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Solid organ transplantation and association with neoplasms

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ABSTRACT

Organ transplantation is now considered the best surgical option for many disorders associated with organ failure. In contrast, the increased risk of cancer in solid-organ transplant recipients is remarkable when compared to the general population. In order to improve survival rates and quality of life following transplantation, the variables that contribute to the development of an increased risk of cancer should be investigated, and potential preventative treatments should be developed. In this review, we discussed solid organ transplantation and its relationship to neoplasm.

Keywords: Cancer, domino, graft, solid organ, transplantation.

Organ transplantation is now considered the best surgical option for many disorders associated with organ failure. In contrast, the increased risk of cancer in solid-organ transplant recipients is remarkable when compared to the general population. In order to improve survival rates and quality of life following transplantation, the variables that contribute to the development of an increased risk of cancer should be investigated, and potential preventative treatments should be developed. In this review, we discussed solid organ transplantation and its relationship to neoplasm.

INTRODUCTION

Solid organ transplantation (SOT) is the last choice for many patients with end-stage organ failure.[1] The twentieth century has been noted as a milestone in the transplantation techniques of internal organs, with the development of vascular anastomosis techniques.[2]

The first successful organ transplantation in humans, allowing the recipient to live another eight years, was a kidney transplant from a twin brother carried out by Joseph Murray in 1954.[3] Various methods in SOT were first tried out on animals as parts of experimental studies, usually around the first half of the 20th century surgery, but they have now mostly become approved approaches in treatment for human cases in the 21th century.[4]

So much so that, according to the current volume of SOT performed in the United States in 2017, nearly 20,000 kidney and nearly 7,000 liver transplants have been performed.[5]

In Türkiye, the main framework of transplantation with healthcare centers built for the procedures was laid in the 1990s, and today, the management of all these centers and the authority to sign off operations related to organ transplantation belong to the organ transplant coordination center, which is affiliated with the Ministry of Health.[4]

LIVING AND CADAVERIC DONOR TRANSPLANTATION

There are two available sources of organ donors: living and cadaveric [donation after brain death (DBD)]. Cadaveric organ transplantation of organs such as the heart, lung, kidney, liver, pancreas or of tissues such as skin, cornea, tendons, and bones from individuals with brain and/or heart death (with different laws enforced in different countries) is an established method

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of transplantation utilized worldwide.[6] It was first legalized in Türkiye with the acceptance of a defined concept of "brain death" in 1968, which was significant progress in the field of transplantation. Brain death is considered to be the irreversible interruption of brain function and indicates that the patient has died clinically and legally.[7] Donation after brain death indicates a lower risk of ischemia compared to donation after circulatory deaths,[8] since organs can still be physiologically well-perfused at the time of the operation.[5]

Despite the superiority of donations after brain deaths to donations after circulatory deaths, there is an obviously greater success achieved in organ transplantations from living donors among all. In a study published in 2000, the five-year survival rates of patients receiving kidneys from living and cadaveric donors were found to be 94% and 76%, respectively which is indicative of this correlation.[9]

SOME DEFINITIONS OF ORGAN TRANSPLANTATION

Graft types

Basically, four different graft types can be defined when it comes to transplantations: Xenografts, allografts, autografts, and isografts.

Autografts are transplants from the patient, whereas xenografts are defined as the transplantation of tissues and/or organs between different species, allografts are established as the transplantation of tissues and/or organs between two individuals of the same species, and isografts are the type of transplants that are exchanged between the members of identical genetic frameworks who are also of the same species; examples of isografts include transplantations between identical twins.[10] The stated graft types are depicted in Figure 1.

Human leukocyte antigen

The region of genes encoding "tissue antigens" necessary for the immune system to recognize self and non-self material is known as the major histocompatibility complex (MHC). In humans, MHC antigens are referred to as human leukocyte antigen (HLA) since they were first defined in leukocytes.[11] The HLA-A, HLA-B, and HLA-DR serotyping is first performed to evaluate the compatibility of donor and recipient before any transplantation. Although new and effective immunosuppressive drugs are put into practice, better results are still obtained with the tissues of the best compatibility. If the recipient's serum has antibodies against HLA antigens from previous blood transfusions, pregnancies, or other transplants, and these anti-HLA antibodies are specific to the donor's antigens, they are called donor-specific antibodies. The presence of anti-HLA antibodies against donor HLA antigens in the recipient before SOT can be demonstrated by *in vitro* screening tests.[12] Anti-HLA antibodies in circulation can cause hyperacute and acute types of rejection, and consequently, yield unsuccessful results in the process.[13]

