

Review: Transplanting kidneys from donors with small renal masses — a strategy to expand the donor pool

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Abstract

Introduction: Renal transplantation is the optimal treatment for end-stage renal disease, but organ demand continues to outstrip supply. The transplantation of kidneys from donors with small renal masses (SRMs) represents a potential avenue to expand the donor pool. We reviewed all published cases of transplants from donors with SRMs and we present followup data, best practices, and outline an actionable series of steps to guide the implementation of such transplants at individual centres.

Methods: A detailed literature search of the MEDLINE/PubMed and SCOPUS databases was performed. Thirty unique data sets met inclusion criteria and described the transplantation of tumorectomized kidneys; nine data sets described the transplantation of contralateral kidneys from donors with SRMs.

Results: A total of 147 tumorectomized kidneys have been transplanted. Pathology revealed 120 to be renal cell carcinomas (RCCs), of which 116 were stage T1a (0.3–4 cm). The mean followup time was 44.2 months (1–200 months). A single suspected tumor recurrence occurred in one patient nine years post-transplantation and it was managed with active surveillance. Twenty-seven kidneys have been transplanted from deceased donors with contralateral renal masses. Pathology revealed 25 to be RCCs, of which 19 were confirmed to be stage T1 (<7 cm). The mean followup time was 46.7 months (0.5–155 months). One recipient developed an RCC and underwent curative allograft nephrectomy.

Conclusions: Careful use of kidneys from donors with SRMs is feasible and safe, with an overall recurrence rate of less than 1.5%. The utilization of such kidneys could help alleviate the organ shortage crisis.

Introduction

Renal transplantation is considered the gold standard of care for end-stage renal disease (ESRD) and offers significant survival, quality of life, and economic benefits.¹⁻³ Despite this, only a minority of patients with ESRD ultimately receive a transplant and organ demand continues to outstrip supply in most developed nations.⁴⁻⁷

Multiple strategies have been implemented to increase organ donation and utilization, including increasing living kidney donation, donations after cardiac death (DCD), the use of expanded criteria donor (ECD) kidneys, and national programs to facilitate kidney-paired donations and transplants for highly sensitized patients.⁸⁻¹⁰ In certain regions, system-wide rescue allocation schemes have been implemented in an effort to minimize the discard rate of deceased donor kidneys.¹¹ Despite such efforts, more than 15% of all deceased donor kidneys are discarded.^{4,6} The reasons for discarding a kidney are complex and may include donor, recipient, and organ factors. One potential factor is the incidental discovery of a renal mass at the time of organ procurement or during donor work-up in the case of living donation. The prevalence of incidental renal cell carcinoma (RCC) among cadaveric donors has previously been measured at 0.9%.¹² While uncommon, this nevertheless represents the annual loss of hundreds of potentially transplantable kidneys in North America alone.

The oncologic management of small renal masses continues to evolve; nephron-sparing surgery, in the form of partial nephrectomy, is considered to be the standard of care for T1a (<4 cm, organ confined) renal masses, when technically feasible.¹³⁻¹⁵ A recent US nation-wide analysis assessing the uptake of partial nephrectomy for the treatment of small renal masses between 2009 and 2012 demonstrated rates of 48% and 33% in teaching and non-teaching institutions, respectively.¹⁶ In Canada, a survey of academic centres revealed a partial nephrectomy rate of 78% for T1a tumours from 1988 to 2014, with an increasing trend over time.¹⁷ Some small renal masses, therefore, continue to be treated with radical nephrectomy. Often, this may be due to technical factors related to the tumour itself, but a proportion of cases result from patient preference for radical nephrectomy. Such kidneys may represent potentially transplantable organs that would otherwise be discarded.

The potential for safely transplanting kidneys with small renal masses was recognized as early as 1982, when Stubenbord *et al.* published a case report describing the transplantation of an allograft following removal of a small calcified renal mass, later confirmed to be an RCC.¹⁸ A number of groups have since published multiple case series describing the transplantation of tumorectomized kidneys from living or deceased donors, as well as kidneys from donors with contralateral renal malignancies. Here, we review and summarize all known cases, to date, of kidneys transplanted from donors with small renal masses, complete with follow-up data. We conclude by outlining a framework for the implementation of a transplant protocol for kidneys recovered from donors with small renal masses, and discuss the potential ethical and logistical pitfalls that may be encountered.

