Radiological Classification of Distinct Patterns of Nonanastomotic Strictures: Can We Predict the Course of the Disease?

Ivo J. Schurink, BSc,[1] Femke H.C. de Goeij, BSc,[1] and Jeroen de Jonge, MD, PhD[1]

Over the last 20 y, the utilization of organs from donation after circulatory death (DCD) is increasing in an attempt to reduce waiting list mortality due to donor organ scarcity. For liver transplantation (LT), this comes at a cost; the incidence of biliary nonanastomotic strictures (NAS, also referred to as ischemic cholangiopathy) is significantly higher. DCD grafts have a NAS incidence ranging from 7% to 34% compared with 1% to 4% in grafts donated after brain death.[1,2] Although the exact mechanism behind the pathophysiology of NAS still is unknown, the main risk factor of the development of NAS is the donor functional warm ischemia.[3] Additional damage may be inflicted by subsequent ischemia-reperfusion injury, immune-mediated processes, and cytotoxic injury from biliary salts.[3,4]

Patients with NAS display a wide range of clinical symptoms. Some patients only have abnormal laboratory values, others predominantly present with pruritus or jaundice, and other patients have severe scarring of the biliary tree with life-threatening episodes of cholangitis. The location of the strictures affects the effectiveness of the endoscopic treatment.[5] In 2007, the first radiological classification for NAS was proposed by the Seoul National University College of Medicine and afterward validated by the Mayo Clinic,[6,7] indicating the position and extend of the strictures. Extrahepatic strictures can be relatively easily treated endoscopically, whereas multifocal intrahepatic strictures are more difficult to treat with low success rates.[5] The overall success rate of endoscopic treatment of biliary strictures in NAS patients varies between 50% and 70%.[5] Eventually, up to 50% of patients developing NAS will need a retransplantation.

Received 7 June 2021. Revision received 24 July 2021.

Accepted 13 August 2021.

[1] *Department of Surgery, Division of Hepato-Pancreato-Biliary and Transplant Surgery, Erasmus MC Transplant Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands.*

The authors declare no conflicts of interest.

All the authors participated in writing the article.

Correspondence: Jeroen de Jonge, MD, PhD, Division of Hepato-Pancreato-Biliary and Transplant Surgery, Department of Surgery, Erasmus MC Transplant Institute, University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. (j.dejonge.1@erasmusmc.nl).

ISSN: 0041-1337/20/1066-1107

DOI: 10.1097/TP.0000000000003929

In this issue of *Transplantation*, Croome et al[8] provide a detailed analysis on the natural history and clinical course of 88 out of 770 DCD LT patients developing NAS, categorizing these patients into 4 subtypes with significantly different clinical outcomes. Patients with the minor form or confluence dominant subtype did have an 80% 5-y graft survival outcome, whereas this was 20% in the multifocal progressive subtype and 0% in the diffuse necrosis subtype. Overall, the 2 severe subtype categories affected 60% of the patients who developed NAS.

This is important new information, adding relevant clinical outcomes to the previously proposed radiological classification, that may serve as a base to differentiate in the management of patients who develop NAS. Patients with the diffuse necrosis and multifocal progressive subtypes could be early relisted based on radiological appearance and prioritized with standard exception points to protect against multiple severe episodes of cholangitis before receiving a retransplantation. On the other hand, in 40% of the NAS patients, the graft can be rescued by (repeated) biliary interventions, saving precious donor livers for others in need.

If radiological imaging is to become an important criterium to predict eventual graft survival, it is important to know the interobserver variability in scoring the subtypes. The authors do not substantiate this with a kappa value but indicate good agreement when development of the biliary stricture over time is analyzed. This may reduce the advantage of the new radiological classification as a single shot diagnostic procedure over the routine clinical follow-up to serve as a decision-making tool for relisting.

In total, only 88 of 770 (11%) patients in this US cohort developed NAS, which is low compared with numbers reported in many European DCD programs. These excellent results are probably due to vigorous donor selection, and it would be necessary to validate the applicability of subtyping NAS in transplant programs with up to 40% DCD contribution, like in many European countries, before it could be considered to shape policy there with regard to retransplantation for NAS.

