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Physiological Markers for Radiation Illness

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Radiation illness is defined as the damage to the organ tissues due to the excessive exposure to ionizing radiation. The exposure to radiation interferes with the process of cell division. Markers can be classified into several categories and are measured with a variety of techniques. The most useful markers are those that are easily collected and immediately available, inexpensive, diagnostic and prognostic, and specific for a given disease These markers might be classified as predictive, prognostic, diagnostic, and dosimetric markers as regard their effects on normal tissues. Markers of physiological effects response to radiation:

1) Markers of Cell Death.

2) Markers of Hypoxia.

3) Cytokines and inflammatory mediators [these cytokines: TGF-β1, Interleukins (IL-1, IL-6, IL-10 and IL-8), intracellular adhesion molecule-1(ICAM-1), Pulmonary Surfactant Proteins, Krebs von den Lungen-6 (KL-6), Thrombomodulin, etc]

4) Polymorphonuclear leukocyte (PMN) and CD34+ markers

5). Other protein markers as Amylase, Flt3-ligand, Citrulline, Plasma oxysterol concentrations as physiological markers of MODS.

6) Gene expression and amplification in response to radiation and the status of microarray analysis. Other markers include:

1.Markers leading to radiation-related side effects including those that can be used to identify subjects at greater risk than normal toxicity, before exposure; **2.**Markers useful for diagnosis, prognosis, biodosimetry, and therapy; **3**.Physiological markers are important available markers for radiation effects on tissues;

4. Cytokines appear to play the role of both causative agent and marker;

5. The evidence has demonstrated a potential value of determining the early response of blood markers to ionizing radiation in predicting latent radiation toxicity, which may be used for planning individualized treatment regimens. The future of research on markers of radiation tolerance is increasingly important due to the growing number of cancer treatment survivors. Although no validated blood markers are currently available for daily practice, further research in this area has become important.

Radiation illness is defined as the damage to the organ tissues due to the excessive exposure to ionizing radiation. The exposure to radiation interferes with the process of cell division[(1)]. Radiation illness results from excessive exposure to ionizing radiation when humans (or other animals) are exposed to very large doses of ionizing radiation[(2)]. Radiation exposure can occur as a single large exposure (acute), or a series of small exposure spread over time (chronic) [(3)].

Poteintial markers of radiation illness: Over the past five decades, those interested in markers of radiation effect have focused primarily on tumor response. More recently, however, the view has broadened to include irradiated normal tissues—markers that predict unusual risk of side-effects, prognosticate during the prodromal and therapeutic phases, diagnose a particular toxicity as radiation-related, and, in the case of bioterror, allow for tissue-specific biodosimetry [(4)]. **Markers profiles** will vary with tissue and time due to the complex nature and protracted course of radiation toxicity. Markers are needed at all stages of the process including markers for both the

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direct effects of the radiation and the indirect and thus potentially reversible radiation effects [5]. It can be classified into several categories and are measured with a variety of techniques. The most useful markers are those that are easily collected and immediately available, inexpensive, diagnostic and prognostic, and specific for a given disease [6].

Markers of physiological effects response to radiation: radiation treatments have multiple physiological effects. In clinical radiation therapy, the majority of tissue being irradiated (often to much lower dose) is actually non-tumor. Thus the majority of physiological changes are likely related to this exposure. Radiation causes cell death through a variety of mechanisms including apoptosis, necrosis, DNA damage, and reproductive inactivation. Radiation damages some cells without killing them, causing the stimulation of pathways involved maturation, angiogenesis, and inflammation. It damages vasculature leading to perfusion dysfunction and hypoxia. The role that cytokines might play in these physiological processes has been extensively studied in recent years[5]. The following sections will briefly discuss some physiological markers of great promise.