Although the first choice in donor selection would be a completely HLA-compatible and genetically unrelated individual, transplantations from donors with 'limited' HLA compatibilities are also usually associated with acceptable results in many cases.[14]

Allograft rejection

There are three major types of allograft rejection: Hyperacute, acute, and chronic rejection. If graft rejection occurs within minutes to hours (hyperacute rejection), previously formed anti-donor antibodies can be blamed. Reactivation of sensitized T-cells can be blamed if it happens within days (accelerated rejection). While primary T-cell activation is thought to be the cause of rejection that occurs days to weeks later (acute rejection), the exact cause of rejection that develops over months to years is unknown (chronic rejection).[15]

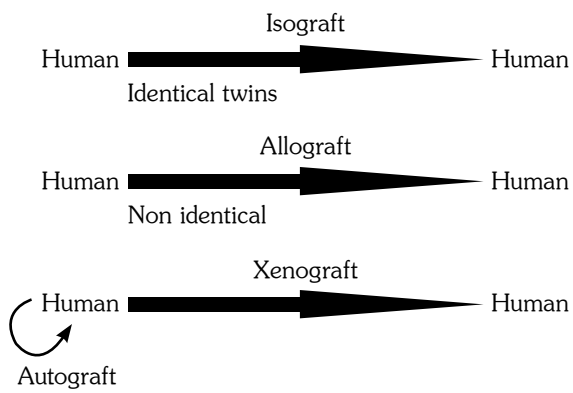

Figure 1. Graft types.

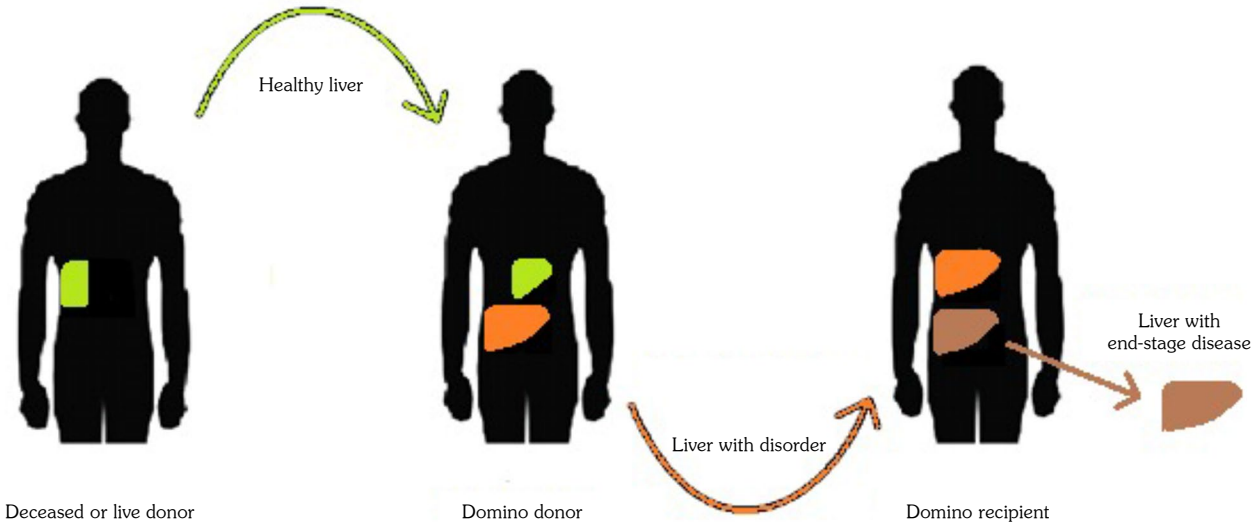

Figure 2. Domino liver transplantation.