Another important detail to take into consideration is to realize that in 2 of the 3 locations of the study, a routine cholangiogram was performed via a surgically placed biliary catheter through the biliary anastomosis. At the third location, radiological imaging was performed if clinically indicated, for example, because of laboratory abnormalities. Obviously, this will impact the pretest change to find abnormalities, and the authors do not indicate in detail if

<zdoi;10.1097/TP.0000000000003929>

there is a difference in subtypes diagnosed through routine or on-demand cholangiographies. Currently, many transplant programs will not routinely use a T-tube and have to rely on magnetic resonance cholangio pancreaticography or endoscopy retrograde cholangio pancreaticography. At the Venice 2020 consensus meeting, the International Liver Transplantation Society workgroup did not recommend routine biliary imaging after DCD LT, as it had few consequences, but given the impact of the new subtype classification on outcome, this may have to be reconsidered.

Finally, machine perfusion techniques are now rapidly emerging in an attempt to mitigate especially ischemic cholangiopathy and NAS. (Dual) hypothermic machine perfusion and normothermic regional perfusion have been shown to reduce NAS formation,[9-11] whereas this has not been shown for normothermic machine perfusion.[9-11] It would be interesting to analyze if these perfusion techniques reduce the overall incidence of all types of NAS equally or transform the severe forms into the less severe forms that do not impact graft survival. An indication for the latter might be in the recent dual hypothermic oxygenated perfusion study, where routine magnetic resonance cholangio pancreaticography was performed, and van Rijn et al[9] showed biliary radiological abnormalities in 65% of asymptomatic patients.

Therefore, in the setting of machine perfusion trials, the radiological subtype classification now published in *Transplantation* may even become a surrogate endpoint for 5-y graft survival, as more relevant markers than transaminase levels are sought.

In summary, the new radiological classification of Croome et al[8] could potentially develop into a decision-making tool in the management of DCD LT recipients with NAS. Also, the classification may provide a new relevant surrogate endpoint for clinical trials looking into the prevention of NAS.

REFERENCES

1. Foley DP, Fernandez LA, Leverson G, et al. Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. *Ann Surg.* 2011;253:817–825.
2. Dubbeld J, Hoekstra H, Farid W, et al. Similar liver transplantation survival with selected cardiac death donors and brain death donors. *Br J Surg.* 2010;97:744–753.
3. Buis CI, Verdonk RC, Van der Jagt EJ, et al. Nonanastomotic biliary strictures after liver transplantation, part 1: radiological features and risk factors for early vs. late presentation. *Liver Transpl.* 2007;13:708–718.
4. Buis CI, Hoekstra H, Verdonk RC, et al. Causes and consequences of ischemic-type biliary lesions after liver transplantation. *J Hepatobiliary Pancreat Surg.* 2006;13:517–524.
5. Zoepf T, Maldonado de Dechêne EJ, Dechêne A, et al. Optimized endoscopic treatment of ischemic-type biliary lesions after liver transplantation. *Gastrointest Endosc.* 2012;76:556–563.
6. Lee HW, Suh KS, Shin WY, et al. Classification and prognosis of intrahepatic biliary stricture after liver transplantation. *Liver Transpl.* 2007;13:1736–1742.
7. Giesbrandt KJ, Bulatao IG, Keaveny AP, et al. Radiologic characterization of ischemic cholangiopathy in donation-after-cardiac-death liver transplants and correlation with clinical outcomes. *AJR Am J Roentgenol.* 2015;205:976–984.
8. Croome KP, Mathur AK, Aqel B, et al. Classification of distinct patterns of ischemic cholangiopathy following DCD liver transplantation: distinct clinical courses and long-term outcomes from a multicenter cohort. *Transplantation.* 2022;106:1206–1214.
9. Van Rijn R, Schurink IJ, de Vries Y, et al; DHOPE-DCD Trial Investigators. Hypothermic machine perfusion in liver transplantation—a randomized trial. *N Engl J Med.* 2021;384:1391–1401.
10. Hessheimer AJ, Coll E, Torres F, et al. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol.* 2019;70:658–665.
11. Nasralla D, Coussios CC, Mergental H, et al; Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature.* 2018;557:50–56.