Methods

Two authors (N.R. and O.C.) performed a detailed literature search of the MEDLINE/PubMed and SCOPUS databases to identify all published literature describing the transplantation of kidneys from donors with small renal masses. A review of abstracts yielded 39 original studies and case reports, as well as 11 review papers; all of these were individually reviewed. Thirty original publications described the transplantation of tumorectomized kidneys only, 5 described the transplantation of both tumorectomized and contra-lateral kidneys, and 4 describe the transplantation of contra-lateral kidneys only. Three publications were excluded from our summary due to insufficient data. Two pairs of studies presented data from the same patient cohorts; in these instances the more recently published and complete data set was used for analysis. Thus, a total of 30 unique data sets describing the transplantation of tumorectomized kidneys were included in our analysis (Table 1), alongside 9 unique data sets describing the transplantation of contra-lateral kidneys from deceased donors with small renal masses (Table 2). Data was extracted using pre-specified parameters and included donor type, donor and recipient age, tumour size and pathology, follow-up time and recurrence, follow-up protocol, immunosuppression regimen, post-operative graft function, and surgical complications. Any discrepancies or disagreements that arose during the review and data collection process were resolved by the senior reviewer (N.R.).

Results

A total of 147 tumorectomized kidneys have been transplanted and included in our summary. Final pathology revealed 120 to be RCCs, 18 to be AMLs, and 9 to be of other benign etiologies. One hundred and thirty (88%) kidneys came from living donors, the majority of which came from patients undergoing radical nephrectomy for treatment of a renal mass, with the largest such series published by Brook *et al.*¹⁹ All of the tumours in the deceased donor kidneys were incidentally discovered. All of the 120 RCCs were stage T1: 116 were T1a (0.3-4 cm), 1 was T1b (4.3 cm) and 3 were identified only as T1 (< 7 cm). Pathological subtype was reported as clear cell for 66 (55%), papillary for 11 (9%), multilocular/cystic for 3 (3%), chromophobe for 2 (2%), and was unspecified or could not be determined for 38 (31%). Follow-up time was specified for 119 of the RCCs and ranged from 1 to 200 months with a mean of 44.2 months. A single tumour recurrence was documented in a 71-year-old male 9 years post-transplant and was characterized by a 1 cm lesion in the allograft, remote from the original tumour site. The patient opted for active surveillance and, at the time of study publication, the lesion had increased by 0.2 cm over an 18-month observation period.¹⁹

The presence or absence of post-operative complications was specifically commented on in 22 of the 30 data sets, accounting for 112 of the tumorectomized kidneys. Among these, there were 5 (4.5%) instances of urine leak, all of which were successfully managed conservatively; 2 (1.8%) instances of bleeding requiring re-operation; and 2 (1.8%) instances of an AV fistula or pseudoaneurysm requiring angioembolization.¹⁸⁻²¹ One-year graft survival could be determined for 129 of the tumorectomized kidneys and was 95%.

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A total of 27 kidneys have been transplanted from deceased donors with contra-lateral renal masses; of these, final pathology confirmed 25 as RCCs, 1 as a tubulo-papillary adenoma and 1 as an oncocytoma. Amongst the RCCs, 19 were stage T1, while the stage was unspecified in 6 cases. Follow-up time was reported for 24 of the RCCs and ranged from 0.5-155 months with a mean of 46.7 months. One kidney in this group was removed 3 months post-transplant due to non-salvageable acute rejection. This patient subsequently died 75 months after the original transplant from a confirmed de-novo renal cancer of his native kidneys, which was deemed unrelated to the transplanted kidney.²² The patient who received a kidney from a donor with a contralateral 1.7 cm tubulo-papillary adenoma underwent a biopsy at 4 months to rule-out rejection; this demonstrated diffuse and poorly differentiated RCC and imaging revealed enlarged adjacent lymph nodes. He subsequently underwent allograft nephrectomy and was monitored for 2 years before receiving a second transplant; three years after his second transplant he remained free of disease.²³ Of note, in this particular case, the recipient of the original donor heart succumbed to metastatic RCC 7 months post-transplant, suggesting circulating cancer cells at the time of organ procurement.

