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Mini Review

Which is the best? Palliative Radiation Therapy to Spleen or Splenectomy

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Abstract

Spleen is one of the most important organ of the reticuloendothelial system and coordinates the immune response. Splenectomy is performed for hypersplenism, and staging of hematological malignancy. In conservatively followed patients, radiation therapy can be used to reduce hypersplenism symptoms. Splenectomy or palliative radiotherapy to spleen may probably cause an immune suppressive condition. This may probably local and systemic complications.

Introduction

The spleen is an organ which has several important physiological functions in the human body. It has 4 main functions; filtration, host defense, storage of erythrocytes, platelets, lymphocytes and reticulocytes, and cytopoiesis. Splenectomy is usually performed depending on factors such as hematological diseases, trauma related injuries and cancer. In conservatively followed patients, radiation therapy can be used to reduce hypersplenism symptoms. Also splenic tissue is exposed to radiation during radiotherapy for gastrointestinal malignancies. Irradiation of the splenic tissue cause a wide range of local and systemic complications. These effects are not fully understood [1-5].

Irradiation of spleen andvarious types of cancer alter immune system functioning. Firstly, if fighting cells of the immune system cannot cope with the development of cancer, they undergo functional changes. As a result of this change, immune cells settled in tumor tissue cause tumor development, spread and neovascularization. Also they may develop their capacity to suppress immune activity. In cancer patients with splenectomy, disorders of the immune system are expected. In those patients, chemoradiotherapy is a risk factor for septic complications [3-8].

Various complications are seen due to splenic irradiation and underlying disease. Especially, this group of patients are at risk for encapsulated microorganisms. In these group of patients, assessment of immune functions along with studies assessing if these patients are susceptible to infection are needed [3,4,8].

Spleen and Its functions

Throughout the history, spleen has been charged with numerous functions and features. In the first century, according to the ancient inscriptions, spleen was called as chair of the laughter, the source of black bile causing melancholy and the place of conflicting emotions. Another meaning of spleen in English is diseased habit. Also for centuries, spleen had been considered as an obstacle to the rapid movement of both human and animals [1].

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Spleen resides in the left upper quadrant of the abdomen. It is a small and purple organ located at the level of 9th and 12nd thoracic vertebrae. Origin of spleen (circulation system, hematological system, mononuclear phagocytic system or lymphatic system) is still debated. Although weighs up to 1-2% of the total body weight, more than 5% of blood volume after a heartbeat passes through the spleen [2-4].

Spleen is the largest reticuloendothelial organ in the body which consist of lymphoid tissues and vessels. According to many scientists, its main task is filtration. Abnormal red blood cells, mature cells, inclusion bodies and foreign particles are filtered in the spleen. It plays a regulatory role in both humoral and cellular immune response. Thus, it contributes to the host defense mechanisms. Production of tuftsin, properdin and specific antibodies against bacteria, T and B lymphocyte maturation, phagocytosis of antibody-labeled cells are some of the immunologic functions it has. In addition to these features, it plays a role in deposition of circulating blood cells and platelets, hematopoiesis, degradation of hemoglobin, iron recycling and plasma volume regulation [2-7].

Paliative radiation therapy to spleen

Splenectomy is usually performed following trauma related injuries, for hematologic disorders, splenic malignancy and during the surgical treatment of gastric and esophageal cancers. In splenectomized patients, a number of histological and physiological changes occur in the immune system. These changes include reduction in the activation of the complement in the alternative way, loss of serum opsonins, changes in immunoglobulin levels and alterations in cellular immunity. Due to immunological changes, splenectomized patients carry increased risk for sepsis [3,4,8-12].