1) Markers of cell death (apoptosis, necrosis, and reproductive inactivation) in response to radiation: radiation-induced cell killing includes apoptosis, necrosis, and reproductive inactivation. Fortunately most solid organ tissues are resistant to apoptosis following irradiation. Such cells alternatively might, sometimes over a long period of time, undergo reproductive death, necrosis, or delayed apoptosis. These mechanisms of cell death occur at a rate too slow to be substantially detectable by circulating markers or with a biopsy. Also, unlike apoptosis, there are very few candidate markers for reproductive or necrotic cell loss. Thus death markers are not yet useful for predictive, prognostic, or diagnostic purposes and their development for use in dosimetry will be a challenge as well. Regarding early side effects of radiation, apoptosis can be extremely important even if its impact on late toxicity is limited **[7].**

Apoptosis signaling can begin with oxidative products and the mitochondrial pathway. Because the process is short lived and most of the signaling proteins are intracellular, to date there are few useful apoptosis-related proteins to consider as molecular markers of radiation effect. However, It is doubtless that the effect of ionizing radiation is accompanied by a stimulation of Fas-ligand expression on the surface of peripheral mononuclear cells and modification of the activating signal to apoptosis through the molecule CD4, CD8, CD3 which caused by proapoptotic effect of radiation**[7]**.

2) Markers of Hypoxia in Response to Radiation: A common pathway of radiation toxicity is microvascular dysfunction. Many genes are upregulated in response to hypoxia including several angiogenic peptides that are easily detected in the circulation. High levels of FGF2 have been seen in long-term survivors of radiation with concurrent fibrovascular complications of radiation[8]. When these subjects were treated with pentoxifylline to improve microcirculation, most had a reduction of their circulating FGF2 protein. Other angiogenic proteins are likely expressed and deserve consideration. The anti-angiogenic effects of radiation on vasculature are likely a combination of decreased localized stem cells and local changes in the cytokine milieu reducing the recruitment of new stem cells from the circulation. Some of these factors might also be available for long-term evaluation as prognostic markers and as targets for therapy[8] .

3) Cytokines and inflammatory mediators in Response to Radiation:

A) Cytokines are a class of proteins and glycoproteins involved in intercellular signaling. Most act through autocrine and paracrine cellular communication but can be found in the circulation. The cytokines and their effects are particularly exciting, as they are themselves are therapeutic targets, making cytokine-mediated disease reversible. Thus cytokine levels can serve as predictive, prognostic, and diagnostic markers for radiation toxicity; they are not, however, specific for the radiation effect **[9]**.

There is a **"cytokine storm"** that occurs shortly after a tissue is irradiated. It can be very prominent in patients undergoing whole body radiation for bone marrow transplant. This shortlived, multi-cytokine expression has led some to speculate that the intensity of that

expression might identify at-risk patients for later toxicity. Most investigators, however, judge this storm to be a general stress response and not a predictive assay. The prediction therefore lies in the slower progressive cascade of cytokines previously described. It remains unclear whether measurements of either the storm or the cascade will be specific and sensitive enough to be useful as biomarkers for anything other than acute biodosimetry[9].

1. TGF-β1 is a multifunctional cytokine activated in response to tissue damage in processes such as inflammation, wounding and healing, initiating a cascade of signaling events. It plays an important role in the inhibition of epithelial cell proliferation and in the development of tissue fibrosis, while it appears to be a mediator of tissue response to radiation therapy. It has been proposed that the risk of normal tissue injury after radiation therapy is not only increased by local production of TGF-β1 but also by exposure of tissues to elevated circulating levels of TGF-β. The role of TGF-β1 in the development of radiation pneumonitis has been extensively studied[10].

The predictive value of TGF-β1, however, is confounded by the tumor effect, as many lung tumors produce TGF-β1. High TGF-β1 levels during radiotherapy may identify not only patients with a higher risk of developing pulmonary toxicity but also patients with a higher risk of treatment failure. Furthermore, the predictive value of the risk of radiation pneumonitis by the presence of increased TGF-β1 levels in the plasma at the end of radiotherapy has not been confirmed by others[11].