Discussion

It is well known that solid organ transplantation increases the overall risk of malignancy in transplant recipients, most likely as a consequence of the post-transplant immunosuppressed state.^{24,25} However, there is no evidence to suggest that immunosuppression has a negative impact on the natural history of localized RCC. Reflecting this, multiple existing clinical guidelines suggest that patients with small (<5 cm), incidentally discovered RCCs need not delay renal transplantation after undergoing surgical treatment, given the low risk of recurrence.^{26,27}

The results of the aforementioned studies suggest that transplantation of tumorectomized kidneys is similarly safe and feasible, with only 1 suspected tumour recurrence demonstrated to date. The data supporting the transplantation of contralateral kidneys is more limited. However, the risk of concomitant metastatic disease for T1a renal masses is < 2% and contralateral kidneys in this setting are therefore expected to be low risk for disease transmission with transplantation. To date, one case of recurrence has been described and occurred in a manner suggesting the presence of circulating cancer cells and/or micrometastases at the time of organ procurement. Taken together, the entire data set herein presented demonstrates a 1.4% recurrence rate amongst recipients of tumorectomized and contra-lateral kidneys from donors with confirmed small RCCs. This rate is comparable to that described in the literature for small renal masses treated with partial nephrectomy.²⁸

While not without risk, the small risk of RCC recurrence needs to be weighed against the risk of remaining on dialysis. In their analysis of 43 patients who received tumorectomized kidneys, Brook *et al.* demonstrated an increased 4-year survival rate over dialysis patients remaining on the waiting-list; survival was comparable to recipients of living unrelated kidneys matched for age, gender and HLA mismatch.¹⁹ Not all kidney transplant candidates would be willing to receive a kidney from a donor with a small renal mass and, indeed, only a subset of patients would be suitable

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recipients. One survey of patients on a transplant list in northern England, however, revealed that 59% would support the use of such kidneys.²⁹

We propose that judicious use of such kidneys in carefully selected patients is warranted and may serve as a reasonable and readily implementable strategy for combating the growing organ shortage crisis. To guide the implementation of such an effort, we outline a number of key considerations based on best practices from the studies hitherto published in the literature. A robust discussion of the ethical implications of transplanting kidneys with small renal masses is presented by Flechner and Campbell³⁰ and serves as a valuable adjunct to the considerations herein presented.

Ethical and legal approval

For any institution interested in transplanting kidneys from donors with small renal masses, we recommend an initial consultation with their respective Ethics and Legal departments. The objective is to review proposed protocols and supporting evidence, such that no transplant program risks running afoul of the ethical and legal criteria pertinent to their particular centre.

Recipient selection and counselling

Patients being newly listed or currently on the transplant wait-list should receive counselling about the potential of receiving a kidney from a donor with a small renal mass. The consent discussion must clearly outline the risk of cancer recurrence and transmission, including the possibility of death from metastatic disease, as well as the risk of surgical complications related to the tumour excision. Specific surgical risks such as bleeding, urine leak and arterio-venous fistula should be discussed. Patients should be informed about the need for ongoing post-transplant surveillance for RCC recurrence, in addition to the standard post-transplant follow-up. We propose that this informed process be conducted in a similar fashion and time as that performed for consideration of ECD and DCD kidneys. Consideration should also be given to establishing a well-defined set of eligibility criteria. In their series, Brook *et al.* limited potential recipients to those older than 60 years of age, with significant co-morbidities, difficulties with vascular access, and/or an expected mortality rate of >50% within 3-4 years.¹⁹ While there is insufficient data to determine an optimal set of recipient criteria, we recommend that both patient life expectancy as well as expected wait-list time be taken into consideration when formulating such criteria. We also recognize that these criteria will, and likely should, differ between individual transplant centres.

