Review Article/บทฟื้นฟูวิชาการ

Radiotherapy as an Immunosuppressive Agent for Allotransplantation: Literature Review and Clinical Experience - Past, Present, and Future

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Abstract

Radiotherapy could function as immunosuppressive agent for allotransplantation due to the ability of ionizing radiation to cause cell death, the technique could be applied to irradiate total body, bone marrow and/or lymphoid tissues of the recipient who receive an allograft as an immunosuppressant to improve the success rate of transplantation. From the past to the present, the radiation techniques in allotransplantation process have been continuously studied and developed across preclinical and clinical settings, in order to achieve better therapeutic outcomes. Currently, total lymphoid irradiation by fractionation and total body irradiation with low dose are most frequently used radiotherapy techniques in allotransplantation process. The advanced radiotherapy techniques such as total marrow and/or lymphoid irradiation by volumetric arc therapy (VMAT) or helical tomotherapy (HT) have gained interests. These advanced techniques could increase therapeutic ratio by improving conformity high radiation dose to the targets and reducing dose to the surrounding normal tissues. This review aims to provide the insights of radiotherapy applications as an immunosuppressive agent for allotransplantation and to share clinical experiences and outcomes.

Keywords: Allotransplantation, Total lymphoid irradiation, Total body irradiation, Total marrow irradiation, Total marrow and lymphoid irradiation

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Introduction

Allotransplantation is the transplantation of cells, tissues, or organs from a genetically non-identical member of the same species. This medical procedure is now widely used in solid organs and hematopoietic stem cell transplantation. However, one of the major limitations of allotransplantation is the immune response of the recipient to the antigen of allograft that could lead to rejection of transplanted cells. Currently, there are two methods that could be used to overcome this limitation-human lymphocyte antigen and immunosuppressive agent. Human lymphocyte antigen (HLA) matching method is based on the selection of genes that related to the immune system or major histocompatibility complex (MHC) in order to determine the compatibility of donors for organ transplant so that the rejection would be minimized. Meanwhile, the immunosuppressive agent method is based on suppression of recipient's immune system, preventing the rejection of transplanted organs and tissues.[1, 2] Suppression of immune system could be achieved via the use of medication such as glucocorticoids, chemotherapeutic agents, or radiotherapy.

This review aims to provide the insights of radiotherapy applications as an immunosuppressive agent for allotransplantation and to share clinical experiences and outcomes. The basic knowledge of immunity and radiotherapy, the advance in radiotherapy techniques for allotransplantation are discussed in detail.

Immune Response Related to Allotransplantation

The immune response in the human body is classified into 2 categories, innate and adaptive immunity. The innate immune response is the initial, rapid, and non-specific immune response against invading organisms or foreign bodies. The cellular barriers such as neutrophils, eosinophils, macrophages, and natural killer T (NKT) cells take responsibility to this immunity. On the other hand, the adaptive immunity is rather complicate, delay, and specific to each antigen. It is initiated by antigen recognition, followed by immune cells specifically designed to attack that antigen in the future. The adaptive immune responses are divided into 2 types, humoral immunity and cell-mediated immunity, which relies on the function of B-lymphocytes and T-lymphocytes. Humoral immunity mediates by antibodies produced by B-lymphocytes while the cell-mediated immunity mediated by T-lymphocytes. For allotransplantation process, T cells play a major role in the rejection of the transplanted cells by releasing cytokines and causing necrosis of transplanted tissues.[2, 3]

Why Radiotherapy Can Be Used in Allotransplantation Process?

Ionizing radiation can cause DNA damage and cell death, especially for rapidly dividing cells such as cells in bone marrow and lymphoid tissues. Ionizing radiation not only leads to chromosomal aberration, but also is responsible for both apoptotic death (a rapid cell death due to cell membrane blebbing, chromatin condensation, and nuclear fragmentation) and mitotic death (improper completion of cell division due to unrepaired or misrepaired DNA damage and cause cell death).[4] Previous report described the significant decrease in numbers of lymphocyte cells in the hemogram of a patient who received accidental radiation exposure.[5] In addition, the Hodgkin's disease patients who received total lymphoid irradiation (TLI) also showed reduce in numbers and functions of B and T lymphocytes, leading to low immune response.[6, 7] As the immunity is produced from cell in bone marrow and lymphoid tissues, applying radiation to bone marrow and lymphoid tissues in the allotransplantation process could cause immunosuppression, thereby decreasing the chance of rejection phenomenon and improving of the success rate of transplantation.[8]

