EUROPEAN COLORECTAL CONGRESS

Spotlight on the colon

1 – 5 December 2019, St.Gallen, Switzerland

Sunday, 1 Dec. 2019

MASTERCLASS

09.00
When the appendix plays nasty: intraoperative surprises, immediate solutions, and long-term treatment options
Justin Davies, Cambridge, UK

09.40
All the secrets of the pelvic floor - common disorders and proven solutions
Julie Cornish, Cardiff, UK

10.20
taTME in 2020 – when the dust settles: current and innovative indications, implementation, and practical advices
Roel Hompes, Amsterdam, NL

11.30
Complete mesocolic excision: indications, surgical approaches, and pitfalls
Paris Tekkis, London, UK

12.10
The views of an Editor and the wisdom of an Expert: contemporary publications with the potential to change and improve practice
Neil Mortensen, Oxford, UK

14.00
To ostomize or not and when? The value and downside of a diverting stoma versus virtual ileostomy versus no stoma
Gabriela Möslein, Wuppertal, DE

14.40
Extended lymph node dissection: indications, surgical anatomy, and technical approaches
Peter Sagar, Leeds, UK

15.20
Is the longer the new better - how to safely extend the interval after neoadjuvant chemoradiotherapy prior to surgery for rectal cancer
Ronan O'Connell, Dublin, IE

16:30
The colorectal anastomosis: time-proven wisdom, innovative configurations, and salvage techniques
André d'Hoore, Leuven BE

17.10
All you need to know about stomas but never dared to ask
Willem Bemelman, Amsterdam, NL

17.50
The EBSQ Coloproctology Examination
Michel Adamina, Winterthur, CH

18.00
Wrap-up
Michel Adamina, Winterthur, CH

Monday, 2 Dec. 2019

SCIENTIFIC PROGRAMME

09.45
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
Pathophysiology and non-operative management of symptomatic uncomplicated diverticular disease
Robin Spiller, Nottingham, UK

10.30
Surgery of acute diverticulitis – evidence, eminence and real life
Willem Bemelman, Amsterdam, NL

11.00
Management of atypical diverticulitis
Dieter Hahnloser, Lausanne, CH

11.30
Hartmann reversal: open, laparoscopic or transanal?
Roel Hompes, Amsterdam, NL

13.30
The surgeon personality – influence on decision making, risk-taking and outcomes
Desmond Winter, Dublin, IE

14.00
SATELLITE SYMPOSIUM
Medtronic

15.00
Clinical applications of image-guided cancer surgery
Cornelis van de Velde, Leiden, NL

16.00
Volvulus of the colon – a treatment algorithm
Peter Sagar, Leeds, UK

16.30
Hereditary colorectal cancer syndromes: tailored surgical treatment
Gabriela Möslein, Wuppertal, DE

17.00
Lars Pahlman and Herand Abcarian (2015)
Herand Abcarian, Chicago, US

17.20
Lars Påhlman Lecture
Steven Wexner, Weston, US

Tuesday, 3 Dec. 2019

09.00
Robotic-assisted versus conventional laparoscopic surgery for rectal cancer
Amjad Parvaiz, Poole, UK

09.30
Robotic multivisceral resection
Paris Tekkis, London, UK

10.00
SATELLITE SYMPOSIUM
Karl Storz

11.30
Neoadjuvant chemotherapy for advanced colon cancer: clinical and pathological Results
Dion Morton, Birmingham, UK
Philip Quirke, Leeds, UK

12.30
Cytoreductive surgery and hyperthermic intraoperative chemotherapy for intestinal and ovarial cancers: lessons learned from 2 decades of clinical trials
Vic Verwaal, Aarhus, DK

14.30
Mechanical bowel obstruction: rush to the OR or stent and dine
Neil Mortensen, Oxford, UK

15.00
Controversies in IBD surgery
André d'Hoore, Leuven, BE

16.00
How to deal with IBD and dysplasia
Janindra Warusavitarne, London, UK

16.30
Perianal Crohn – avoiding delay and best surgical practice
Justin Davies, Cambridge, UK

17.00
Perianal Crohn – stem cells therapy and current medical approach
Gerhard Rogler, Zürich, CH

Wednesday, 4 Dec. 2019

09.00
Is anastomotic leak an infectious disease
Ronan O'Connell, Dublin, IE

09.30
Is it time to invest in robotic surgery?
Antonino Spinelli, Milan, IT

10.00
SATELLITE SYMPOSIUM
Intuitive

11.00
New developments in robotic systems
Alberto Arezzo, Torino, IT

12.00
Posterior component separation for abdominal wall reconstruction: evolution from open to minimal invasive using the robotic platform
Filip Muysoms, Gent, BE

14.00
Coloproctology 4.0 – the networked surgeon
Richard Brady, Newcastle upon Tyne, UK

14.30
SATELLITE SYMPOSIUM
Olympus

15.30
The elderly colorectal patient – functional outcomes and patient reported outcomes
Isacco Montroni, Faenza, IT

16.30
The microbiome and colorectal cancer
Philip Quirke, Leeds, UK

17.00
Surgical management of rectal endometriosis
Eric Rullier, Bordeaux, FR

17.30
EAES Presidential Lecture 3D printing for the general surgeon
Andrea Pietrabissa, Pavia, IT

Thursday, 5 Dec. 2019

09.00
Management of locoregionally advanced colon cancer
Torbjörn Holm, Stockholm, SE

09.30
ROUNDTABLE
Herand Abcarian, Chicago, US
Bill Heald, Basingstoke, UK

10.30
Artificial intelligence in colorectal surgery
Michele Diana, Strasbourg, FR

11.30
The mesentery in colonic diseases
Calvin Coffey, Luimneach, IE

12.00
Technical pearls and typical mistakes in minimal invasive colectomy
Antonio Lacy, Barcelona, ES

12.30
Choosing the right anastomotic technique in colon surgery
Roberto Persiani, Rom, IT

13.00
Precision surgery: past, present and future
Brendan Moran, Basingstoke, UK

13.30
Poster award
Michel Adamina, Winterthur, CH

Information & Registration

www.colorectalsurgery.eu

Original article

Effect of donor nephrectomy time during circulatory-dead donor kidney retrieval on transplant graft failure