Sepsis caused by splenectomy related immune deficiency may led to serious infections and multiple organ dysfunction including the lungs and liver. Spleen plays a significant role in response to encapsulated pneumococcus septicemia with marginal zone macrophages, marginal zone B cells that react to capsular antigens and IgM secreting memory B cells [13-15]. Asplenic individuals carry risk for developing sepsis 0.2 to 0.5% per year and 5% throughout life. It is mostly seen in the first two years after splenectomy and have high mortality rate of between 50-60% [4,5,13,16-18]. Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis are the most common encapsulated microorganisms that have been found to be responsible for sepsis after splenectomy [19-23]. In blood culture of many patients with suspected sepsis, gram positive bacterium Streptococcus pneumoniae has been isolated in 50-90% of the time [23,25]. Yet the another retrospective study, in 66% of the cases pneumococcus were responsible for sepsis after splenectomy [25]. Pneumococcal infections can be seen in all age groups but spesifically in the older ages, rate of infection rises. Nowadays antimicrobial resistance to S. pneumoniae has become a major issue. Even from the third generation sefelosporins, seftriaxone may remain ineffective. At this point, besides antibiotic effect, it may be necessary to strengthen the immune response. According to guidelines, in order to reduce morbidity and mortality, patient education, immunization and lifelong on-demand antimicrobial therapy are recommended [16,21,23,26-28].

In the beginning, although it didnt take much attention, as a result of the studies conducted later, asplenia or splenectomy was found to cause serious infections. With the better understanding of these infections, importance of spleen in the immune system was revealed and preserving spleen as much as possible have gained growing importance and indications for splenectomy have began to change over the years. Today, more attention is paid to protect spleen particularly after trauma related injuries and during malignant diseases. However, splenectomy still holds a chief role particularly in the treatment of hereditary spherocytosis and hemolytic anemia [8,9].

Palliative radiation therapy (RT) is another treatment option in disease caused hypersplenism. In the beginnig of 20th century, splenic RT was used in the treatment of leukemia as the only effective antineoplastic therapy, but with the introduction of antineoplastic drugs, RT indications were limited to palliation of patients with splenomegaly. Radiotherapy has being used for hypersplenism symptoms in myeloproliferative and lymphoproliferative malignancies so far. The main purpose of RT is to relieve symptoms secondary to splenomegaly such as pancytopenia, abdominal pain and compressive symptoms. In particular, patients in the terminal stage, or conservatively followed patients are best candidates for RT due to reduction in narcotic use. Also decreased costs and lower toxicity may it an preferrable option [8,29-33].

Despite being used for years, immunologic and systemic effects are not fully known. Splenic RT reduces the effects of spleen in the reticuloendothelial system. It is known that spleen stores lymphocytes. A significant proportion of malignant lymphocyte clones are destroyed by radiotherapy. Thus, by reducing the number of lymphocytes, splenomegaly regresses and T suppressor lymphocytes responsible for anemia and thrombocytopenia are eradicated. RT kills neoplastic cells directly. Moreover, as a result of irridation, cytokine release are increased. Radiation therapy to spleen may led to secondary autoimmune problems or bone marrow failure that might affect the course of the disease [29,34-36]. Weinmann and colleagues reported that irridation of spleen in leukemia should be considered not only as an anti-neoplastic agent but also an immunomodulatory therapy [29]. In lymphoid leukemia, after splenic RT, complete remission was found to be related to induction of systemic effects [37,38]. In the case report of Markus et al, results of splenic rt in autoimmune hemolytic anemia patients were shared and they reported that spleen irradiation only affects the spleen destruction but at lower doses, this situation may be different [39].

The spleen in radiation dose-volume relationship

There are limited number of studies evaluating total dose and fraction scheme, treatment efficacy and treatment related toxicity in splenic RT. Unfortunately, current studies are far from giving information about chronic and immune side-effects after irradiation of spleen. Different fraction schemes have been tested. Hypofractionated treatments or intermittant treatment schemes were administered to minimize acute hematologic toxicity. Today, For splenic RT, daily doses of 0.5-1 Gy, two or three fractions per week (intermittent or hypofractionated) and total dose of 3.5-6 Gy have been accepted generally [31,33,35,38-40]. In the previous work of elderly patients with myeloproliferative diseases who developed symptomatic splenomegaly, we used palliative RT 2-3 fractions per week, at a daily dose of 0.5 Gy, mean total dose of 7.5 Gy. Post-treatment evaluation revealed 100% reduction in abdominal pain, 64% shrinkage of spleen size. Pancytopenia was found to be an acute toxicity during the treatment, but chronic toxicity was not observed in any patient. Better response was observed and remission was longer at higher doses [8]. In another work, Bouabdallah et al., (0.4-0.5 Gy/f dose) observed pain palliation (90%) and objective response (81%). In 35% of the patiens they reported that myelotoxicity was seen [31]. Permantier and colleagues used 4.5 Gy/18 fractions/ 3.5 weeks; Wienmann et al., used small single fraction mean dose of 0.25Gy, 1-9 Gy in total; Elliot et al., used in a fraction 0.3-13.65Gy, 2-17Gy in total [29,41,42]. McFarland et al., used hypofractionated (two fractions per week) doses, 6 fractions in total. For every week they used doses of 0.5Gy, 0.75 Gy and 1 Gy respectively [35]. In these studies, treatment efficacy so that in what extent it reduced hypersplenism symptoms were analyzed. But dose-volume relation, immunological and systemic effects were not assessed.

