Infants born with hypoplastic left heart syndrome who undergo a surgical procedure with a right ventricle-pulmonary artery (RV-PA) shunt are more likely to survive their first year and not require a heart transplant than those who have the procedure with the traditional approach, a modified Blalock-Taussig (MBT) shunt.

These are the findings of a Single Ventricle Reconstruction trial published in the May 27 issue of the *New England Journal of Medicine* and led by Richard G. Ohye, M.D., head of the Division of Pediatric Cardiovascular Surgery and the Surgical Director of Pediatric Heart Transplant Program, Department of Surgery at the University of Michigan’s C.S. Mott Children’s Hospital. After the first year, however, the two surgical procedures yielded similar results.

Hypoplastic left heart syndrome is the most common severe heart birth defect. Occurring in about 1,000 children every year in the United States, it accounts for roughly about 8 percent of all congenital heart defects.

Under Ohye's leadership, the first North American, multi-institutional randomized prospective trial ever conducted in congenital heart surgery was completed by the Pediatric Heart Network with funding from the National Heart, Lung and Blood Institute of the National Institutes of Health. It enrolled 549 newborns with congenital heart disease to compare two surgical procedures that are commonly used to treat infants born with HLHS to determine whether one procedure had better outcomes than the other.

The SVR trial was conducted at 15 North American clinical sites that are part of the NHLBI's Pediatric Heart Network.

Typically, three surgeries are needed to treat a single right ventricle, according to the study authors. The first procedure, the Norwood procedure, is usually performed within the first two weeks of life and is one of the highest-risk procedures in congenital heart surgery. A shunt is implanted to provide a connection for blood to flow from the heart to the pulmonary arteries, so that blood can pick up oxygen and release carbon dioxide. Children later undergo a second surgery at four to six months of age, and the third procedure, known as the Fontan procedure, at 18 to 48 months.

“We found that the RV-PA shunt did better over the course of the first year.”

Maggie and Maddie, two unrelated girls from South Dakota, were referred by their physician to C.S. Mott Children’s Hospital for surgery to repair their complex congenital heart defects. At center is Richard G. Ohye, M.D., head of the Division of Pediatric Cardiovascular Surgery and the Surgical Director of Pediatric Heart Transplant Program.

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For prospective parents who carry genes for certain inherited genetic disorders, the potential of passing those vulnerabilities to their children can be daunting.

But a relatively novel technique known as pre-implantation genetic diagnosis is easing those worries. Just recently, the University of Michigan’s Center for Reproductive Medicine began offering this service to identify in embryos genetic disorders with significant morbidities in which quality of life is dramatically affected.

Also referred to as PGD, the term refers to a procedure used in conjunction with in vitro fertilization to detect genetic diseases before pregnancy.

Pre-implantation genetic diagnosis is performed when one or both genetic parents have a known genetic abnormality and testing is performed on an embryo to determine if it also carries the genetic abnormality. Only unaffected embryos are implanted.

“If a family member has an inherited genetic disease, parents can reduce the risk of passing along this disease by using this technology,” says Senait Fisseha, M.D., J.D., an assistant professor in the U-M Department of Obstetrics and Gynecology who specializes in reproductive endocrinology and infertility.

During the process, embryos are created using in vitro fertilization, and on the third day — when the embryos reach six- to eight-cell stage — a biopsy is performed to remove one or two cells and determine whether they carry the genetic abnormality. Embryos that are found to not carry the genetic defect are then transferred to the womb.

PGD is often used to look for a specific disorder in couples with high risk of transmitting an inherited condition. This can be a monogenic disorder, meaning the condition is due to a single gene defect of varying etiologies, including autosomal recessive, autosomal dominant or X-linked disorders.

Disorders commonly diagnosed using PGD include cystic fibrosis, Beta-thalassemia, sickle cell disease, spinal muscular atrophy, myotonic dystrophy, Huntington’s disease, Charcot-Marie-Tooth disease, Fragile X syndrome, hemophilia A and Duchenne muscular dystrophy.

“With a very strong medical genetics program at University of Michigan, our center is well situated to offer PGD services to those patients in a very timely and efficient manner,” says Fisseha.

“We are discouraging women from using this method for anything other than identifying single gene defects,” she adds. “Although pre-implantation genetic screening has been used to screen for aneuploidies (abnormal number of chromosomes) in women of advanced reproductive age, there is strong scientific evidence that the addition of this procedure doesn’t improve live birth rates.”

The Center for Reproductive Medicine is a long-time leader in fertility services in the state of Michigan. In addition to PGD and a full range of fertility services, it has also offered fertility preservation counseling and services to cancer patients since 2003.