L. Heylen[1], J. Pirenne[2,3], U. Samuel[6], I. Tieken[6], M. Coemans[4], M. Naesens[1,4], B. Sprangers[1,5] and I. Jochmans[2,3]

Departments of [1]Nephrology and [2]Abdominal Transplant Surgery, University Hospitals Leuven, and [3]Abdominal Transplantation, Transplantation Research Group, [4]Nephrology and Renal Transplantation Research Group, and [5]Molecular Immunology, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium, and [6]Eurotransplant International Foundation, Leiden, the Netherlands

Correspondence to: Dr I. Jochmans, Department of Abdominal Transplant Surgery, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium (e-mail: ina.jochmans@uzleuven.be; @heylen_line, @ijochmans)

Background: When the blood supply ceases in a deceased organ donor, ischaemic injury starts. Kidneys are cooled to reduce cellular metabolism and minimize ischaemic injury. This cooling is slow and kidneys are lukewarm during nephrectomy. Smaller single-centre studies have shown that prolonged donor nephrectomy time decreases early kidney transplant function, but the effect on long-term outcome has never been investigated in large multicentre cohort studies.

Methods: The relationship between donor nephrectomy time and death-censored graft survival was evaluated in recipients of single adult-to-adult, first-time deceased-donor kidneys transplanted in the Eurotransplant region between 2004 and 2013.

Results: A total of 13 914 recipients were included. Median donor nephrectomy time was 51 (i.q.r. 39–65) min. Kidneys donated after circulatory death had longer nephrectomy times than those from brain-dead donors: median 57 (43–78) *versus* 50 (39–64) min respectively ($P < 0{\cdot}001$). Donor nephrectomy time was independently associated with graft loss when kidneys were donated after circulatory death: adjusted hazard ratio (HR) 1·05 (95 per cent c.i. 1·01 to 1·09) per 10-min increase ($P = 0{\cdot}026$). The magnitude of this effect was comparable to the effect of each hour of additional cold ischaemia: HR 1·04 (1·01 to 1·07) per h ($P = 0{\cdot}004$). For kidneys donated after brain death, there was no effect of nephrectomy time on graft survival: adjusted HR 1·01 (0·98 to 1·04) per 10 min ($P = 0{\cdot}464$).

Conclusion: Prolonged donor nephrectomy time impairs graft outcome in kidneys donated after circulatory death. Keeping this short, together with efficient cooling during nephrectomy, might improve outcome.

Presented to a meeting of the European Society of Organ Transplantation, Barcelona, Spain, September 2017; published in abstract form as *Transpl Int* 2017; **30** (Suppl 2): 124.

Paper accepted 27 June 2019

Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.11316

Introduction

Kidney transplantation is the treatment of choice for patients with end-stage renal disease, improving survival and quality of life[1,2]. Despite all efforts in recent decades, long-term outcome has not improved[3]. One factor with a negative influence on transplant outcome is ischaemia–reperfusion injury of the graft, an inevitable problem during organ transplantation[4].

Cold storage, currently the standard for graft preservation, aims to minimize ischaemic injury by storing the kidney at around 4°C. Metabolism decreases with decreasing temperature, reducing the effect of ischaemia. Cooling the kidney in the donor is accomplished by a combination of intravascular and topical cooling. Intravascular cooling consists of flushing the kidney with an ice-cold preservation solution through the aorta after aortic cross-clamp. Topical cooling means that the organs are covered with ice slush. Despite these manoeuvres, the kidney cools slowly and its temperature might not reach 0–4°C inside the donor body[5]. Until the kidney has cooled down, best achieved by storage on ice, it will continue to experience higher metabolic rates. The time it takes to remove the kidney from the donor body,

called the extraction time or donor nephrectomy time, might be harmful, and might influence outcome after transplantation.

Previously Osband and Zaki[6] described an increased risk of early graft failure (defined as all-cause graft failure in the first 3 months after transplantation) in 316 transplants according to donor nephrectomy time divided into 30-min intervals (0–29, 30–60 and over 60 min)[6]. In a follow-up study[7] of 576 transplants, donor nephrectomy time above 60 min increased the risk of early graft failure, although this did not reach significance when adjusted for other variables. The study, however, was small, and might have been underpowered to detect significant differences.

Whether or not donor nephrectomy time impairs long-term graft outcome has not been investigated. This study aimed to evaluate the effect of donor nephrectomy time during organ retrieval on graft outcome in a large multicentre cohort using the follow-up registry of Eurotransplant.