History of Radiotherapy for Human Allotransplantation

Human Solid Organ Allotransplantation

Ionizing radiation has been used as an immunosuppression since early 1950. Irradiation to the graft bed and adjacent lymphatic tissue could affect the host rejection by interfering with the cellular transportation system that delivers antigen from graft to the host and damaging host cells invasion. The clinical trials suggested several benefits of local allograft irradiation as a second-line therapy in selected patients whose treatment failed from conventional antirejection treatment for kidney transplantation.[9-11] In the early 1960, whole body irradiation prior to renal transplantation aiming for antibody suppression was investigated. However, severe complications limited the use of this technique.[11, 12] The extracorporeal blood irradiations, which refers to irradiation of blood components while circulated outside the body and subsequently pumped back to the body, and the intracorporeal blood irradiation, which placing beta-emitting isotopes into the right atrium, arterial prosthesis or abdominal aorta, were also studied in renal transplantation. These techniques were considerably difficult and had unreliable immunosuppressive effect, resulting in unfrequently uses.[11, 12] In 1980, the TLI technique was introduced to facilitate in human renal, cardiac, and bone marrow transplantations as it exhibited successful immune suppression in Hodgkin's lymphoma patients.[11, 13] Nowadays, TLI is still in use.

Human Hematopoietic Stem Cell Allotransplantation

There were previous reports in 1950s that the leukemic patients who had low immunity from previously exposed accidental radiation were received bone marrow transplantation for treatment. Even though the engrafts were successful, these patients still died due to relapsed diseases or severe treatment-related complications.[14, 15] The advancement in the processes of hematopoietic stem cell transplantation and HLA typing have been made since 1970. Total body irradiation (TBI) based transplant conditioning regimens were applied in many clinical trials of leukemia patients. Initially, the TBI regimens were started from single large radiation dose of 9 - 10 Gray (Gy) and subsequently reduced to lower radiation dose fractionation in order to avoid severe radiation complications, especially fatal radiation pneumonitis.[16-21] The relapsed free survival outcomes were acceptable. Numbers of clinical studies reported significant longer survival and lower risk of disease relapsed in the leukemia pediatric patient whom treated with TBI-based transplant conditioning regimens over chemotherapy only regimens.[22-26] The data are demonstrated in Table 1.

Table 1 Results of TBI-Based Conditioning Regimens vs Chemotherapy - Only Regimens for Pediatric Leukemia

Author, Year	Conditioning Regimens	Results
Ringden et al, 1994[22]	Cy/Bu (N = 88) vs Cy/TBI 10-12 Gy/1-7 Fx (N = 79)	3 years OS 62% vs 76%
Ringden et al, 1996[23]	Bu/Cy (N = 237) vs Cy/TBI, radiation dose not mentioned (N = 237)	2 years DFS 14% vs 34% Relapsed 82% vs 62%
Davies et al, 2000[24]	Bu/Cy (N = 176) vs Cy/TBI 12 Gy/6 Fx/3 days (N = 451)	3 years OS 40% vs 55% 3 years DFS 35% vs 50%
Bunin et al, 2003[25]	Eto/Cy/Bu (N = 21) vs Eto/Cy/TBI 12 Gy/6 Fx/3 days (N = 22)	3 years DFS 29% vs 58%
Eapen et al, 2006[26]	POG (N = 19) vs POG/TBI 12 Gy/6 Fx/3 days (N = 92)	RR of relapse 1.33 vs 0.49

Abbreviation: Bu, busulphan; Cy, cyclophosphamide; DFS, disease free survival; ETO, etoposide; Fx, fraction(s); Gy, gray; N, number of patients; OS, overall survival; POG, pediatric oncology group protocol 9110, 9310, 9411; RR, relative risk; TBI, total body irradiation.

Radiotherapy Techniques for Human Allotransplantation

Nowadays, many techniques have been developed for human allotransplantation treatment. Each technique has been optimized specifically for each transplantation procedure in order to maximize the treatment outcome and minimize risk of treatment complications.

