Estimation of Albumin and Globulin in Pre and Post Radio-Therapeutic Patients: A Review

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Abstract: *Cancer is the second deadliest disease worldwide that often results in death. Treatment of cancer causes many side effects and reduces the overall survival of the patients with a high cancer recurrence rate. Some chemical markers are used as a prognostic marker to predict the overall survival and cancer recurrence rate, but they cause many side effects. For resolving these problems, certain biological inflammatory markers are reported (Example C-reactive protein, Neutrophil-lymphocyte ratio, Body Mass Index, Albumin, Globulin, Albumin Globulin Ratio, Total bilirubin, Direct bilirubin, etc.) that can reduce the side effects and can be used for the prediction of cancer recurrence and overall survival of the cancer patients. The current review is done to explore studies done to evaluate the side effects of radiotherapy and the role of serum protein parameters [1] especially Albumin Globulin Ratio (AGR) as indicator of radiotherapy side effects and whether it can be used as an inflammatory marker for prognosis of cancer patients undergoing radiotherapy. Method: We conducted a thorough electronic search by Cochrane, EMBASE and PubMed to identify relevant studies. Studies published on the role of serum protein patterns in cancer patients undergoing radiotherapy have been selected, analyzed and summarized. Results: A number of studies suggests the effect of radiotherapy on serum protein levels besides causing other tissue damages.*

Keywords: Albumin, globulin ratio (AGR), Cancer, radiotherapy, side effects, serum protein electrophoresis

1. Introduction

Cancer is the second leading cause of death in the world due to its recurrence property and high doses of therapies that causes side effects and decreases the overall survival of patient. But the treatment is improving day by day. Cancer is a disease that results in abnormal proliferation of the cell uncontrollably that ultimately destroys body tissues. Any cell that looses their potency of division is termed as cancerous cell. When cell deny undergoing apoptosis and starts continuous division, it forms tumour (benign). The condition when tumour cell invades the cellular lining and spread throughout the body is called malignancy or metastases [2]. Lung cancer, breast cancer, colorectal cancer, prostate cancer, skin (non-melanoma) cancer, stomach cancer and liver cancer are some common types of cancer found worldwide with a high death rate[3][4]. Cancer shows general symptoms and mostly occurs at old age due to slow development. According to National Cancer Institute (NCI), there are five stages of cancer i.e., Stage 0, Stage 1, Stage 2, Stage 3 and stage 4. Improper lifestyle habits along with the consumption of toxic compounds e.g., tobacco, weed, alcohol, etc. increases the risk of cancer. By changing some habits and lifestyle, cancer can be prevented. Various types of treatments are available for cancer from which, chemotherapy, radiotherapy and surgery are three main aspects. The effect of treatment varies from person to person due to different body response. Some persons requires one type of treatment method to cure whereas; in most of the cases concurrent or combination of therapies are given to the patient that reduces the chances of side effects and cancer recurrence with a high reduction in cancer cells and a high overall survival rate of the cancer patient. Concurrent therapy involves surgery + radiotherapy/ chemotherapy or radiotherapy along with chemotherapy given to the patients[5-7].

Surgery includes removal of tumour from certain body parts. It is the best method to remove benign tumour, but the chances of cancer recurrence remains maximum. Chemotherapy involves treatment through chemicals that reduces the size of tumour by killing the cancer cells. Radiotherapy involves radiation-based treatment[5-7]. A high dose of radio waves are targeted at the tumour site. The high intensity of radiation results in burning of cancerous cells that reduces the size of tumour. X-rays, radioactive rays, proton rays, Cherenkov rays, etc. are used as a source to kill cancerous cells. There are various machines used in radiotherapy for cancer treatment e.g., X-rays, Cobalt accelerator, Dual energy linear accelerator, Halcyon medical accelerator, Image guided radiotherapy (IGRT), Intensity modulated radiotherapy (IMRT), Proton accelerator, etc. External beam radiotherapy and internal beam radiotherapy are the two main forms of radiation therapy. Systemic radiotherapy is also known as radiolabelled iodine or I-131 therapy is frequently used for the treatment of thyroid cancer. Systematic radiotherapy involves treatment that travels in blood stream seeking to kill cancer cells. Preoperative (before surgery), Intraoperative (during surgery) and Postoperative (after surgery) are the three main aspects of combinatorial radiotherapy with surgery [8].

Chemotherapy, radiotherapy, surgery and combinatorial therapy are most effective and frequently used treatment methods but, they also have certain side effects (either short-term or long-term). Side effects include cardiac or lung problem, thyroid problem, menopause, nausea, vomiting, diarrhoea, sometime skin changes, hair loss, fatigue etc. Researchers world over have explored and found certain parameters that can be used to estimate the effects of radiotherapy over the patient so that they can be targeted to reduce the side effects along with the reduction of cancer recurrence chances[8]. Some of the parameters involve C-reactive protein, Lactate dehydrogenase, Body Mass index, Low density lipoprotein, high density lipoprotein, Albumin

Globulin ratio, Neutrophil lymphocyte ratio, etc. From all the mentioned parameters, Albumin Globulin Ratio is found to be the most effective parameter to predict the overall survival and chances of cancer recurrence in the patient suffering with certain type of cancer. It is generally found that high doses of radiotherapy can efficiently treat cancer, but also changes the concentration of blood serum proteins[9].