Methods

Eurotransplant[8] is an international non-profit organization that manages patient-oriented allocation and cross-border exchange of deceased-donor organs to achieve the best possible match between available donor organs and patients on the transplant waiting list in eight countries: Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia. The Eurotransplant follow-up registry records data for all kidney transplants performed in 72 kidney transplant centres in its region. Data are collected on a voluntary basis in order to develop best practice recommendations and policies in the Eurotransplant Kidney Advisory Committee (ETKAC) to improve organ allocation and transplant outcomes. The study proposal was approved by the ETKAC and local institutional review boards. Data submitted to this registry for all adult recipients of first solitary kidney transplants from adult deceased donors undertaken between 1 January 2004 and 31 December 2013 were analysed. Donor nephrectomy time was defined as the interval between the start of aortic cold flush in the donor and the end of nephrectomy when the kidney was placed on ice on the back table. Cold ischaemia time was defined as the interval between the start of aortic cold flush in the donor until the kidney left the ice to be implanted in the recipient. Donor asystolic warm ischaemia time in circulatory-dead donation was defined as the interval between circulatory arrest and the start of cold flush in the donor. Time to graft failure was taken as the interval from transplantation to graft nephrectomy or return to dialysis, whichever came first, and censored for death of a patient with a functioning graft. These data are collected prospectively in the Eurotransplant follow-up registry.

Expanded criteria donation was defined as donation of any kidney procured from a brain-dead donor aged at least 60 years or any brain-dead donor aged 50–59 years with two of the following: stroke as the cause of death,

Table 1 Baseline characteristics

	No. of people*
Donors	
Age (years)†	56 (46–66)
Sex ratio (M : F)	7242 : 6672
Donor type	
DBD	12 855 (92·4)
DCD	1059 (7·6)
History of diabetes‡	
No	5719 (83·4)
Yes	1135 (16·6)
History of hypertension‡	
No	3886 (43·3)
Yes	5094 (56·7)
DBD donor criteria‡	
Standard	5326 (44·4)
Expanded	6672 (55·6)
Last creatinine (mg/dl)†§	0·86 (0·66–1·13)
Donor weight (kg)†¶	78 (70–85)
Thoracoabdominal donation	
Abdominal donation only	8596 (61·8)
Thoracic and abdominal donation	5318 (38·2)
Multiple abdominal organ donation	
Kidney only	20 (0·1)
Liver/pancreas also	13 894 (99·9)
No. of kidneys procured	
1	155 (1·1)
2	13 759 (98·9)
Recipients	
Age (years)†	58 (47–65)
Sex ratio (M : F)	8839 : 5075
No. of HLA mismatches†#	3 (2–4)
Process	
Donor nephrectomy time (min)†	51 (39–65)
Cold ischaemia time (h)†**	13·4 (10·0–17·1)
Anastomosis time (min)†,††	36 (29–45)
Preservation fluid‡	
HTK	9702 (70·3)
UW	3921 (28·4)
Other	186 (1·3)

*With percentages in parentheses unless indicated otherwise; †values are median (i.q.r.). ‡Data missing for this variable; §five, ¶three, #139, **2243 and ††3364 missing values. DBD, donation after brain death; DCD, donation after circulatory death; HTK, histidine–tryptophan–ketoglutarate; UW, University of Wisconsin solution.

medical history of hypertension, and terminal creatinine exceeding 1·5 mg/dl (133 μmol/l); this was in contrast to standard-criteria donation after brain death[9].

Statistical analysis

Follow-up analysis of the study population included all data submitted to Eurotransplant by 5 November 2015. Recipients of double, or *en bloc* kidney transplants were excluded. Only recipients for whom complete data on both donor nephrectomy time and graft survival were available were included in the study. This study focused specifically on transplantations from adult donors to adult recipients (aged at least 18 years), receiving their first transplant.

Donor nephrectomy times for transplants with different characteristics were compared using Wilcoxon tests. Associations between donor nephrectomy time and continuous data were assessed with Spearman correlation.

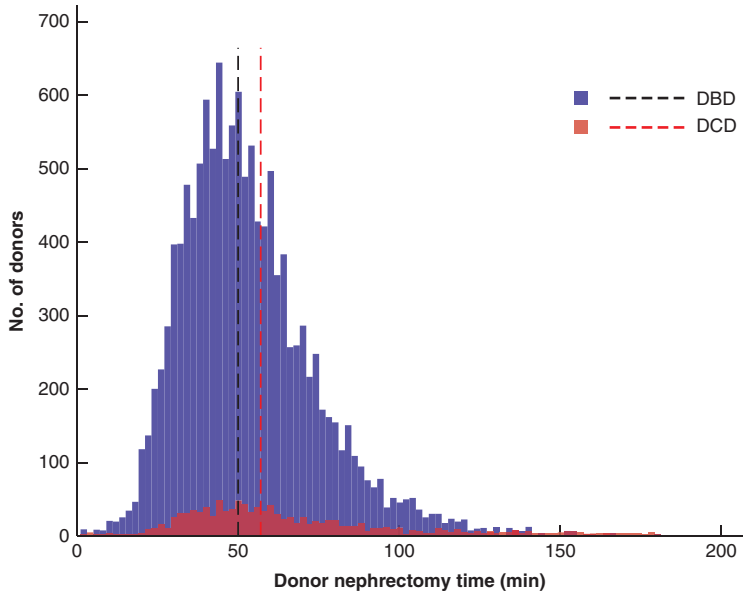
Kidney transplant outcome was graft failure (death-censored graft survival). Unadjusted and adjusted Cox proportional hazards regression analyses were used to evaluate the effect of donor nephrectomy time on transplant outcome. Transplant variables for inclusion in the multivariable models were factors shown to affect transplant outcome in this cohort based on the results of a previous study[10]. In addition, factors that could confound the association between donor nephrectomy time and outcome were considered. As this study focused on first kidney transplants only, retransplantation was not a co-factor in the analyses. The adjusted analyses included only transplants for which complete data on all co-variables were available. Although this reduced the final number of transplants analysed, no imputation of missing values was done and only the original data were analysed. Transplant centre was included in the multivariable model as a random effect. There was no violation of non-proportionality of hazards of donor nephrectomy time in the multivariable model. Interaction analyses were undertaken to determine whether the effect of donor nephrectomy time was modified by donor age and cold ischaemia time (as donor nephrectomy time is an integral part of cold ischaemia time).