Graft-versus-host disease

Graft-versus-host disease is a complex clinical syndrome with organ dysfunction resulting from a severe immune-based reaction mediated by healthy T-lymphocytes of the donor that were given to the patient.[16] As a result of this reaction, systemic lupus erythematosus and pathological symptoms similar to those of a number of conditions, such as vascular diseases, lymphoproliferative disorders, and aplastic anemia, may develop.[17]

Domino transplantation

The basis of this method is to carry out the transplantation of multiple patients at the same time by admitting multiple attendees to the operation:

Figure 2 shows liver transplantation being carried out from first a healthy donor, to a patient with metabolic disease and from the patient with the metabolic disease to a patient with end-stage liver disease.[18]

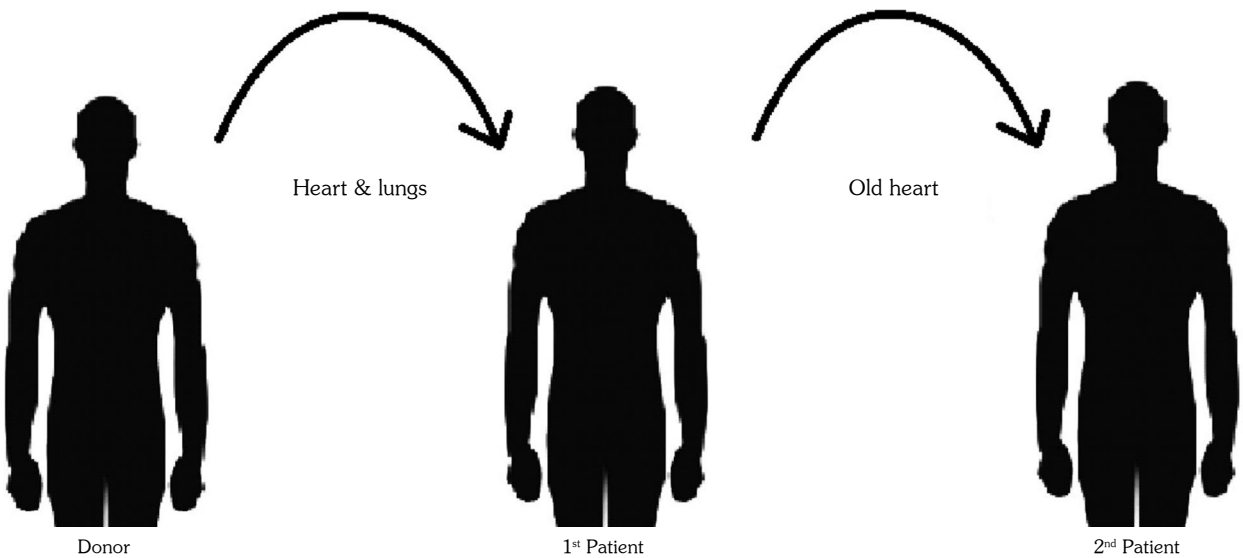

Figure 3. Domino heart-lung transplantation.

Another demonstration of this method is given in Figure 3, where a heart taken from an *en-bloc* heart and lung receiver is used for a second recipient. This offers patients with end-stage heart failure a significant advantage.[19,20]

Another organ that will serve as an example of domino transplantation is the kidney. Problems such as ABO blood group incompatibility and HLA incompatibility are common in kidney transplants, and kidney exchange transplantation methods such as the domino chain can help to eliminate these issues.[21]

SOLID ORGAN TRANSPLANTATION

Liver transplantation

Liver transplantation is the transplantation of healthy liver tissue from a living or cadaver donor to patients who have lost their liver function due to various diseases. Welch has scientifically defined ectopic liver transplantation in 1955. Francis Moore described the technique of orthotopic liver transplantation on dogs in 1958. Starzl et al.[22] performed the first liver transplantation in 1963. Of the first five transplanted cases, survival was set at a maximum of only 23 days. Ischemia-reperfusion injury and tissue rejection resulted in liver failure or sepsis. In 1967, Starzl, advised by Calne, began using anti-thymocyte globulin and more successful results were achieved.