Serum is the plasma without clotting agent. In other words, when clotting factors are removed from the blood it turns to serum. Serum is the protein rich fluid that can be used for *in vitro* cell culture due to its protein rich property. It contains albumin, globulin and Immunoglobulin G proteins in it. Albumin is the most abundantly found serum protein among others;it covers 55% of the total serum protein with a molecular weight of 690000 KDa. Synthesis of albumin is done by liver. It prevents leakiness of blood vessels, transports insoluble molecules, grows and heals tissues, maintains osmotic pressure of plasma and also act as a source of amino acid. It is a positively charged globular protein whose deficiency can cause malnutrition, cachexia, liver disease, nephrotic syndrome, protein-losingenteropathies, severe burn, etc. Whereas, its efficiency can cause severe dehydration. Globulin proteins are the glycoproteins having molecular weight of 90000 to 130000 KDa. They have 4 classalpha-1, alpha-2, beta-1 and gamma globulin from which, some are synthesized by liver and some are synthesized by the immune system. Globulin proteins help to maintain High density lipoprotein, prevent iron loss, provide immunity, etc. They contain 38% of total serum protein.Alpha and Beta globulin helps to transport proteins, lipids, hormones, vitamins and minerals in body. Whereas; gamma globulin act as immunoglobulin that make up the largest portion of globulin.Our body contains maximum amount of immunoglobulin, that has the capacity to kill microorganisms. They act as a substrate to form other substances. They act as antibodies that bind to foreign antigen to destroy them by immune system. Alpha 1, Alpha 2 and Beta 1 has positive charge whereas; Gamma globulin has negative charge. An increase in gamma globulin will cause multiple myeloma or bone cancer[11][12].

Albumin Globulin Ratio – A ratio of albumin and globulin is used as an early sign of many disorders. In a healthy person, the ratio is seemed to be more than 1. For calculating Albumin Globulin Ratio, following formula is used [10]:-

$$AGR = Albumin / (Total\ Serum\ protein - albumin)$$

Electrophoretic Separation - Separation and quantification of serum proteins can be done by using electrophoresis. Electrophoresis is a technique used for separation of charged biomolecules according to their size under the influence of electric field in such a way that molecules having a small size and low molecular weight moves faster as compared to the molecules having high molecular weight and larger size. In serum electrophoresis, five bands were obtained after electrophoretic separation(i.e., Albumin, alpha-1, alpha-2, beta and gamma globulin). The quantification of bands is done by densitometry [1]. The ranges of bands are compared with the standard range and an increase or decrease in

concentration of protein results to be a cause of disease. Albumin and globulin ratios are then calculated.

Table: Standard reference ranges of serum protein Electrophoresis are[1]:-

Serum Protein	Reference Range (g/dL)
Total protein	6.4-8.3
Albumin	3.5-5.0
Globulin	2.3-3.4
Alpha-1 globulin	0.1-0.3
Alpha-2 globulin	0.6-1.0
Beta globulin	0.7-1.1
A/G Ratio	0.90-2.0

Several studies have been done to evaluate the AG ratio in cancer patients undergoing therapy. It is found that a low serum Albumin Globulin ratio is a good prognostic marker for cancer patients; whereas, individual serum albumin level is not linked to the inflammatory factors. On the other hand, a high serum globulin level (gamma globulin) decreases the overall survival of the patients. This concludes that a low AGR with a high globulin level can be used as a good predictor for poor survival in certain cancer.In other words, patients having a low AGR value have a poor overall survival and a high cancer recurrence rate whereas; patients having high AGR values have a good overall survival with a low cancer recurrence rate[9].

It is also found that AGR is the best inflammatory marker among all other biological inflammatory markers (e.g. C-reactive protein, Albumin, Globulin, Neutrophil-Lymphocyte ratio, Platelet-Lymphocyte ratio, Monocyte-Lymphocyte ratio, Albumin Globulin ratio, Total Bilirubin count, Direct Bilirubin count, etc.) that were used to predict the overall survival, cancer recurrence rate and side effects of radiotherapy over cancer patients[10][11].

Low total protein can cause liver, kidney and digestive disorders whereas; a high total protein in blood can be a symptom of any chronic infection or bone marrow disorder. A low Albumin Globulin Ratio indicated autoimmune disorder in which, self immune system attacks on healthy cells, cirrhosis, liver inflammation or bone marrow tumour whereas; an increase in Albumin Globulin Ratio can be a sign of liver, kidney or intestinal disease and also linked with low thyroid activity and leukaemia[13]. During Multiple myeloma, an extra band is observed in the serum protein electrophoresis with a peak concentration; the band is said to beIgM band[1].

2. Conclusion

Thus, reviewing the various studies done on serum protein markers of cancer patients undergoing radiotherapy, AG ratio can be regarded as a good prognostic marker for cancer patients undergoing radiotherapy and to understand the serological changes occurring in body during radiotherapy, where the use of this inflammatory marker over chemical marker shows approximately no side effects over the patient and helps to understand the effect of radiotherapy over the serological proteins in body and the helps to predict the chances of side effects caused due to radiotherapy. Hence, study is required to understand the changes occurring in

blood of cancer patients due to radiotherapy and to understand their overall survival and cancer recurrence rate so that some modifications can be done in the treatment that will reduce the side effects and increase quality of life of cancer patients.

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