Currently available fertility preservation options include freezing eggs, sperm, ovarian or testicular tissue, and embryos as well as hormonal treatment to potentially minimize ovarian damage from chemotherapy.

FOR MORE INFORMATION
Visit pre-implantation genetic diagnosis or fertility preservation services, U-M Center for Reproductive Medicine at www.uofmhealth.org/fertility
Liver cancer is the third most common cause of cancer-related death worldwide. Because about 90 percent of cases occur in patients with cirrhosis of the liver, mostly due to viral hepatitis, surveillance can lead to early detection. Surveillance using biomarkers — substances whose detection indicates a particular disease state — have the potential to aid this effort. But current widely used biomarkers are not ideal for early detection of liver cancer, according to a University of Michigan researcher.

Anna S. Lok, M.D., F.R.C.P., professor of Internal Medicine, found some unexpected results in a study of biomarkers that are used to complement ultrasound in the early detection of hepatocellular carcinoma. Her study was published earlier this year in *Gastroenterology*. Lok and her colleagues analyzed the use of des-gamma-carboxy prothrombin (DCP) and the most widely used biomarker, alpha fetoprotein (AFP).

“Most surprising was the finding that patient demographics influenced both des-gamma-carboxy prothrombin and alpha fetoprotein values, but in opposite directions,” says Lok. “This observation merits further investigation, as it might impact the accuracy of these biomarkers in the detection of liver cancer in men versus women and in patients of various races and ethnicity.”

The survival of patients with most malignancies has improved over the last decade, but five-year survival of patients with hepatocellular carcinoma (HCC) has remained less than 10 percent. The poor outcome of patients with HCC is related to late detection, with more than two-thirds of patients diagnosed at advanced stages of disease. A major problem with HCC surveillance is the lack of reliable tests. While AFP is the most widely used biomarker for HCC surveillance, experience with DCP is limited.

“Until better serum markers are available, ultrasonography remains the preferred tool for HCC surveillance. However, reliable biomarkers to complement ultrasound may improve the detection of early HCC in clinical practice where interpretation of ultrasound is variable,” says Lok. In this study, using serum samples from the 12 months prior to diagnosis, the diagnosis of early HCC was triggered by surveillance ultrasound in only 58 percent of patients — indicating that it is also not ideal.

“We need more studies to determine if combining both markers will improve the detection of early HCC.”

DCP was not superior to AFP in the early detection of HCC in patients with advanced hepatitis C. Neither AFP alone, DCP alone, nor the combination of AFP and DCP was sufficiently accurate to be used for HCC surveillance. The combination of both markers enhanced the sensitivity, indicating that these two markers are complementary, and is an area of further research.

“We need more studies to determine if combining both markers will improve the detection of early HCC,” says Lok. “That can help us establish the optimal cutoff values for patient recall and further testing. We know that early detection can be crucial to patient survival.”

In the meantime, U-M researchers continue their search for novel biomarkers. Recent work by David Lubman, Ph.D., published in the *Journal of Proteome Research*, identifies novel glycoproteins that can distinguish early stage HCC from cancer-free individuals. This work was validated in a cohort of patients from a large National Cancer Institute study lead by Jorge A. Marrero, M.D.

Even though further studies are needed, it is exciting that new tests may be available in the future for the early detection of HCC.

**FOR MORE INFORMATION**

Visit the University of Michigan liver cancer program at [www.mcancer.org/livercancer](http://www.mcancer.org/livercancer)
As professor of Radiology, associate chair for clinical affairs in the U-M Department of Radiology and the director of U-M’s Cardiothoracic Radiology Division, Ella Kazerooni, M.D., F.A.C.R., knows first-hand the importance of minimization when it comes to CT scans. The U-M Health System conducted more than 112,000 CT scans last year.

In 2008, Kazerooni and her colleagues found that a surprising percentage of radiologists were unaware of methods to adjust mA and kvp during CT procedures on their own machines – “a tool that is available on all CT scanners, no matter what generation machine we’re talking about,” she explains.

“Radiologists play a key role in radiation safety in their institutions, and are responsible for the radiation exposure delivered to their patients by the protocols they define,” she says.

“Following the ALARA principle, as low as reasonably achievable, while maintaining diagnostic quality, is the challenge to all radiologists. Education, such as enrolling in Maintenance of Certification through the American Board of Radiology, to make sure one’s knowledge is up to date, is one way to make sure radiologists have the knowledge they need to meet this challenge.”

Kazerooni is a fellow of both the American College of Chest Physicians and the American College of Radiology. A 1988 graduate of the U-M Medical School, she completed her residency in radiology at U-M in 1992, followed by fellowship training in thoracic radiology at Massachusetts General Hospital.

Radiation exposure is something patients are thinking about more and more.