Total Lymphoid Irradiation (TLI)

TLI is the technique of selective radiotherapy with low dose radiation fractionation to the lymphoid organs, major lymph node bearing areas, thymus, and spleen, while avoiding irradiated non-lymphoid organs in the head, chest, abdomen, and pelvis. After TLI treatment, a long-lasting reduction in the numbers and function of helper T cells and certain subsets of B cells were observed, indicating that this particular technique could be applied as an immunosuppression for allotransplantation.[7, 11, 27] In clinical trials of solid organ (cardiac and renal) transplantations, the TLI dose regimen was approximately 1 to 1.25 Gy per fraction with accumulation to total dose of 10.5 - 40.5 Gy.[28-31] In part of bone marrow transplantation for hematologic diseases (aplastic anemia and thalassemia), the TLI dose regimen was in the range of 5 - 24.5 Gy with a single or fractionated irradiation.[32-36] The results were reported with the emphasis on the efficacy of engraftment, the decrease rate of long-term rejection, and benefit on survival outcome. The data are shown in Table 2 and Table 3.

Total Body Irradiation (TBI)

TBI is a special technique that can deliver radiation to a patient's whole body with the uniform dose distribution throughout the body (±10% of the prescribed dose).[37] This technique is used mostly in leukemic patients as a part of the preparatory cytoreductive conditioning regimen for eliminating lymphocytes and allowing the engraftment of donor bone marrow prior to bone marrow transplantation. The conditioning regimen is referred to the process of using chemotherapy or chemo-radiotherapy to reduce the tumor burden and to suppress the recipient's immune system before undergoing allogeneic hemopoietic stem cell transplantation.[38] The conditioning regimen can be divided into 2 subgroups, myeloablative and non-myeloablative (reduce-intensity).[38-41] For myeloablative conditioning regimen, the high dose TBI, which is referred to irradiation in total dose of 12 Gy by low dose rate of 2 Gy per fraction twice daily for 3 consecutive days, were combined with alkylating chemotherapy agents. This regimen allows rapid successful engraftment, even in unrelated or mismatched donor and recipient. However, the delay or irreversible recovery of immunity and treatment-related morbidity as well as mortality such as endocrine dysfunction, fibrosis of normal tissue are concerned. Therefore, non-myeloablative conditioning regimen has been developed by using low total dose of 2 to 8 Gy in order to decrease toxicities and mortality rate from radiation complications. The benefits of non-myeloablative conditioning regimen are early recovery of immunity and reversible immunosuppression from treatment. With regards to the risk of long-term disease relapsed, the data remains unclear. This technique is particularly considered in elderly patient with had comorbid diseases or previously received high-dose chemotherapy.

Total Marrow Irradiation (TMI) / Total Marrow and Lymphoid Irradiation (TMLI)

TMI and TMLI are a more targeted form of TBI. The target volumes of TMI and TMLI can be precisely focused on major marrow sites and/or lymphoid tissues. Since 2000, the advance in radiotherapy techniques such as volumetric modulated arc therapy (VMAT) and helical tomotherapy (HT) along with image guided radiotherapy and modern treatment planning system have been applied in TMI and TMLI in order to improve therapeutic ratio by increasing radiation conformity to target of hematopoietic or lymphoid tissues and to reduce radiation to the surrounding normal tissues. Application of these advanced techniques as immunosuppressive agents could improve the allotransplant treatment outcome. The preclinical dosimetric and pilot clinical studies were investigated; of which the results are demonstrated in Table 4.[42-45]

Table 2 Results of TLI for Solid Organ Transplantation

Author, Year	Rational for TLI	Radiation Dose of TLI	Results	Follow-up Time
Najarian et al, 1982[28]	Prevent allograft rejection renal transplantation (N = 22)	Vary from 1 - 1.25 Gy/Fx; 10.5 - 40.5 Gy	Prolong 1 year graft survival with TLI	5 - 36 months
Salter et al, 1995[29]	Reduce post allograft rejection cardiac transplantation in previous rejection (N = 47)	0.8 Gy/Fx twice weekly; 8 Gy	The graft rejection frequency decrease vary from 0.67 - 1.8 to 0.07 - 0.13 episodes/patient/month with TLI	Mean 15 ± 1.2 months
Wolden et al, 1997[30]	Intractable allograft rejection cardiac transplantation (N = 47)	0.8 Gy/Fx twice weekly; 8 Gy	Rejection rate drop from 0.46 to 0.14 and to 0.06 episodes/patient/month before, during, and after TLI ($P < 0.001$)	Mean 3.1 years
Tallaj et al, 2011[31]	Recalcitrant cellular cardiac allograft rejection (N = 73)	0.8 Gy/Fx twice weekly; 8 Gy	Decrease in hazard for early rejection (first 12 months) RR = 0.36	18 years