All tests were two sided and $P < 0{\cdot}050$ was considered significant. R version 3.1.3 (running in RStudio, Boston, Massachusetts, USA) was used for all statistical analyses. Hazard ratio (HR) plots were designed using the simPH package in RStudio[11]. No random effect was included in the model used to design the HR plots as this did not significantly change the HRs and the simPH package does not support random effects.

Results

A total of 32 040 deceased-donor kidney transplants were performed in the Eurotransplant region between 1 January 2004 and 31 December 2013. Some 4680 retransplants, 265

Fig. 1 Histogram of donor nephrectomy time for brain-death and circulatory-death donation



DBD, donation after brain death; DCD, donation after circulatory death. The dashed line represents the median donor nephrectomy time in each group.

double or *en bloc* transplants, 888 transplants in recipients aged below 18 years at the time of transplantation, as well as 695 transplants from donors aged below 18 years were excluded. In addition, 11 019 transplants were excluded for which no outcome data were available, and 579 for which donor nephrectomy times were missing or reported to be 0 min or over 180 min. The final cohort comprised 13 914 adult recipients of first solitary kidney transplants from adult deceased donors.

Median follow-up after transplantation was 2·39 (i.q.r. 1·00–4·73) years. *Table 1* shows characteristics of the donors and recipients at the time of transplantation. Median donor nephrectomy time was 51 (i.q.r. 39–65) min (*Fig. 1*).

Determinants of donor nephrectomy time

First, the donor and retrieval characteristics that determine the donor nephrectomy time were explored (*Table 2*). As expected, donor nephrectomy time was longer when both kidneys were procured, and when other abdominal organs or thoracic organs were also procured. In addition, donor nephrectomy time was longer after circulatory death compared with that after brain death: median 57 (i.q.r. 43–78) *versus* 50 (39–64) min respectively ($P < 0{\cdot}001$). Donor nephrectomy time was longer in younger donors, and in donors without diabetes or hypertension, presumably because these fitter donors were more frequently selected as multiple organ donors. There was a very weak but statistically significant positive correlation with cold ischaemia time ($r_S = 0{\cdot}03$, $P = 0{\cdot}003$), explained by the fact that donor nephrectomy time is an integral part of cold ischaemia time. Donor weight also correlated positively with donor nephrectomy time ($r_S = 0{\cdot}04$, $P < 0{\cdot}001$). Donor nephrectomy time was shorter for right compared with left kidneys, reflecting their earlier extraction: median 49 (38–63) *versus* 53 (41–67) min ($P < 0{\cdot}001$).

Table 2 Variables associated with donor nephrectomy time in unadjusted comparisons

	Donor nephrectomy time (min)*	r_S	P†
Thoracoabdominal donation			< 0·001
Abdominal donation only	47 (37–60)		
Thoracic and abdominal donation	57 (45–72)		
Multiple abdominal organ donation			< 0·001
Kidney only	36 (28–41)		
Liver/pancreas also	51 (39–65)		
No. of kidneys procured			< 0·001
1	44 (34–58)		
2	51 (39–65)		
Donor history of diabetes			< 0·001
No	52 (40–68)		
Yes	49 (38–62)		
Donor history of hypertension			< 0·001
No	53 (40–70)		
Yes	49 (38–63)		
Donor type			< 0·001
DCD	57 (43–78)		
DBD	50 (39–64)		
DBD donor criteria			< 0·001
Standard	54 (41–70)		
Expanded	48 (38–60)		
Age (years)		−0·18	< 0·001‡
Cold ischaemia time (min)		0·03	0·003‡
Donor weight (kg)		0·04	< 0·001‡