2. Interleukins; Interleukins are a group of cytokines (secreted signaling molecules) that are seen to be expressed by white blood cells as a means of communication. Currently, interleukins are produced by a wide variety of cells and function at various levels of the immune system.

a. **IL-1, IL-6: IL -1**, produced by macrophages, induces acute phase reaction and fever. **IL-6**, produced by macrophages and T helper 2 cells, is a pleiotropic cytokine regulating many inflammatory and immunologic processes and induces an acute phase reaction to injuries[12].

The immediate response to radiation-induced tissue damage involves expression of inflammatory cytokines, such as TNF-α, IL-1 and IL-6. These cytokines are produced locally within the treatment field and bind to receptors on the same or adjacent cells of the same type (autocrine response), on cells within the same tissues (paracrine response), or they stimulate cells that are distant from the field of injury (endocrine response) by entering the circulation. Subsequently, a cascade of cytokine activity is triggered to bring immune and inflammatory cells to the site of injury. The inflammatory cytokines released by irradiated tissues induce the synthesis of cell adhesion molecules within the vascular endothelium [13].

The inflammatory response of lung tissue to radiation-induced injury is mediated through many types of cytokines. Interleukins IL-1α and IL-6 are inflammatory cytokines that participate in acute phase responses. Their activities include activation of lymphocytes, regulation of fever, precipitation of fibrovascular responses and chemotaxis for mononuclear cells. The primary source of IL-1α is monocytes and alveolar macrophages whereas IL-6 is synthesized by a variety of cells, including alveolar macrophages, type II pneumocytes, T-lymphocytes and fibroblasts. Existing evidence shows that IL-1α is involved in the regulation of the expression of IL-6[13].

b. **IL-10** is an anti-inflammatory cytokine produced by monocytes and macrophages. One of its main functions is to down-regulate inflammation by blocking the production of proinflammatory cytokines (e.g. IL-6) and reducing the function of antigen-presenting cells[14].

A combination of decreased IL-10 and elevated IL-6 blood levels during radiotherapy correlates with the development of radiation pneumonitis. Thus, early changes of circulating IL-6 and IL-10 levels during the course of radiation therapy may be used as predictors for the risk of radiation pneumonitis [12].

c) **IL-8** was originally identified as a neutrophil chemotactic factor, isolated from human mononuclear cells, but it also induces chemotactic responses in basophils and T-lymphocytes. IL-8 has been shown to be capable of inducing migration of endothelial cells, expressing angiogenic activities, as well

as inducing loss of focal adhesion in fibroblasts, resulting in chemotaxis and chemokinesis. Despite its neutrophil chemotactic activity, chronic up-regulation of IL-8 may result in long-term impaired neutrophil migration. Thus it is likely that patients expressing high circulating levels of interleukin-8 may experience impaired neutrophil migration to sites of radiation-induced tissue damage, ameliorating the proliferation of profibrotic changes in symptomatic lung injury. It has also been demonstrated than high levels of IL-8 in non-small cell lung cancer patients are highly associated with progression of disease [(15)].

3. The application of intracellular adhesion molecules-1 (ICAM-1) measurements in serum and bronchoalveolar lavage (BAL) fluid in patients with lung malignancy who receive chest radiotherapy for the prediction of radiationpneumonitis has been investigated by Ishii and Kitamura. They found that pre-treatment serum levels of ICAM-1 were elevated in cancer patients, compared to healthy individuals, irrespective of the development of pneumonitis. The observed increase is believed to be correlated to the presence of disease since previous reports have observed elevated concentrations of serum ICAM-1 in malignancy [(16)].

4. Pulmonary Surfactant Proteins: Ionizing radiation induces an increased alveolar surfactant that could leak into the blood through radiationinduced endothelial cell damage of the vessel wall [(17)]. A series of experiments using a rabbit model reported these leaked pulmonary surfactant apoproteins in the serum to be an accurate marker and predictor for later lethal radiation pneumonitis. Serum pulmonary surfactant proteins A (SP-A) and D (SP-D) were reported to be useful markers for the early detection of radiation pneumonitis after thoracic irradiation [(17)].