Abbreviation: Fx, fraction(s); Gy, gray; N, number of patients; RR, relative risk; TLI, total lymphoid irradiation.

Table 3 Results of TLI for Hematologic Disease

Author, Year	Disease	Radiation Dose of TLI	Results	Follow-up Time
Arranz et al, 1994[32]	Aplastic anemia (N = 21)	7 Gy in 1 Fx	Actuarial survival is 62% at 8.6 years	Median 5 years
Gaziev et al, 1999[33]	Aplastic anemia (N = 17)	7.5 Gy in 1 Fx	Actuarial survival 76%	Median 11 years
Inamoto et al, 2008[34]	Aplastic anemia (N = 49)	7.5 Gy in 1 Fx or 5 Gy in 1 Fx plus TBI 5 Gy	Overall survival 81%	Median 7 years
Hongeng et al, 2007[35]	Thalassemia (N = 8)	5 Gy in 1 Fx or 5 Gy in 2 Fx	1 year disease free survival 75%	Median 1.6 years
Lee et al, 2012[36]	Aplastic anemia (N = 20)	7.5 Gy in 1 Fx or 10 Gy in 2 Fx	5 years survival 85% 10 years survival 83.1%	Median 7.8 years

Abbreviation: Fx, fraction(s); Gy, gray; N, number of patients; TLI, total lymphoid irradiation.

Table 4 The Dosimetric Study of TMI and TMLI

Author, Year	Radiation Technique	Study Design	Results
Hui et al, 2005[42]	HT	Dosimetric study of TBI and TMI	Accepted homogeneity and conformal radiation dose with feasibility for clinical application
Wong et al, 2006[43]	HT	Dosimetric study of TMI and TMLI compare to TBI	Potential advantages of dosimetry and feasibility of TMI, TMLI over TBI
Schultheiss et al, 2007[44]	HT	Dosimetric study of TMI compare to TBI	TMI reduce average radiation dose to OAR around 51% compare to TBI
Han et al, 2012[45]	HT vs VMAT	Dosimetric study of TMLI compare between HT vs VMAT	No significant difference of dosimetric study between 2 techniques

Abbreviation: HT, helical tomotherapy; VMAT, volumetric modulated arc therapy.

Future Direction of Radiotherapy for Human Allotransplantation

Potential Use of Proton Beam

The proton beam provides physical advantage with a property called "Bragg-peak" which allows radiation beam deposit within the target and minimize radiation exit dose that photon beam based treatment could not offer. Currently, proton radiotherapy has been used in many malignant and benign tumors such as base of skull tumor, craniospinal irradiation in pediatric malignancies. However, in allotransplant treatment process, the possibility of using proton beam is inconclusive. The data of dosimetric feasibility is limit, only preclinical study is investigated for TBI.[46]

Potential Use of Radioimmunotherapy

The antibodies conjugated with radionuclides can deliver continuous low-dose rate irradiation directly to the targeted cells and sparing normal tissue toxicity, hence providing potentials of using radioimmunotherapy. The results from Phase II clinical study highlighted the efficacy of using radioimmunotherapy as part of non-myeloablative conditioning regimens during bone marrow transplantation for non-Hodgkins' lymphoma.[47] The clinical application of radioimmunotherapy is currently investigated.