During radiotherapy of localized gastrointestinal tract malignancy spleen is also at at risk. Different types of side effects are seen in acute or late stages prportional to splenic volume in RT field and RT dose. These side effects are most noticeable in the early stages as thrombocytopenia or pancytopenia, and in the late stages splenic atrophy, sepsis or increased risk for infection [8,16,18].

Irradiation of spleen results in local and systemic effects. When irradiated at high-doses, it is thought to be effective via different mechanisms like splenectomy. Murray irradiated rabbit spleen with 8Gy and examined pathological changes; in 3 hours time he observed nuclear change in white pulp lymphocytes and in red pulp excluding reticular cells and blood cells, all cells died. Erythroblasts and myeloblasts appeared again within 14 days. he also reported that in 9 days lymphopoesis and in 3 weeks myelopoiesis resumed [34]. In several studies of patients with lymphomas and hematologic malignancies, when spleen was irradiated at a dose of 12-40 Gy (2 Gy fractions/day), deterioration was shown in hematologic functions such as filtration and storage [16,18]. In several studies of patients with lymphomas and hematologic malignancies, when spleen was irradiated at a dose of 12-40 Gy (2 Gy fractions/day), deterioration was shown in hematologic functions such as filtration and storage [10,18,21]. During histopathological examination of the spleen after splenic RT to Hodgkin Lymphoma, changes in both white and red pulp and vascular structures were seen [32]. When individuals with altered splenic functions were compared with normal individuals, they were found to have lower levels of IgM and IgG levels and release of immunglobuls were slower [14,15].

Because spleen is not a contouring organ, dose-volume relation hasnt been studied much. But, RT is known to effect splenic functions and cause atrophia. Therefore, in clinical practice, every effort has been taken to deliver very low doses to spleen. Yet, optimum dose is not known clearly. Also, this subject is quite limited in the literature. Different total doses and fraction schemes have been studied. Coleman et al., worked with patients who had Hodgkin or non-Hodgkin lymphoma. They used 40 Gy splenic irradiation and reported that after 4 to 5 years, functional hyposplenia developed [40]. Spencer and associates observed that in patients with ovarian cancer, when abdomen was irradiated with 20 Gy, splenic atrophia wasnt observed [30]. In another study of 20 Gy splenic radiotherapy, due to Howell-Jolly bodies in blood, similar effects to splenectomy were seen [43]. Splenic atrophy was seen mostly after 2-40 Gy [16,29,44]. Trip and friends reported that spleen on average received 40 Gy irradiation in gastric cancer patients [45]. In another study of postoperative chemoradiotherapy receiving gastric cancer patients, spleen volume and functions were evaluated. In patients receiving higher splenic doses, more reduction in spleen volume was observed and in this group of patients, due to functional hyposplenia pneumonia and fatal sepsis were seen more frequently [16]. Dailey et al., found significant reduction in spleen size; but they didnt see any effect on spleen size during chemotherapy [32]. Highest reduction byone-third in sizewas observed in the first year after the treatment [16].

Conclusion

In patients who are exposed to splenic irradiation, if dose-volume relation is described, it will guide to identify hyposplenia or asplenia earlier. In addition, immunosuppression occured after splenic irradition may have serious results. In such patients, in addition to studies evaluating if these patients are susceptible to infections, studies evaluating immune functions are needed.

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