Japan Academy Prize to:

Koichi Tanaka President, Kobe International Frontier Medical Center Professor Emeritus, Kyoto University

for "Establishment and Development of Living Donor Liver Transplantation"



Outline of the work:

Based on animal studies, Dr. Koichi Tanaka conceived the idea of living donor liver transplantation (LDLT) using a part of the liver from a healthy donor. In 1990, he first performed LDLT with great success, and by the time of his retirement from Kyoto University, he had performed 1,054 cases of LDLT. Dr. Tanaka's work can be summarized into three categories:

- (I) development of surgical techniques and perioperative management;
- (II) major clinical research and development for the improvement of clinical outcomes as represented by (1) clinical trial of a new immunosuppressant, tacrolimus; (2) withdrawal of immunosuppressant and clinical immunotolerance; (3) HBV transmission from HBc antibody-positive donors; (4) ABO-incompatible liver transplantation; (5) domino transplantation in familial amyloid polyneuropathy; and (6) new indication criteria for liver cancer; and
- (III) promotion and education of and international contribution to LDLT.

His clinical experiences in LDLT in both Japan and overseas have accumulated over 2,000 cases. He has improved transplantation outcomes and established donor's safety.

(I) Development of surgical techniques

In pediatric liver transplantation, hepatic artery thrombosis frequently develops after LDLT, thereby leading to graft death. Dr. Tanaka's team introduced the world's first microsurgery for reconstruction of the hepatic artery, reducing the incidence of this problem. This method has become the global standard technique. When the graft size is too large for neonatal and infantile cases, recipients do not have enough blood flow into the liver; therefore, graft failure develops as a result of graft ischemia. In addition, an artificial patch is sometimes required for abdominal wall closure to prevent compression of the large-for-size graft. To overcome these problems, Dr. Tanaka developed the reduced sized graft (mono segment graft) on the basis of clinical data, showing that 4% GRWR (ratio of graft volume to recipient weight) is the maximum allowable graft size.

On the other hand, small-for-size grafts are a major concern in adult patients because they frequently cause small-for-size graft syndrome, potentially leading to graft dysfunction and patient death. However, there had been no scientific data on the graft volume required for patient survival. By analyzing the correlation between graft GRWR and graft survival rates, obtained from the results of left lobe liver graft transplantation, Dr. Tanaka concluded that grafts with GRWR below 0.8% showed significantly reduced the survival rate. Based on the experience at Kyoto University, the use of grafts with GRWR over 0.8% has now become the global standard criteria. He then introduced the right liver graft to expand adult LDLT in this study. Then, he had developed an alternative method using a left lobe graft (small-for-size graft) based on a

portal caval shunt to decrease portal hypertension. This technique could decrease GRWR to 0.6% and expand the indication of left lobe grafts as well as improve donor's safety. In addition to his contribution in LDLT, this study has been applied to divide a brain death donor liver to be used for two recipients.

(II) Clinical research and development

- (1) Dr. Tanaka was involved in the clinical trial and approval of tacrolimus, a new immunosuppressant developed in Japan. His work on pharmacokinetic and pharmacodynamic analysis of tacrolimus led to the determination of appropriate doses for both pediatric and adult recipients.
- (2) Dr. Tanaka has studied the possibility of clinical immunotolerance induction. The result was astounding: 30% of patients discontinued their medication, 60% continued their regimen at reduced doses, and only 10% had signs of rejection during reduced dosing and resumed medication during the study period. These findings demonstrated the possibility of clinical implementation of immunotolerance and opened the new path for basic research on its mechanism(s).
- (3) In hepatology, in the HB antigen-negative, HBs antibody-positive, and HBc antibody-positive state is defined as seroconversion, and it had been considered that HBV does not exist in the body. However, Dr. Tanaka revealed that many recipients became HB antigen-positive after transplantation from HBc antibody-positive donors. He demonstrated that HBV DNA present in the donor's liver tissue was brought into the recipient's circulation. He further showed that recipients with an HBc antibody-positive graft could be prevented from becoming HBV carriers using prophylactic antiviral drugs and immunoglobulin.
- (4) Dr. Tanaka studied ABO-incompatible liver transplantation performed between 1990 and 2000. He revealed that compared with compatible LDLT, two factors affected patient survival: age and high titers of anti-A or anti-B. The cause of death was intrahepatic biliary stricture or hepatic necrosis related to impaired microcirculation in the liver. He succeeded in improving patient survival using plasmapheresis and continuous infusion of prostaglandin E1 via the hepatic artery. However, patient survival with this method was still inferior compared with compatible transplantation. Subsequently, a new immunosuppressant, rituximab, was introduced and led to similar patient survival. Therefore, ABO incompatible liver transplantation became no longer contraindicated.
- (5) Dr. Tanaka performed the first domino LDLT in the world. The liver was obtained from the first recipient with familial amyloid neuropathy and transplanted to the secondary recipient. This method, although requiring long-term follow-up, has paved the way for new donor pool expansion.
- (6) The Milan criteria (one tumor 5cm or less in diameter and no more than three tumors, each 3cm or less in diameter) are used as global indication criteria of deceased donor liver transplantation for liver cancer patients. Dr. Tanaka studied the possibility of expanding the criteria for advanced liver cancer patients. He classified the recipients into two groups, namely Milan criteria-met and -unmet groups, and statistically compared the long-term survival rate between them. He concluded that recipients with 10 tumor nodules or less and a maximum diameter of less than 5cm in the Milan criteria-unmet group showed no difference in the 5-year survival rate compared with those in the Milan criteria-met group.

(III) Promotion and education of and international contribution to LDLT

Dr. Tanaka assisted introduction of LDLT to 36 hospitals in Japan. This accounts for half of the hospitals where LDLT were performed. At Kyoto University Hospital, he trained not only many Japanese surgeons but also foreign surgeons from Europe, Asia, and America. He also traveled overseas in a cooperative effort to implement LDLT in nine different countries. Since 1999, he had served as the council member of the International Liver Transplantation Society for 6 years and greatly contributed to the development and growth of this particular field.

Selected Publications

- Tanaka, K., Tokunaga, Y., Zaima, M., Sakai, Y., Yamamoto, Y., Ueda, J., Takada, Y., Yamaguchi, M., Kitayama, T., Kitakada, Y., Yamaoka, Y. and Ozawa, K. Graft transection and warm perfusion in situ in canine partial orthotopic liver transplantation. Transplantation Int. 213-218, 1988.
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