Clinical Experience of Radiotherapy for Human Allotransplantation in Ramathibodi Hospital

At Ramathibodi Hospital, TBI is the radiation technique that most frequently used. This technique is a part of myeloablative conditioning regimen for allogeneic stem cell transplantation in pediatric patients. Total radiation dose of 12 Gy were applied to allotransplanted patient with 2 Gy twice daily for three consecutive days by conventional lateral opposed field in supine position. In 2017, we published the clinical results of 44 pediatric leukemic patients, which were treated with our TBI-based myeloablative-conditioning regimen for allogeneic stem cell transplantation between 1997 and 2011.[48] With the median follow-up time of 6 years, the results showed 3, 5, and 10 years overall survival rate of 72.5%, 70%, and 63%, respectively. The disease free survival rates were 85.5% for 3 years, 82.5% for 5 years, and 82.5% for 10 years. Most common acute complication during TBI treatment was low-grade fever. No acute complication related death was reported. The most common late complication was hypogonadotropic hypogonadism. Rate of acute and chronic graft versus host disease were 8.4% and 3.5%, respectively.

Though less frequent, we also applied TLI technique for allotransplantation. This technique composed of 2 radiation fields, mantle and inverted Y field, for irradiated total lymphoid tissue in the body. The mantle field is used for irradiation of lymphoid tissue in the upper side of diaphragm while the inverted Y field is used for irradiation of the lower side. We applied this technique in 5 patients. Prior to bone marrow transplantation, one adult with beta-thalassemia were received radiation dose of 5 Gy in single fraction while another adult with aplastic anemia were received total dose of 5 Gy in 2 fractions. The other cases were children who received total dose of 5 Gy in 2 fractions for 1 week before kidney transplantation and bone marrow transplantation for beta-thalassemia. The example of treatment plan was shown in Figure 1 and Figure 2. We observed successful engraftment without severe complications in all cases with prolonged survival more than 5 years (unpublished results).

Recently, we are investigating preclinical dosimetric study, aiming to evaluate the feasibility of VMAT planning technique for TBI and TMI. The unpublished preliminary data suggested that VMAT technique for TBI could improve dose conformality and homogeneity when compared to conventional TBI technique. Moreover, the novel TMI by VMAT could further reduce dose of the other organ at risks apart from lungs. The example of color wash dose distribution of VMAT-TMI is shown in Figure 3. With the benefits of these techniques provided, we anticipate to apply these advanced techniques for clinical study in the future.

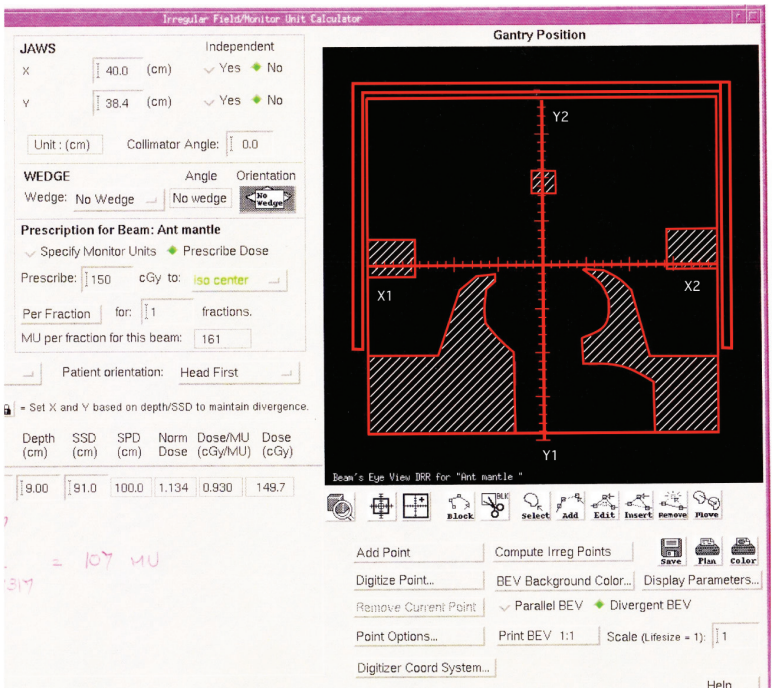

Figure 1 *The Mantle Field for Lymphoid Irradiation in Upper Side of Diaphragm*

The field extended from the inferior portion of the mandibles included cervical, supra and infraclavicular, axilla, mediastinal and hilar lymph node regions with shielded larynx, shoulder, and lungs.