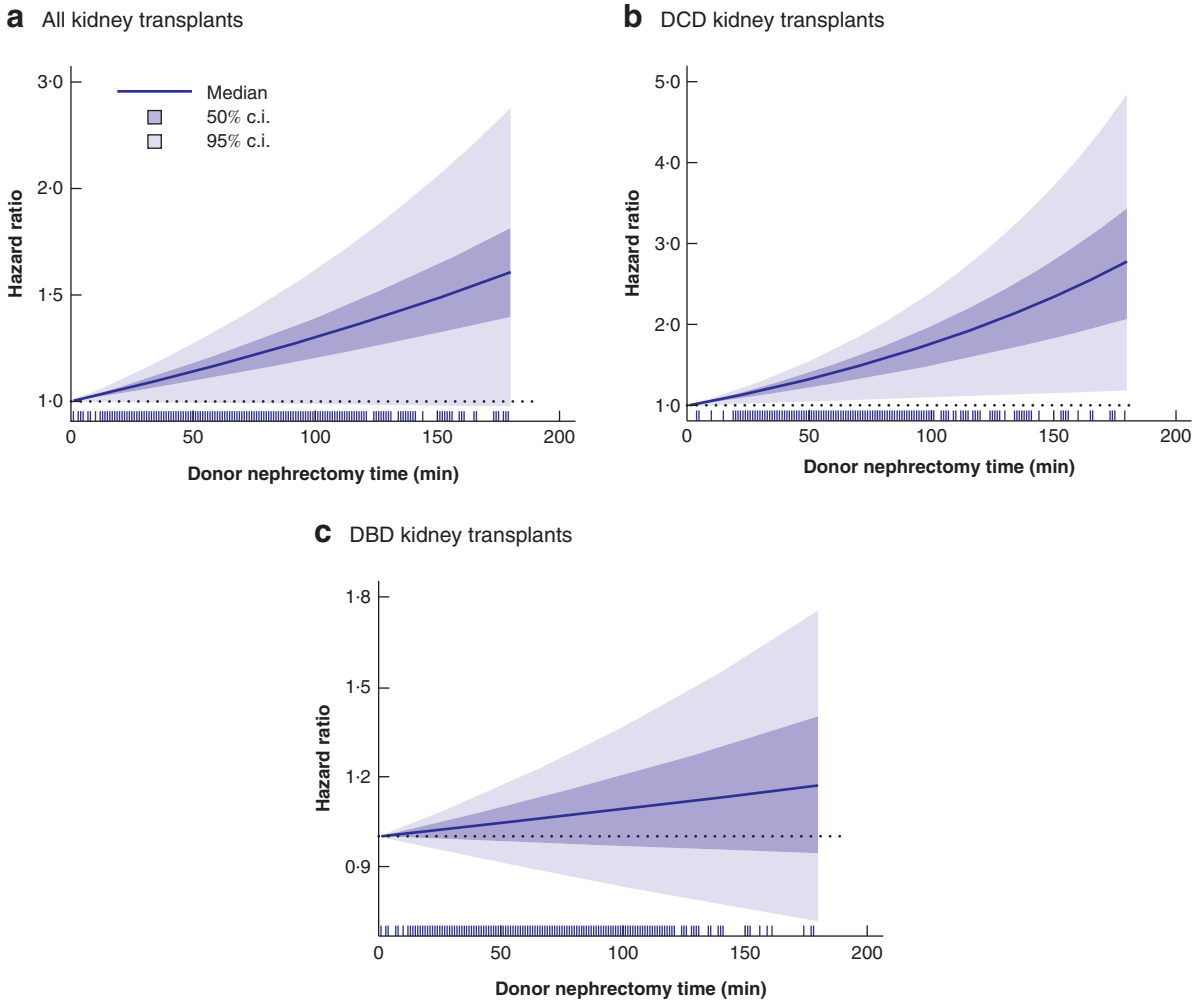
*Values are median (i.q.r.). DBD, donation after brain death; DCD, donation after circulatory death. †Wilcoxon test, except ‡Spearman's correlation.

Donor nephrectomy time and graft survival in whole cohort

In the unadjusted analysis, donor nephrectomy time did not influence graft survival for all kidneys from deceased donors: unadjusted hazard ratio 0·98 (95 per cent c.i. 0·98 to 1·01) for every 10-min increase in donor nephrectomy time ($P = 0{\cdot}289$). However, as described above, donor nephrectomy time depended heavily on donor characteristics, and was longer in younger donors, confounding the unadjusted survival analysis. Therefore, a Cox regression model was adjusted for all variables known to influence graft survival independently based on a previous study[10] of the same Eurotransplant registry (donor age, donor diabetes, donor hypertension, donor last serum creatinine measurement, type of donation, recipient age, number of HLA mismatches, cold ischaemia time and anastomosis time as fixed effects, and transplant centre as a random effect), and other potential confounding factors such as thoracoabdominal donation, multiple abdominal organ donation, dual *versus* single kidney donation and donor weight. As only first renal transplants were included, no adjustment for retransplantation was needed. After adjustment for these factors, donor nephrectomy time was associated with graft failure, although this did not reach statistical significance: adjusted HR 1·02 (95 per cent c.i. 1·00 to 1·05) for every 10-min increase in donor nephrectomy time ($P = 0{\cdot}062$) (*Fig. 2a*; *Table S1*, supporting information).

As right kidneys are often extracted first, explaining their shorter donor nephrectomy times, graft survival of right and left kidneys was compared. There was no difference in graft survival between right and left kidneys, either in the unadjusted ($P = 0{\cdot}749$) or adjusted ($P = 0{\cdot}491$) analysis.

Fig. 2 Adjusted hazard ratio for graft failure (death censored) in relation to donor nephrectomy time



a All kidneys, **b** donation after circulatory death (DCD) kidneys and **c** donation after brain death (DBD) kidneys. The dashes along the *x*-axis show the distribution of donor nephrectomy time. Dotted line indicates a hazard ratio of 1·00.

Effect of donor nephrectomy time on graft survival in different types of donation

The effect of donor nephrectomy time on outcome in recipients of kidneys from circulatory-dead and brain-dead donors was evaluated separately. Similar to the observation in the complete cohort, donor nephrectomy time was not associated with kidney transplant survival in the unadjusted analyses for the kidneys donated after circulatory death: HR 1·02 (95 per cent c.i. 0·98 to 1·05) for every 10-min increase in donor nephrectomy time ($P = 0·310$). On the contrary, faster extraction of poorer quality kidneys seemed to evoke an inverse association in the unadjusted analysis of kidneys from brain-dead donors: HR 0·98 (0·97 to 1·00) for every 10-min increase in donor nephrectomy time ($P = 0·048$). Given the confounding present in the unadjusted analyses, Kaplan–Meier curves are not interpretable, and therefore not shown.