Donor counselling

In all patients found to harbour an incidentally discovered small renal mass, a referral should be sent to a urologist for consideration of nephron-sparing surgery. The patient should be counselled about all currently accepted management options including active surveillance, ablative therapies, nephron-sparing surgery and radical nephrectomy. It is imperative that these patients be counselled primarily from the standpoint of oncologic control and preservation of renal function and not as potential kidney donors. Failure to adopt this mindset may jeopardize patient care, compromise trust in the transplant community, and expose those involved in their care to ethical and legal ramifications. It is our recommendation that the subject of kidney donation not be raised until the

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decision to proceed with radical nephrectomy has been independently made and well documented. Furthermore, it is important that the process be expedited so as not to cause any unnecessary delay in definitive treatment of the tumour. We recommend that the transplant surgeon not be involved in the final decision about tumour management so as to avoid any potential conflict of interest. Likewise, patients being evaluated for living kidney donation who are found to have an incidental renal mass should be referred to a urologist for a full discussion about the appropriate oncologic management of small renal masses. Only once this discussion has been completed should living donation be entertained, provided both donor and recipient still wish to pursue this course of action.

Donor workup and investigations

All potential living donors found to have a small renal mass should undergo full clinical and radiographic evaluation including history, physical exam, abdominal CT, chest x-ray and laboratory investigations. It is important that such patients be counselled about the risk of metachronous tumours of the contralateral kidney, which can occur in up to 0.8% of cases.³¹ This figure may be higher if a papillary subtype of RCC is confirmed on final pathology. When appropriate, clinicians should screen patients for genetic syndromes that are associated with an increased risk of renal tumours, such as Von Hippel-Lindau or Tuberous Sclerosis Complex. Genetic testing should be offered to these patients and their families when indicated. Finally, a differential renal scan should be considered in all donors to ensure adequate nephron function in the contra-lateral kidney prior to undergoing radical nephrectomy.

Deceased donors with incidentally discovered renal tumours should undergo careful intra-operative assessment to rule out the presence of metastatic disease, including sternotomy and inspection of the thoracic organs. In their series, Pandanaboyana *et al.* used back-table ultrasound to inspect all contra-lateral kidneys and rule out the presence of a synchronous or metastatic tumour.³² The families of deceased donors with small incidentally discovered masses should be informed about the findings, and potential recipients of other organs from the same donor should be counselled accordingly.

We recommend that only kidneys from donors with T1a tumours (<4 cm; organ confined) be considered for transplantation. At the time of organ procurement, a sample of tissue can be sent for frozen section analysis at the discretion of the transplant surgeon; while this should reliably confirm the diagnosis, recently published data casts doubt on its utility in accurately predicting surgical margins and changing management.³³

Immunosuppression

Contemporary immunosuppression in kidney transplant recipients most commonly consists of a calcineurin inhibitor (CNI), an anti-proliferative agent and a systemic corticosteroid. Mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus, are alternate maintenance agents for CNIs and are used most commonly in the setting of refractory CNI toxicity.³⁴ These drugs have well characterized anti-neoplastic properties; everolimus, for example, is currently approved for treatment of metastatic RCC.³⁵ In the transplant setting, the use of sirolimus has been associated with a decreased incidence of renal and cutaneous malignancies, but an increased risk of prostate

cancer.³⁶ Instances of tumour regression after conversion to mTOR inhibitors have also been reported in some de-novo post-transplant malignancies; however, data for the regression of solid tumours is limited.³⁷ In the reviewed data series presented, 5 studies used an mTOR inhibitor in their maintenance immunosuppression regimen as a matter of course, accounting for 34 patients.^{20,21,38-40} Based on the published literature, it is unclear if the use of mTOR inhibitors would reduce the risk of RCC recurrence, and a definitive recommendation cannot be made at this time.

Followup protocol

There is no universally established follow-up regimen for patients with small, localized renal malignancies.²⁸ Among the studies herein reviewed, 8 specified a follow-up protocol. The frequency of imaging ranged from every 3 to 12 months and included a combination of ultrasound, chest x-ray and CT scans. In the absence of definitive guidelines, we recommend a conservative approach comprised of ultrasound, chest x-ray, abdominal CT, and laboratory investigations (CBC, BMP, LFTs including ALP, and Calcium) as outlined in Table 3.

Data collection and monitoring

At centres instituting a practice of transplanting kidneys from donors with small renal masses we recommend a well-defined patient roster for the purposes of tracking patient outcomes. Patients discharged back to the care of their primary care physicians should be instructed to report any suspected tumour recurrence to the original transplant centre.

