). Six tumors were found in discarded kidneys, whereas 26 tumors were observed and suspected during donor safety assessment using US and/or at the back table and diagnosed on intraoperative frozen section analysis. In all cases, the contralateral kidney, without the suspected or assessed neoplasia, became a graft, whereas none of the neoplastic kidneys were transplanted. Four years after the end of our observational, retrospective study, no signs of neoplastic transmission have been recorded. However, our observations indicate a lack of standardized procedures, especially in sampling before transplantation. It is crucial that the surgeon and the nephrologist understand what to ask the pathologist, and, equally, a specialized pathologist in donor eligibility should know the key information to give the clinician.

Frozen section diagnosis of renal cell tumors can be challenging, firstly because it is rarely requested in routine practice and secondly due to several morphological pitfalls, including clear-cell component, spindle-cell component, nuclear grade, and cystic and oncocytic changes [13]. Additionally, new histological entities included in the latest WHO report [22] introduced challenging differential diagnoses between clear cell papillary RCC (indolent by definition) and ccRCC [25]. Intraoperative diagnosis should assess and answer specific questions: size, malignant behavior, nuclear grade, necrosis. The evaluation of tumor size is crucial for tumor staging [8,26]. This is the key information that a pathologist should evaluate during an intraoperative consultation in order to classify the risk of tumor transmission according to the Italian guidelines [18,21]. For an accurate frozen section diagnosis, the pathologist has to macroscopically detect the appropriate area to submit and, when possible, examine the entire lesion. Macroscopically, hemorrhage and/or necrosis are suspected features, and microscopically, areas of high tumor grade (G3 or G4 according to WHO [22]) must be determined, along with sarcomatoid/rhabdoid differentiation or necrosis, which are features that exclude the donor candidate suitability. Our study found that clear cell RCC represented 34.4% of

renal lesions in ECD, of which only 18.2% were deemed to be high grade (G3 according to WHO [22]), followed by papillary RCC at 18.7%. In our experience, margins were not evaluated because none of the kidneys that presented the lesions became grafts.

In our single-center experience from the Bologna Team for Transplantation, the National Second Opinion defined 14 donors of our series as standard risk on the bases of the histological frozen-section diagnosis, surgical evaluation, and clinical history.

The current literature supports using kidneys with incidental low-grade RCC where polar resection and free surgical margins can be assessed [27,28]. The kidneys with incidental neoplastic lesions found at the time of the donor evaluation were not used in our series, even though they have been reported as plausible candidates [29]. To preserve the kidney, surgeons should perform a specific kind of resection: a lumpectomy or wedge resection with a rim of preserved renal parenchyma to allow the gross and microscopic assessment of margins. However, until now, no standardized surgical protocols have been approved for evaluation of suspected renal lesions in ECD. After successful attempts over several years, practitioners have wanted to use of kidneys with low grade, pT1a RCCs with wide and free margins [28,30,31]. Our study showed a non-standardized attitude in both procedures and processes. Due to the variability of the samples received (lumpectomies, wedge resection, nephrectomies, or fragments), assessment of neoplastic margins was not always possible. According to a recent observational study [32], a wedge resection may be the optimal approach for small, polar tumors to preserve the remaining renal parenchyma and to use the organ to increase the organ pool, especially for recipients who risk leaving the transplant list (due to age) or who can no longer tolerate dialysis.

The main limitations of the present study are that it is a retrospective monocentric study that has a risk of selection bias as far as RCC incidence and behavior are concerned. Moreover, the sample size of the final cases of donors with RCC is relatively low for assessing the true risk of cancer transmission. Conversely, the low incidence of RCC in our donor population and the absence of proven cancer transmissions in follow-up are strong proof of the safety of our donor risk assessment procedure.

In conclusion, our experience suggests that organs with small, incidental, low-grade RCC (pT1a) from deceased

donors can be accepted in order to increase the organ pool. Lumpectomies and fragmented specimens should be avoided, since intraoperative diagnosis of the whole renal lesions should be used to assess tumor size, malignant/benign lesion, and malignant nuclear grade as well as presence/absence of necrosis, which are mandatory features for determining the risk of neoplastic transmission. According to our results, analyzing frozen sections of suspicious renal lesions is a reliable procedure, since in only one case was the intraoperative diagnosis discordant with the definitive report.

The use of kidneys with neoplastic lesions might represent an interesting and valuable option to increase the grafting pool. Nevertheless, we need more standardized studies and definitive guidelines to improve surgical procedures and histological assessments.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors' contributions

All authors contributed to the study concept and design. Material preparation, data collection and analysis were performed by Francesca Ambrosi, Costantino Ricci, and Antonia D'Errico. Manuscript drafting was performed by Francesca Ambrosi, Francesco Vasuri, and Deborah Malvi. All authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

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