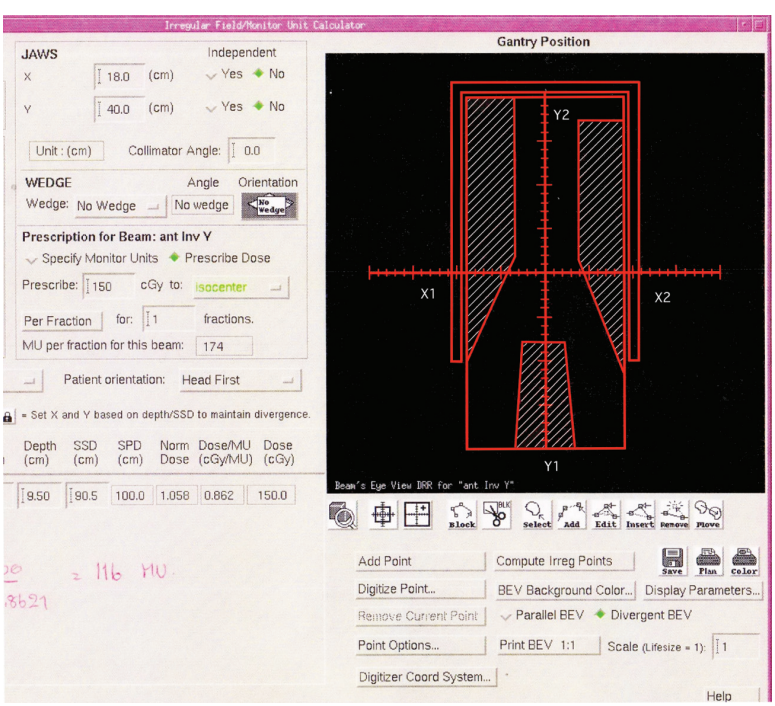

Figure 2 *The Inverted Y Field for Lymphoid Irradiation in Lower Side of Diaphragm*

The field included spleen, para-aortic, bilateral pelvic, and inguinal-femoral lymph node regions.

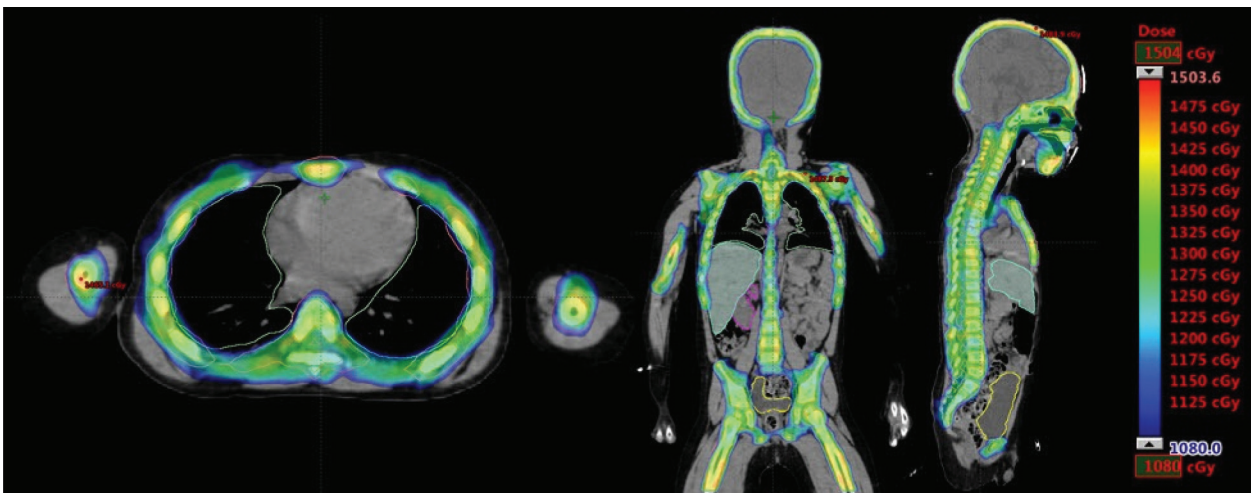

Figure 3 *VMAT-TMI Radiation Dose Distribution*

The color wash presented the radiation dose distribution in VMAT planning technique for total marrow irradiation (total dose 12 Gy in 6 fraction). Dose distribution range is from 10.8 Gy to 15 Gy. The lowest dose is shown in blue color and the highest dose is shown in red color.