For adjusted survival analyses, the Cox regression model used in the total cohort was applied to each donor type separately. In circulatory-dead donor transplants, prolonged donor nephrectomy time significantly increased the risk of graft loss: adjusted HR 1·05 (1·01 to 1·09) for every 10-min increase ($P = 0·026$) (*Fig. 2b* and *Table 3*). In brain-dead donor transplants, donor nephrectomy time had no effect on graft loss: adjusted HR 1·01 (0·98 to 1·04) for every 10-min increase ($P = 0·464$) (*Fig. 2c* and *Table 4*). The magnitude of the detrimental effect of each additional

Table 3 Multivariable Cox proportional hazards regression analysis for graft survival in transplants from circulatory-dead donors

	Adjusted hazard ratio	*P*
Donor nephrectomy time (per 10-min increase)	1·05 (1·01, 1·09)	0·026
Anastomosis time (per 10-min increase)	1·17 (1·07, 1·28)	< 0·001
Cold ischaemia time (per h increase)	1·04 (1·01, 1·07)	0·004
Donor age (per year increase)	1·03 (1·02, 1·04)	< 0·001
Donor diabetes	1·72 (1·05, 2·81)	0·031
Donor hypertension	1·23 (0·90, 1·68)	0·196
Donor last serum creatinine measurement	1·12 (0·72, 1·73)	0·620
Donor weight	1·01 (1·00, 1·02)	0·938
Recipient age (per year increase)	0·98 (0·97, 0·99)	0·003
No. of HLA mismatches (per each mismatch increase)	0·99 (0·88, 1·11)	0·844
Thoracoabdominal donation	0·77 (0·56, 1·08)	0·102
Multiple abdominal organ donation	0·18 (0·04, 0·90)	0·037
Dual *versus* single kidney donation	0·96 (0·30, 3·09)	0·938

Values in parentheses are 95 per cent confidence intervals. The analysis included 746 transplants. Transplant centre was adjusted for as a random effect.

Table 4 Multivariable Cox proportional hazards regression analysis for graft survival in transplants from brain-dead donors

	Adjusted hazard ratio	*P*
Donor nephrectomy time (per 10-min increase)	1·01 (0·98, 1·04)	0·464
Anastomosis time (per 10-min increase)	1·05 (1·01, 1·09)	0·018
Cold ischaemia time (per h increase)	1·01 (1·00, 1·02)	0·141
Donor age (per year increase)	1·02 (1·01, 1·02)	< 0·001
Donor diabetes	1·14 (0·94, 1·39)	0·197
Donor hypertension	1·14 (0·97, 1·33)	0·104
Donor last serum creatinine measurement	1·11 (1·00, 1·24)	0·043
Donor weight	1·00 (0·99, 1·00)	0·362
Recipient age (per year increase)	0·98 (0·97, 0·98)	< 0·001
No. of HLA mismatches (per each mismatch increase)	1·07 (1·03, 1·12)	0·003
Thoracoabdominal donation	0·90 (0·76, 1·05)	0·216
Multiple abdominal organ donation	1·61 (0·20, 12·89)	0·654
Dual *versus* single kidney donation	0·89 (0·49, 1·63)	0·711

Values in parentheses are 95 per cent confidence intervals. The analysis included 615 transplants. Transplant centre was adjusted for as a random effect.

10 min of donor nephrectomy time on graft loss in kidneys from circulatory-dead donors was comparable to that of every additional hour of cold ischaemia: adjusted HR 1·04 (1·01 to1·07) for every hour increase ($P = 0·004$).

When the multivariable Cox regression model in kidney transplants from circulatory-dead donors was adjusted for donor asystolic warm ischaemia time, donor nephrectomy time remained associated with reduced graft survival: HR 1·06 (1·01 to 1·11) for every 10-min increase ($P = 0·014$). There was no significant interaction between the two ($P = 0·562$), but the effect of the sum of donor asystolic and extraction ischaemia time on graft survival was more pronounced than the effect of its components: HR 1·07 (1·03 to 1·11) for every 10-min increase ($P = 0·001$).

As donor nephrectomy time is an integral part of cold ischaemia time, the interaction between cold ischaemia time and donor nephrectomy time was evaluated. There was no interaction between the two ($P = 0·699$). There was also no interaction between donor age and donor nephrectomy time ($P = 0·273$).

Discussion

In this study of data in the Eurotransplant follow-up registry, prolonged kidney donor nephrectomy time during organ retrieval from circulatory-dead donors, but not from brain-dead donors, increased the risk of graft failure after kidney transplantation. Every additional 10 min of donor nephrectomy time had an effect comparable to that of each additional hour of cold ischaemia.

During organ retrieval, cold preservation fluid is flushed through the arteries, and the abdomen is filled with slush ice. Volume and type of preservation fluid used, as well as duration, vary between donor centres, and there are limited studies of these different practices. Although the kidney temperature will decrease as a result of the cold flush and additional topical cooling with ice, it will not reach temperatures comparable to those achieved with preservation on ice (around 4°C)[12]. At this temperature, the metabolism slows significantly, reducing ischaemic injury. The metabolic threshold at which oxygen demand becomes greatly diminished is believed to be around 15°C[13,14]. During extraction, kidney temperature is unlikely to be below this threshold. There is surprisingly little literature on kidney temperature during retrieval. In a pig model of multiple organ retrieval, the rate of temperature decrease of the right kidney varied between 0·6°C per min and 1·3°C per min during the procedure[5], although data from Mikhalski and colleagues[15] suggested that there is some rebound of temperature after the initial cooling by cold flush. They measured kidney temperature during retrieval and observed an average mean(s.d.) kidney retrieval temperature of 23(4)°C for kidneys donated after circulatory death and 19(4)°C for those donated after brain death, significantly above the metabolic threshold[15]. At these temperatures, the kidney is more susceptible to ischaemic injury. Therefore, prolonged donor nephrectomy time is likely to harm the graft.