Type II pneumocytes are suggested to be early targets of radiation pneumonitis, releasing surfactants into the alveoli shortly after radiation exposure and maintaining this release for days or weeks. Moreover, the permeability of endothelial cells is increased facilitating surfactants in the alveoli in entering the systemic blood circulation. Four surfactant proteins (SP-A, SP-B, SP-C and SP-D) have been identified within pulmonary surfactant [(18)].

The development of radiation pneumonitis was due to overproduction, not proteolysis of surfactant proteins. With these lung tissue-specific biochemical markers capable of detecting early radiation pneumonitis, more intensive radiotherapeutic strategies would be feasible [(17)].

5. KL-6; the lung epithelium-specific protein **Krebs von den Lungen-6**, is believed to be produced and secreted by type II pneumocytes. KL-6 offers a new perspective as a marker in interstitial lung disease. Serum KL-6 is elevated in a majority of patients with interstitial lung disease and is normal in patients with bacterial pneumonia or in healthy subjects. KL-6 levels depend on the number of regenerating type II epithelial cells and the integrity of the alveolar-capillary membrane. KL-6 is chemotactic for human fibroblasts and may also play a functional role in fibrosis. KL-6 was reported to reflect the severity of radiation inflamation, and the increase (>1.5-fold) was associated with serious radiation inflamation that was refractory to steroid therapy [(17)].

KL-6 is a useful marker for prediction of the occurrence of radiation pneumonitis after single, fractional, high-dose stereotactic irradiation of lung tumors.37. In a study of 39 patients treated with fractionated radiation therapy, blood KL-6 levels at 40 Gy of thoracic radiotherapy were found to be elevated significantly in patients who developed radiation pneumonitis compared with patients without radiation pneumonitis [(19)].

6. Thrombomodulin: Thrombomodulin (TM) is a transmembrane endothelial cell glycoprotein functioning as an endogenous anticoagulant to maintain the normal thrombohemorrhagic balance. During inflammation, radiation and microvascular injury, thrombomodulin is down-regulated as well as released from the endothelial cell membrane into the circulation. Plasma thrombomodulin levels decreased during the early phase of radiation therapy in most patients, returning to baseline levels towards the end of treatment. Patients who did not develop radiation pneumonitis exhibited a moderate but statistically significant decrease in thrombomodulin levels, compared to patients who developed pneumonitis, particularly during the first 2 weeks of

treatment. These findings suggest that a decreased release of thrombomodulin early during radiation therapy may be associated with reduced pulmonary toxicity. However, further studies are required to assess the use of plasma thrombomodulin as an early marker of pulmonary damage [20].

B) Chemokines are chemotactic proteins that recruit inflammatory cells to irradiated tissues and, like interleukins, can activate inflammatory cells. Prolonged or high expression of these proteins, as with the angiogenic peptides, has been associated with delayed radiation side effects that emulate autoimmune disease [15].

C) Growth factors is double-edged swords that cause the proliferation and maturation of stem and progenitor cells. These typically reduce the early side effects of radiation but can be a cause of deleterious changes to organ architecture and premature differentiation of stem cells leading to later organ dysfunction [21].

4) Polymorphonuclear leukocyte (PMN) and CD34+ markers in response to radiation:

PMN: Ionizing radiation damages the lymphohematopoietic system via direct effects on viability and/or function of hematopoietic stendprogenitor cells and via abnormal production of cytokines (i.e., growth factors). Other tisues that have a rapid turnover (including the gastrointestinal tract and skin) are also profoundly affected by acute radiation exposure. A major issue in selection of appropriate therapy for bone marrow failure (i.e., the bone marrow syndrome) is early assessment of radiation dose. Although several biological markers are available for assessing dose received, the absolute polymorphonuclear neutrophil (PMN) and/or lymphocyte counts, together with clinical presentation (i.e., time to onset of nausea and vomiting, etc.) still provide the most practical and timely assessment of radiation dose[22].