Conclusions

Over the past 60 years, the radiotherapy for human allotransplantation has been continuously developed in order to improve treatment outcome. Several traditional radiotherapy techniques were discarded due to severe complications or unsuccessful outcome. Currently, the majority of treatments are based on fractionation TLI and low dose TBI. We foresee that in the future, with the innovation of radiotherapy machine and software planning system, the improvement of conformity with high radiation dose to the targets and reduce dose to surrounding normal tissue will be focused. In addition, the clinical replacement of new radiotherapy techniques such as TMI, TMLI or even proton radiotherapy or radioimmunotherapy to the conventional TLI, TBI techniques still to be further explored.

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Review Article/บทฟื้นฟูวิชาการ

การทบทวนบทความและประสบการณ์ทางคลินิกเรื่องการใช้รังสีรักษาเพื่อกดภูมิคุ้มกันในการเปลี่ยนถ่ายอวัยวะ จากอดีต ปัจจุบัน สู่อนาคต

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บทคัดย่อ

การฉายรังสีสามารถนำมาใช้ในกระบวนการเปลี่ยนถ่ายอวัยวะเพื่อช่วยกดภูมิคุ้มกันของร่างกายไม่ให้เกิดการต่อต้านอวัยวะที่ปลูกถ่าย เนื่องด้วยคุณสมบัติของรังสีที่ก่อให้เกิดไอออนจะทำให้เกิดการตายของเซลล์ที่โดนรังสี จากอดีตจนถึงปัจจุบันเทคนิคการฉายรังสีเพื่อช่วยกดภูมิคุ้มกันในกระบวนการเปลี่ยนถ่ายอวัยวะได้มีการศึกษาและพัฒนาอย่างต่อเนื่องในเชิงฟิสิกส์และคลินิก เพื่อนำมาสู่เทคนิคที่เหมาะสมที่สุดในการรักษาผู้ป่วย ปัจจุบันเทคนิคการฉายรังสีที่ได้รับการยอมรับเพื่อช่วยกดภูมิคุ้มกันสำหรับผู้ป่วยที่เข้าสู่กระบวนการเปลี่ยนถ่ายอวัยวะ คือ การฉายรังสีบริเวณเนื้อเยื่อน้ำเหลืองและการฉายรังสีทั่วทั้งลำตัวด้วย ปริมาณรังสีขนาดต่ำ ในอนาคตการศึกษาค้นคว้ามุ่งเน้นไปที่การฉายรังสีด้วยเทคนิคขั้นสูงที่สามารถปรับรังสีขนาดสูงให้จำเพาะเจาะจงเฉพาะบริเวณเนื้อเยื่อที่ต้องการรักษา โดยสามารถลดปริมาณรังสีต่อเนื้อเยื่อปกติที่อยู่บริเวณรอบข้างได้ในเวลาเดียวกันหรืออาจมีการปรับเปลี่ยนใช้ชนิดของรังสีที่มีคุณสมบัติทางด้านฟิสิกส์ที่มีความจำเพาะเจาะจงมากขึ้น เพื่อช่วยเพิ่มอัตราความสำเร็จในกระบวนการรักษา โดยผู้ป่วยได้รับผลแทรกซ้อนจากการรักษาลดลง และช่วยเพิ่มคุณภาพชีวิตในระยะยาว บทความนี้มีวัตถุประสงค์เพื่อเผยแพร่ความรู้และความเข้าใจของการใช้รังสีรักษา โดยการสืบค้นและทบทวนบทความทางการแพทย์ที่เกี่ยวข้องกับความรู้พื้นฐาน ประวัติศาสตร์ เทคนิคการรักษา และผลลัพธ์ทางคลินิกที่เกี่ยวข้องกับการใช้รังสีรักษาเพื่อกดภูมิคุ้มกันในการเปลี่ยนถ่ายอวัยวะ รวมทั้งแบ่งปันประสบการณ์ทางคลินิกเกี่ยวกับการใช้รังสีรักษา

คำสำคัญ: การเปลี่ยนถ่ายอวัยวะ การฉายรังสีบริเวณเนื้อเยื่อน้ำเหลือง การฉายรังสีทั่วทั้งตัว การฉายรังสีบริเวณไขกระดูก การฉายรังสีบริเวณไขกระดูกและเนื้อเยื่อน้ำเหลือง

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