Donor nephrectomy time is influenced by several aspects of organ donation. Donor nephrectomy times in the present study were longer when both kidneys were procured, and when other abdominal organs or thoracic organs were procured. Osband and co-workers[7] described a linear increase with the number of organs being recovered, with an average mean increase of 6 min for each additional organ. Evidently, multiple organ donors have fewer co-morbidities than donors in whom only the kidney is considered suitable for transplantation, confounding any unadjusted analysis. Donor nephrectomy time was indeed longer for younger donors, and in donors without diabetes or hypertension in the present study. Moreover, kidneys from younger donors might even tolerate ischaemic injury better[16]. Unsurprisingly, donor nephrectomy time did not influence graft survival in the unadjusted analyses, which were strongly confounded.

However, when adjusted for donor, transplant and recipient characteristics, longer donor nephrectomy time did increase the risk of graft failure in recipients of kidneys from circulatory-dead donors, but not in recipients of kidneys from brain-dead donors. Donor nephrectomy time was longer for kidneys donated after circulatory death, which is not surprising. During organ retrieval in these donors, the entire dissection of the abdominal compartment is done after the aortic cross-clamp. A super-rapid retrieval technique is used in which the aortic cold flush is started within minutes after laparotomy, whereas more preparatory dissection is done before aortic clamping and cold flushing in the classical retrieval technique[17,18]. The vulnerability to donor nephrectomy time of kidneys from circulatory-dead donors in contrast to those from brain-dead donors could be due to the superimposed preceding exposure of these kidneys to normothermic ischaemia starting at withdrawal of therapy[19], a phase known to cause significant changes at the cellular and subcellular level[20].

Donor warm ischaemia time after circulatory arrest correlates with transplant survival in kidneys from donors after circulatory death[10]. Donor asystolic time is the sole explanation for the inferior outcome of kidneys from circulatory-dead donors compared with those from brain-dead donors that has been observed in the Eurotransplant registry[10]. When kept short, the outcome of kidneys donated after circulatory death is comparable to that of kidneys from standard-criteria brain-dead donors. In this study, there was no interaction between donor asystolic time and donor nephrectomy time, but the effect of the two ischaemia times together was more pronounced than the effect of its components. The longer donor nephrectomy time for circulatory-dead donor kidneys could not, in itself, explain the inferior outcome of these organs, as including this variable in the multivariable survival analysis did not remove the significant effect of donor type on outcome.

That extraction can influence graft outcome of kidneys from circulatory-dead donors, but not those from brain-dead donors, is also in line with a previous study[21], in which the duration of anastomosis was significantly more detrimental to graft survival in recipients of kidneys donated after circulatory death[21]. Similar observations have been made regarding the effect of cold ischaemia time on graft survival[22]. Of note, kidneys from circulatory-dead donors were excluded from the study by Osband and Zaki[6].

The finding that prolonged donor nephrectomy time impairs outcome in donation after circulatory death is of particular importance because it is a factor amenable to improvement: first, by reducing the duration of nephrectomy and, second, by improving the efficiency of kidney cooling. Although the effect of the surgeon's experience cannot be investigated in this data set, it would be reasonable to assume that more experienced surgeons are likely to perform the nephrectomy more quickly. Therefore, the present findings support the importance of training in retrieval surgery and the performance of a critical number of procedures under supervision before carrying out the procedure independently[23]. This is particularly true in donation after circulatory death procedures, where kidneys suffer more surgical injury during retrieval than in donation after brain death[24]. In addition, kidneys from circulatory-dead donors already face additional warm ischaemia injury after circulatory arrest of the donor, which translates into inferior early and late outcomes compared with standard brain-dead donor transplants[10,25].

More attention should also be paid to keeping the kidneys cold during retrieval. Aortic flush is usually stopped after a certain volume of cold preservation solution has been perfused, or, in other countries, after a predefined interval. Whether cold perfusion should be continued until the kidneys have cooled down further should be studied. Furthermore, it is essential that donor nephrectomy is not delayed. In multiple organ retrieval with recovery of thoracic organs, procurement teams could work in parallel so that the abdominal organs do not wait until the thoracic organs have been recovered. In addition, the liver and pancreas may require some additional back-table work before they can be packed and stored. The present data suggest that it would be prudent not to keep the kidneys in the donor body while waiting for this additional back-table work to be completed before nephrectomy is undertaken. Assistants could be available to pack the organs simultaneously. Finally, after extraction, the kidneys should

be transferred to the back table and ice box as quickly as possible.

Innovative organ procurement techniques such as normothermic regional perfusion[26], where the circulation of oxygenated blood is restored in the (thoraco)abdominal cavity, allow a less hurried procurement, where the dissection phase of the organs can take place before the cold aortic flush is started. It might be that in this setting, as in donation after brain death, donor nephrectomy times could be shorter and outcomes improved.

The strength of the present analysis is the use of a large cohort of transplant recipients in the Eurotransplant region. A limitation inherent to this registry study, based on data from many different centres and countries, is the lack of detailed information regarding donor and recipient characteristics, and the potential for incomplete data registration. In contrast to the USA and UK transplant registries, outcome data submission to the Eurotransplant follow-up registry is not mandatory, explaining the high frequency of missing data in this registry. Although the possibility of selection bias cannot be excluded, results of previous studies[10,21] from this database have been confirmed in other large cohort studies[27], and characteristics of transplants included *versus* excluded were also comparable in these previous studies.