CD34: Limited information is available regarding CD34+ cell frequency as a measure of radiation-induced damage to the bone marrow. Primitive hematopoietic stem cells are known to express the CD 34 surface antigen, a 110 kDa glycoprotein encoded by a gene located on human chromosome l q. Since a subpopulation of radioresistant hematopoietic stem cells may persist after exposure to high-dose radiation, the primary goal of therapy is to provide an adequate number of lymphohematopoietic stem cells for a finite (rather than indefinite) period, after which endogenous stem cells may reinstate lymphohematopoiesk[23]. At this time, the absolute PMN and leukocyte counts appear to be the most rapid and useful parameters to assess biological dose to the bone marrow. Studies examining the frequency of CD34+ cells after exposure must be completed to determine the sensitivity, specificity and predictive value of this parameter in selection of individuals for cytokine therapy and/or stem cell transplantation[23].

5) Protein markers in response to radiation: Marchetti et al.[24] agreed that the first 48 h after a radiological accident involving masses of people are crucial. In that time period, the accident victims should be processed by an emergency triage system where the patients are scored on the basis of both clinical and biological criteria. In such a scenario, the patients are scored and temporarily placed into three levels: 1) patients with a score of 1 can be followed up on an outpatient basis or be treated by the equivalent of a day care hospital; 2) patients with a score of 2 are those patients who need maximum medical attention if they are to survive; 3) patients with a score of 3 are those patients who are predicted to develop MOF (multi-organ failure) and, unfortunately, have almost no chance of recovery [25]. It has been pointed out that the dose itself is not sufficient to predict multiple organ dysfunction syndromes (MODS). It was argued that at the level of the organ, biological dosimetric indicators should be complemented by bioindicators of prognosis and diagnosis. Some of these indicators appeared promising. Fms-related tyrosine kinase 3 ligand (Flt3-L) to assess the hematopoietic system, citrulline as an indicator of the digestive tract, and several oxysterols as lipid metabolism and vascular markers. They refer to either structural or functional alterations. The final aim is to establish a cartographic system of organ damage to predict MODS and, eventually, to multi organ failure[26].

6) Gene expression and amplification in response to radiation and the status of microarray analysis: While mRNA expression profiles is of great interest and is

expected to continue to grow rapidly. Most clinical studies to date feature cultured cells and are thus limited to lymphocytes and fibroblasts. Based on the assumption that ionizing radiation hypersensitivity may reflect inherited genetic defects associated with abnormal transcriptional responses to radiation, the investigation of differences in the transcriptional response by high through-put gene expression profiling may be a valid approach to identifying individuals at risk of side effects[27]. In recent years, microarray technology has been increasingly used in the field of cancer research, and analysis of gene expression have been conducted on irradiated cells from cancer and normal tissue, or on lymphocytes in order to understand the side effects of ionizing radiation toxicity. The majority of the studies used RNA from biopsies in an attempt to identify prognostic classifiers[28]. Many analysis have been conducted on normal tissues to understand their constitutive response to ionizing radiation and possibly to identify distinctive genes for sensitive individuals that could be used as biomarkers for predicting radiosensitivity. The first studies by Quarmby et al.[29] on gene expression were conducted on single genes or on gene families such as cytokines, TNF-α or growth factors involved in mediating ionizing radiation toxicity. In another study by Rieger et al.[30] using more advanced arrays with far more transcripts, 14 patients with unusual skin reactions were compared with 43 others with more normal responses. They found 24 genes that predicted toxicity in 9 of 14 patients; however, the genes represented by their transcripts differed from those identified by Quarmby et al.[29].