However, in the CT Awareness of Radiation Exposure Study (CARES), a web-based survey of 150 radiologists across the country, Ella Kazerooni, M.D., M.S., and her colleagues from the U-M Health System found that radiologists themselves ranked minimizing exposure below such attributes as top image quality and avoidance of repeat scans.

In addition, they found that:

- 11 percent of respondents didn’t know that reducing a setting called mA would reduce radiation exposure, and 39 percent didn’t know they could reduce the mA on their scanner.
- Only 49 percent knew they had access to a mechanism to reduce kvp, another standard feature.
- 55 percent overall, and 77 percent of academic radiologists, reported they actually used dose reduction strategies in the past six months.
- 25 percent applied a triggering mechanism for cardiac CT.
- 7 percent or less had taken advantage of newer technology such as 3D dose modulation, noise indexing or bowtie filters.
- Radiologists were more likely to reduce dose for teenagers, young adults, children and women of child-bearing age.

The U-M Health System has taken many steps to help minimize radiation exposure, including those below, and offers this summary to help others adopt the same practices for their own patients. More details on how these reductions in dosage were achieved are available on request from Kazerooni via M-LINE.

- The CT scanner at C.S. Mott Children’s Hospital was replaced with a new GE HD 750 that employs a new method of image reconstruction, allowing CT radiation doses to be decreased by as much as 50 percent without a substantial loss in image quality. This is a great advance for lighter-weight and pediatric patients. The scanner joins three GE HD 750 CT scanners at University Hospital, which are primarily for adult patients.
U-M DEPRESSION CENTER LAUNCHES NEW ONLINE TOOLKIT FOR PATIENTS

The U-M Depression Center recently launched an online toolkit (www.depressiontoolkit.org) for patients and families experiencing clinical depression, bipolar disorder and related illnesses.

The site provides educational information about diagnosis, evidenced-based treatment options, useful self-management strategies and additional coping resources for patients and families. It includes helpful tools, assessments and checklists that patients can use on their own or in partnership with clinicians. The toolkit was made possible by generous gifts from the Ravitz Foundation and the Depression Center Community Volunteers to help increase mental health awareness.

In all, any effort to reduce radiation exposure also has the potential to reduce patient concern. “It’s great to be able to put patients’ minds at ease with confidence,” Kazerooni says.

FOR MORE INFORMATION
Visit the University of Michigan Department of Radiology at http://www.med.umich.edu/rad/

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“Through a Blue Cross Blue Shield of Michigan quality improvement study of 40 hospitals and imaging practices called the Advanced Cardiovascular Imaging Consortium (ACIC), U-M’s Cardiac CT team reduced average CT radiation exposure by 43 percent – from 21 milliSievert to 9 mSv.

“U-M carefully selects and trains CT technologists for whom attention to detail is of the utmost importance. “There are numerous technical parameters to choose from now when performing these examinations. You want technologists who are willing to go that extra mile to get it right,” says Kazerooni.

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U-M OFFERS NOVEL PROTOCOL FOR INOPERABLE TUMORS

Tumors that occur in the portion of the bile duct that falls outside the liver are extremely difficult to remove surgically. Even when surgery is an option, the cancer frequently recurs. Surgeons at the U-M Comprehensive Cancer Center have started using a new option to treat bile duct cancer (also called cholangiocarcinoma): liver transplantation.

Patients with bile duct cancer that is not surgically treatable and has not spread to other organs are first treated with combined chemotherapy and radiation. After additional studies to prove the cancer has not spread, patients are listed for liver transplantation.

Because these patients don’t have chronic liver disease like a typical transplant candidate, the United Network for Organ Sharing approved an automatic 22 points on the liver allocation system, giving patients a fair spot on the list and typically allowing liver transplantation to take place within three to six months. During surgery, doctors remove all of the liver and bile duct and perform the liver transplant.

“This is a tumor we have always struggled with,” says Christopher Sonnenday, M.D., M.H.S., assistant professor of surgery at U-M. Sonnenday, a transplant surgeon, is part of U-M’s Multidisciplinary Liver Tumor Clinic. The team includes gastroenterologists, surgeons (including transplant surgeons), radiation oncologists, medical oncologists, radiologists and pathologists who focus exclusively on liver and bile duct tumors.

Liver transplantation is an accepted form of treatment for the other major type of liver cancer, hepatocellular carcinoma. But U-M is one of a small number of centers around the country to offer the transplant protocol for cholangiocarcinoma.

“It is a labor-intense treatment that involves a multidisciplinary approach,” says Sonnenday, who performed the first transplant for cholangiocarcinoma in April.

Robert “Buzz” Gehle was diagnosed with cholangiocarcinoma in October 2009 and it soon became clear that traditional surgery would not be an option.