Acknowledgements

No preregistration exists for the research reported in this article.

Disclosure: The authors declare no conflict of interest.

References

1 Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients *vs* cadaveric renal transplant recipients. *JAMA* 1993; **270**: 1339–1343.

2 Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725–1730.

3 Coemans M, Süsal C, Döhler B, Anglicheau D, Giral M, Bestard O *et al.* Analyses of the short- and long-term graft survival after kidney transplantation in Europe between 1986 and 2015. *Kidney Int* 2018; **94**: 964–973.

4 Debout A, Foucher Y, Trébern-Launay K, Legendre C, Kreis H, Mourad G *et al.* Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. *Kidney Int* 2015; **87**: 343–349.

5 Savioz D, Jeanjacquot A, Savioz M, Ludwig C, Chilcott M, Bolle JF *et al.* Optimization of the kinetics of cooling of kidneys: a pig model. *Eur Surg Res* 1999; **31**: 3–8.

6 Osband AJ, Zaki RF. Extraction time of kidneys during organ procurement impacts function. *Clin Transplant* 2011; **25**: 235–238.

7 Osband AJ, James NT, Segev DL. Extraction time of kidneys from deceased donors and impact on outcomes. *Am J Transplant* 2016; **16**: 700–703.

8 https://www.eurotransplant.org/ [accessed 7 December 2018].

9 Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW *et al.* Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002; **74**: 1281–1286.

10 Heylen L, Jochmans I, Samuel U, Tieken I, Naesens M, Pirenne J *et al.* The duration of asystolic ischemia determines the risk of graft failure after circulatory-dead donor kidney transplantation: a Eurotransplant cohort study. *Am J Transplant* 2018; **18**: 881–889.

11 Gandrud C. simPH: an R package for illustrating estimates from Cox proportional hazard models including for interactive and nonlinear effects. *J Stat Softw* 2015; **65**: 1–20.

12 Feuillu B, Cormier L, Frimat L, Kessler M, Amrani M, Mangin P *et al.* Kidney warming during transplantation. *Transpl Int* 2003; **16**: 307–312.

13 Ward JP. Determination of the optimum temperature for regional renal hypothermia during temporary renal ischaemia. *Br J Urol* 1975; **47**: 17–24.

14 Russell JC, Chambers MM. Comparative temperature dependence of (Na+ + K+)-ATPase. *Physiol Chem Phys* 1976; **8**: 237–251.

15 Mikhalski D, Buggenhout A, Donckier V, Katsanos G, Loi P, Lucidi V *et al.* What about the temperature of the donor and the abdominal organs during DCD and DBD procurement and do the alterations of the temperature during multi-organ procurement interfere transplant liver and kidneys outcome? *Belgian Transplantation Society Annual Meeting*, Brussels, 2015.

16 Tullius SG, Reutzel-Selke A, Egermann F, Nieminen-Kelhä M, Jonas S, Bechstein WO *et al.* Contribution of prolonged ischemia and donor age to chronic renal allograft dysfunction. *J Am Soc Nephrol* 2000; **11**: 1317–1324.

17 Starzl TE, Hakala TR, Shaw BW Jr, Hardesty RL, Rosenthal TJ, Griffith BP *et al.* A flexible procedure for multiple cadaveric organ procurement. *Surg Gynecol Obstet* 1984; **158**: 223–230.

18 Casavilla A, Ramirez C, Shapiro R, Nghiem D, Miracle K, Bronsther O *et al.* Experience with liver and kidney allografts from non-heart-beating donors. *Transplantation* 1995; **59**: 197–203.

19 Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. *Br J Anaesth* 2012; **108**(Suppl 2): i108–i121.
20 Rhee JY, Alroy J, Freeman RB. Characterization of the withdrawal phase in a porcine donation after the cardiac death model. *Am J Transplant* 2011; **11**: 1169–1175.
21 Heylen L, Pirenne J, Samuel U, Tieken I, Naesens M, Sprangers B *et al.* The impact of anastomosis time during kidney transplantation on graft loss: a Eurotransplant cohort study. *Am J Transplant* 2017; **17**: 724–732.
22 Summers DM, Johnson RJ, Hudson A, Collett D, Watson CJ, Bradley JA. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. *Lancet* 2013; **381**: 727–734.
23 de Graauw JA, Mihály S, Deme O, Hofker HS, Baranski AG, Gobée OP *et al.* Exchange of best practices within the European Union: surgery standardization of abdominal organ retrieval. *Transplant Proc* 2014; **46**: 2070–2074.
24 Ausania F, White SA, Pocock P, Manas DM. Kidney damage during organ recovery in donation after circulatory death donors: data from UK National Transplant Database. *Am J Transplant* 2012; **12**: 932–936.
25 Barlow AD, Metcalfe MS, Johari Y, Elwell R, Veitch PS, Nicholson ML. Case-matched comparison of long-term results of non-heart beating and heart-beating donor renal transplants. *Br J Surg* 2009; **96**: 685–691.
26 Oniscu GC, Randle LV, Muiesan P, Butler AJ, Currie IS, Perera MT *et al. In situ* normothermic regional perfusion for controlled donation after circulatory death – the United Kingdom experience. *Am J Transplant* 2014; **14**: 2846–2854.
27 Tennankore KK, Kim SJ, Alwayn IP, Kiberd BA. Prolonged warm ischemia time is associated with graft failure and mortality after kidney transplantation. *Kidney Int* 2016; **89**: 648–658.

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.