Limitations

Our review has several limitations. Much of the available data has been published in the form of case reports or small case series, and there exists a risk of publication bias. There is some heterogeneity of the data, making detailed comparisons or statistical analysis difficult. The follow-up data presented was generally limited to the medium-term, with only a few long-term cases. Nevertheless, the very low rate of recurrence in this setting is still reassuring and suggests that the oncologic risk is not significantly affected by the immunosuppressed state.

Conclusions

Kidneys recovered and restored from donors with small renal masses are often suitable for subsequent transplantation. Post-transplant immunosuppression does not appear to alter the natural history of localized RCC; observed recurrence rates are minimal and in keeping with those expected from small renal masses in non-transplant patients. To the best of our knowledge, this review represents the most comprehensive summary of such cases to date. Potential recipients should be carefully selected and extensively counselled about the potential use of such kidneys; a rigorous informed consent process is necessary for both living donors and any intended recipients. We argue that the existing data supports judicious use of such kidneys to expand the donor pool and help alleviate the current organ shortage. Centres that implement the use of these transplants should do so in a structured and protocolized manner, and long-term follow-up should be instituted to monitor for recurrence.

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Figures and Tables

Table 1. Summary of published data sets describing the transplantation of tumorectomized kidneys

Publication	Location	Donor type	Pathology	Tumor size, cm (mean)	Recipient Age, yr (mean)	Followup, mo. (mean)	Recurrence
Wang 2018 ⁴¹	China	Living	7 RCC	2.1–3.5 (2.8)	29–57 (46.9)	31–58 (39.9)	None
Lim 2017 ⁴⁰	South Korea	Living	2 RCC	0.9, 0.7	52, 34	>32	None
Nyame 2017 ⁴²	USA	Living	1 AML	2.6	Not specified	24	None
Pandanaboyana 2016 ³²	UK	Deceased	3 RCC	<7	3–63 (40)	12–51 (33)	None
McGregor 2016 ⁴³	Canada	Living	1 AML	2.2 cm	Not specified	12	None
Ogawa 2015 ⁴⁴	Japan	Living	10 RCC	1.5–3.9 (3.1)	46–66 (56.1)	32–58 (46.1)	None
Lugo-Baruqui 2015 ⁴⁵	USA	Living	4 RCC	0.9–2.5 (1.4)	20–79 (57.1)	36	None
*Musquera 2013 ²⁰	Spain	Living & Deceased (4; 4)	7 RCC 1 lipoma	0.3–4.3 (1.5) 1.4	38–73 (53.4)	1–57 (32.3)	None
He 2013 ²¹	Australia	Living	20 RCC 1 AML	1.7–3.3 (2.5)	49–80 (66.3)	6–55 (28.3) ^ε	None
Khurana 2013 ⁴⁶	USA	Deceased	1 RCC	0.7	58	8	None
Singh 2013 ⁴⁷	India	Living	1 AML	4.3	Not specified	1	None
Valente 2012 ⁴⁸	Italy	Deceased	1 RCC	0.8	39	52	None
Abboudi 2012 ⁴⁹	Netherlands	Living	1 AML	7	54	36	None
Ali 2012 ⁵⁰	UK	Living	2 RCC	0.5, 1.4	57, 51	48, 72	None
Melgosa Hijosa 2012 ³⁹	Spain	Living	1 RCC	2.5	3	96	None
Meyyappan 2012 ⁵¹	India	Deceased	1 RMICT	2	36	3	None
^δ Brook 2010 ¹⁹ & Nicoll 2008 ⁵²	Australia	Living & Deceased (38; 3)	31 RCC 5 AML 3 complex cysts 2 oncocytomas	1–2.9 (2.2)	(60.9)	(32)	1 suspected (108 mo.)