“I elected to do this because my alternative was to go home and die,” says Gehle, who is proud to call himself the “poster boy” for this protocol.

The surgery went well, and afterward Gehle recovered quickly, since he was not in extreme liver failure like most transplant patients. He had some setbacks along the way but says he’s getting stronger every day.

Cholangiocarcinoma patients who undergo non-transplant surgery have a 30 percent to 40 percent five-year survival rate. For patients who cannot have surgery, survival is only 5 percent to 10 percent.

Early data for the transplant protocol suggests five-year survival of 75 percent to 85 percent, which is similar to overall liver transplant survival rates.

“Survival is markedly better, and the risk of cancer returning is smaller, maybe 20 percent. This is far better than anything we do for bile duct cancer in general.”

FOR MORE INFORMATION
Visit the University of Michigan liver cancer program at www.mcancer.org/livercancer
For Referring Physician Consult Guidelines, visit www.med.umich.edu/consult/livertransplant

FIND MORE ON THE WEB
Preview a video of Dr. Sonnenday and a liver transplant, visit http://www.michigantransplant.org/liver/cavoplasty.htm
FINDING CLINICAL STUDIES AT U-M JUST GOT EASIER

As part of a larger effort to educate the public about the importance of clinical research and improve participation in studies, U-M has renamed its “Engage” website. The new site, www.UMClinicalStudies.org, includes a searchable database of more than 400 open studies at U-M, including eligibility, contact information and other important details. The new site is easier to navigate for both researchers and potential volunteers, based on extensive feedback from community members, and U-M physicians and staff.

The Registry, a secure database that matches interested volunteers with appropriate studies, now gives volunteers the option of being contacted when there is a potential match with a study that meets their criteria.

“As physicians we know that, unfortunately, a significant percentage of research studies end uncompleted largely because there were not enough patients enrolled,” says Kenneth Pienta, M.D., director of the Michigan Institute for Clinical and Health Research (MICH-R). “We hope our colleagues in the community will use this tool to help connect their patients to studies that may be of benefit to them — and future generations.”

PEDIATRIC CME WEBINARS

Join us for complimentary CME webcasts on new approaches for diagnosing and treating common pediatric conditions. Each 15-minute presentation is followed by interactive Q&A.

FOR MORE INFORMATION

Visit www.mottchildren.org/medbreaks.

For additional CME opportunities, visit www.cme.med.umich.edu.
In the SVR trial, Ohye and his colleagues randomly assigned participants shortly after birth to receive one of two types of shunts for their initial surgery, as part of the Norwood procedure. About half of the newborn participants received an MBT shunt, which places the shunt from a branch off of the aorta. The other participants received the newer type of RV-PA shunt, which is placed between the right ventricle and the pulmonary arteries.

The researchers followed study patients for at least 14 months, evaluating the number of deaths and heart transplantations in each group at one year as well as the number of complications linked to each type of shunt.

“We found that the RV-PA shunt did better over the course of the first year,” Ohye says. “We also found, though, that they had tended to have a few more complications. The two shunts showed similar results after about two years. I think the jury’s still out over the long run which is going to be better.”

Researchers reported that after 12 months, 74 percent of infants with the RV-PA shunt survived and didn’t need a heart transplant, compared to 64 percent of infants with the MBT shunt. The newborns with the RV-PA shunt, however, had more complications requiring additional interventions, such as insertions of stents or balloons to keep shunts open.

“We are continuing to follow these children, and this longer follow-up will be important to determine which shunt is superior in the long run,” Ohye says. Researchers are conducting a follow-up study to analyze the effects of the procedures in children 2 to 6 years of age.

“We are grateful for the help of our referring physicians in informing the patients of the SVR study, thus greatly facilitating the recruitment of patients,” Ohye says. “We hope to continue to engage our outside referring doctors to be active participants in research. We see us all as one team.”

U-M achieves amongst the highest survivals for HLHS and related single ventricle abnormalities of all the 15 centers in the SVR trial.

Prior to the early 1980s, there was no operation for HLHS; all infants born with the defect died as newborns. Since then, survivals have improved dramatically. During the 1990s, hospital survivals for the first operation were only about 40 percent. Now, at experienced centers, they’re above 90 percent.

“It is important to test anything we do to manage our patients in a rigorous scientific way, and it’s the first time that we’ve ever gotten together many centers — 15 in this case — and agreed that this was really important to do,” Ohye adds. “We showed that we can do it and that we believe that it’s important to do for our kids.”

FIND MORE ON THE WEB

Visit U-M C.S. Mott Children’s Hospital at www.mottchildren.org

Visit Congenital Heart Center at www.umcongenitalheart.org