Liver transplantation may be the only treatment option in patients with cirrhosis, hepatocellular cancer, and acute liver failure within the Milan criteria.[23] Thanks to advances in surgical techniques, organ transfer methodologies, and immunosuppressive therapy, the survival rate after transplantation has increased from around 30% in the second half of the twentieth century, to 80% today.[22]

Lung transplantation

Lung transplantation is a treatment option for some advanced lung diseases. The success of the operation depends on the selection of a good donor. Dr. Joel Cooper and his team performed the first isolated lung transplantation in 1983.[24] The International Society of Heart and Lung Transplantation (ISHLT) announced that by July 2013, 47.647 lung transplants and 3.772 combined heart-lung transplants had been reported worldwide.[25]

Heart transplantation

Dr. Christiaan Barnard performed the first heart transplantation in South Africa in 1967. The first patient only survived for 18 days.[26] Heart transplantation is the most important treatment for end-stage heart failure. In the following years, heart transplantation, which has later become widespread throughout the world, was performed 5074 times in 2015.[27] The survival rate is high in the absence of concomitant diseases such as diabetes and hypertension.[26]

Kidney transplantation

The first successful kidney transplantation was performed between twin siblings in 1954.[28] Kidney transplantation is the most desired and cost-effective modality of renal replacement therapy for patients with irreversible chronic kidney failure (end-stage renal disease, Stage 5 chronic kidney disease). Despite emerging evidence that patients who receive a transplant early in the course of their disease have the best outcomes, renal replacement therapy is used as the first line of treatment for very few patients with end-stage renal disease.[29]

CANCER DEVELOPMENT AFTER SOLID ORGAN TRANSPLANTATION

A promising increase in survival rates after transplantation has been observed with the developments in organ transplantation methodologies in the past few decades but an increased risk of developing cancer, still awaits transplant recipients, despite this prolonged survival. Solid organ transplant patient has a 5-fold increased risk of developing cancer compared to the general population.[30]

The increase in lymphoma and skin malignancy prevalence was noted in the earlier days of organ transplantations by Starzl and Penn.[31,32] There is a high risk of developing various types of solid organ tumors, non-Hodgkin's lymphomas, and vulvar, vaginal, anal, oral, and renal cancers in organ transplant recipients; but the risk of developing esophageal, gastric, colon, bladder, lung and thyroid gland cancers are in comparison, stands smaller.[33,34]

ETIOLOGY

The etiology of increased cancer risk after SOT is multifactorial. Decreased immune function after suppressors, activation of oncogenic viruses, chronic stimulation of the immune system, the carcinogenic effect of immunosuppressants, pre-existing cancer risk factors, factors associated with end-stage organ failure, and dialysis-induced factors for kidney recipients are some of the most prominent factors associated with increased cancer risk after transplantation.[32]

Immunosuppressive drugs and carcinogenesis

Some immunosuppressive drugs such as calcineurin inhibitors and azathioprine have been demonstrated to have mechanisms that increase carcinogenesis independent of their immunosuppressive properties.[35] In contrast, more novel agents such as mycophenolate mofetil and mammalian target of rapamycin may have antitumor properties.[36]

Immunosuppressive and oncogenic organisms

Immunosuppression may cause malignancies by increasing oncogenic viral or bacterial factors. Immunosuppressive drugs inhibit anti-viral T-cell responses, too which can lead to opportunistic and persistent infections as side effects in patients.[37] Oncogenic viruses can cause many post-transplant cancers. Human papilloma virus can cause cancers in the cervix, vulva, vagina, penis, anus, and oral cavity.[38] The Epstein-Barr virus can cause Hodgkin's lymphoma and non-Hodgkin's lymphoma.[39] Other infection-related cancers are Kaposi's sarcoma (human herpesvirus 8),[40] hepatocellular carcinoma (Hepatitis C and hepatitis B virus),[41] and gastric cancer (*Helicobacter pylori*).[42]

In conclusion, considering all the data, organ transplantation is sometimes the gold standard for many diseases. However, there is a significantly increased risk of neoplasms brought about by this treatment as patients move on with their lives. The reasons that cause this risk are the suppression of immune functions and the ability of some oncogenic organisms to cause opportunistic infections. To avoid this, immunosuppressive drugs without oncogenic properties and that are more specific for the tissue in which the organ/tissue rejection might be taking place can be developed. Also, the risk of cancer development in patients after transplantation can be reduced by developing some agents that will eliminate the mechanisms that cause cancer formation. Since organ transplantation cannot be abandoned as a treatment method, the agents associated with the procedure that can induce increased cancer risks in the patients should be tackled instead.

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