Transplanting kidneys from donors with small renal masses

Bycroft 2010 ⁵³	UK	Living	1 RCC	0.7	49	Not specified	Not specified
Sener 2009 ⁵⁴	USA	Living	3 RCC 2 AML	1.0–2.2 (1.6) 1.1, 2.3	47–56 (51) 58, 61	9–31 (18.3) 1, 41	None None
Manami 2008 ⁵⁵	Japan	Living	8 RCC 2 AML 1 cavernous angioma 1 calcified cyst	1.2–3.5 (2.4) 3.5, -- 2.5 --	28–69 (50.8) 56, 47 48 67	3–145 (52.3) 107, 16 90 13	None None None None
Johannes 2008 ⁵⁶	USA	Living	1 AML	1.5	55	18	None
Ghafari 2007 ⁵⁷	Iran	Living	1 RCC	0.5	12	15	None
Dainys 2007 ³⁸	Lithuania	Living	1 RCC	2	38	>72	None
Buell 2005 ⁵⁸ & Penn 1995 ²²	USA	Living & Deceased (11; 3)	14 RCC	0.5–4 (2.1) ^ε	(40.8)	14–200 (88) ^ε	None
Hetet 2004 ⁵⁹	France	Living	1 AML	0.7	29	24	None
Lasaponara 2000 ⁶⁰	Italy	Living	1 RCC	1	Not specified	138	None
Chen 2000 ⁶¹	USA	Living	1 AML	7	62	Not specified	None
Weiss 1998 ⁶²	USA	Living	1 RCC	1	45	120	None
Bissada 1993 ⁶³	USA	Living	1 AML	3	44	2	None
Stubenbord 1982 ¹⁸	USA	Deceased	1 RCC	3	Not specified	96	None

*Tumor size and followup time provided for entire cohort of 10 patients as a whole, which includes two patients who received contra-lateral kidneys from Table 2. ^δAverage recipient age and followup time provided for entire cohort of 43 patients as a whole, which includes two patients who received contra-lateral kidneys from Table 2. ^εIn these instances medians, accompanied by minimum and maximum values, were reported by the authors. We provide here an estimated mean for the cohort in question, calculated using techniques available in the published literature, in order to allow for a comparison across studies.⁶⁷ AML: angiomyolipoma; RCC: renal cell carcinoma.

Table 2. Summary of published data sets describing the transplantation of contra-lateral kidneys from donors with small renal masses

Publication	Location	Donor type	Pathology	Tumor size, cm (mean)	Recipient age, yr (mean)	Followup, mo. (mean)	Recurrence
Pandanaboyana et al, 2016 ¹⁸	UK	Deceased	2 RCC 1 oncocytoma	<7	41, 56 48	24, 25 64	None --
Morris et al, 2015 ⁶⁴	Greece	Deceased	1 RCC	2.5	Not specified	48	None
*Musquera et al, 2013 ²⁰	Spain	Deceased	2 RCC	0.3–4.3 (1.5)	54, 57	1–57 (32.3)	None
Valente et al, 2012 ⁴⁸	Italy	Deceased	2 RCC	0.2, 1.5	45, 50	22, 56	None
^o Brook et al, 2010 ¹⁹ & Nicoll et al, 2008 ⁵²	Australia	Deceased	2 RCC	1–2.9 (2.2)	(60.9)	(32)	None
Barrou et al, 2001 ²³	France	Deceased	1 tubulo-papillary adenoma	1.7	63	4	1 confirmed (4 mo.)
Carver et al, 2001 ⁶⁵	USA	Deceased	1 RCC	1.0	65	48	None
Penn, 1995 ²²	USA	Deceased	14 RCC	≤4 cm in 7 unknown in 7	Not specified	0.5–155 (55)	None
Pliskin et al, 1998 ⁶⁶	USA	Deceased	1 RCC	2.7	46	Not specified	Not specified

*Tumor size and followup time provided for entire cohort of 10 patients as a whole, which includes 8 patients who received tumorectomized kidneys from Table 1. ^o Average recipient age and followup time provided for entire cohort of 43 patients as a whole, which includes 41 patients who received tumorectomized kidneys from Table 1. RCC: renal cell carcinoma.

Table 3. Suggested cancer-specific followup protocol for patients receiving a transplant kidney from a donor with a small renal mass

Time frame post-transplantation	Suggested investigations
0–2 years	Ultrasound every 3 months alternating with abdominal CT every 6 months Chest x-ray every 3 months Laboratory investigations every 3 months
2–5 years	Ultrasound every 6 months alternating with abdominal CT every 12 months Chest x-ray every 6 months Laboratory investigations every 6 months
5+ years	Ultrasound every 12 months Chest x-ray every 12 months Laboratory investigations every 12 months

CT: computed tomography.