Future of research for molecular markers of normal tissue tolerance: We do not yet have adequate markers for the vast majority of clinical needs, and their discovery remains a very high priority in radiation research. The need for these markers has intensified due to the growing number of cancer survivors at risk for developing toxicity from radiation, chemotherapy, surgery, and combinations of all three. Currently the number of cancer treatment survivors is numbered at over 10 million in the United States and is growing rapidly. This number dwarfs the number of new cancers detected each year. The National Cancer Institute has identified survivorship research as a high priority over the next decade. Cooperative clinical trial groups are beginning to design studies aimed at determining the best management of treatment related side effects (rather than just how to manage cancers). Concurrent with the growing number of cancer-treatment survivors is the real risk for radiological exposure of otherwise healthy victims in an accident, an act of terror, or war related scenarios. Taken together, the need for better markers is growing rapidly and is of high importance considering the lack of currently available markers. As the cooperative group clinical trials grow, and the funding for research in the area increases, progress in identifying markers for prediction, prognostication, mitigation, and therapy is expected to be rapid in the next decade.

Conclusion:

- Markers of radiation-related side effects include those that can be used to identify subjects at risk of greater than normal toxicity, before exposure.
- Markers useful for diagnosis, prognosis, biodosimetry, and therapy.
- The available markers are often organ-specific, and some are in routine use; however, there are currently very few markers and many organs-at-risk have no satisfactory markers.
- The most useful markers are those that are most specific and quantitatively predictive of side-effect severity.
- The available markers include physiological markers. Among these markers, cytokines appear to play the role of both causative agent and marker.
- The evidence has demonstrated a potential value of determining the early response of blood markers to ionizing radiation in predicting latent radiation toxicity, which may be used for planning individualized treatment regimens.
- Gene expression profiles might ultimately play a role in better understanding normal tissue tolerances to radiation.
- The future of research on markers of radiation tolerance is increasingly important due to the growing number of cancer treatment survivors.

• Although no validated blood markers are currently available for daily practice, further research in this area has become important.

Referernces:

1. Donnelly EH, Nemhauser JB, Smith JM *et al.* (2010). "Acute radiation syndrome: assessment and management". South. Med. J., 103 (6): 541–6.
2. Stewart FA (2007). Gene expression arrays as a tool to unravel mechanisms of normal tissue radiation injury and prediction of response. World J. Gastroenterol.,13(19):2669–2674.
3. Reeves GI and Ainsworth EJ (1995). "Description of the chronic radiation syndrome in humans irradiated in the former Soviet Union". Radiat. Res., 142 (2):242–3
4. Chapman JD and Allalunis-Turner MJ (1991). Cellular and molecular targets in normal tissue radiation injury. In: Gutin, PH.; Liebel, SA.; Sheline, GE., editors. Radiation Injury to The Nervous System. New York: Raven;. Pp. 1-16.
5. Finkelstein JN, Johnston CJ, Baggs R and Rubin P (1994). Early alterations in extracellular matrix and transforming growth factor beta gene expression in mouse lung indicative of late radiation fibrosis. Int. J. Radiat. Oncol. Biol. Phys., 28 (3):621–631.
6. Stewart FA (2007). Gene expression arrays as a tool to unravel mechanisms of normal tissue radiation injury and prediction of response. World J. Gastroenterol., 13(19):2669–2674.
7. Dertinger SD, Miller RK, Brewer K, Smudzin T, Torous DK, Roberts DJ *et al.* (2007). Automated human blood micronucleated reticulocyte measurements for rapid assessment of chromosomal damage. Mutat. Res., 626 (12): 111–119.
8. Okunieff P, Chen Y, Maguire DJ and Huser AM (2008). Molecular Markers of Radiation-related Normal Tissue Toxicity. Cancer Metastasis Rev., 27 (3): 363–374.
9. Zhou YC, Liu JY, Li J, Zhang J, Xu YQ, Zhang HW, Qiu LB *et al.* (2011). Ionizing radiation promotes migration and invasion of cancer cells through transforming growth factor-beta-mediated epithelial-mesenchymal transition. Int. J. Radiat. Oncol. Biol. Phys., 81(5):1530-7.
10. De Jaeger K, Seppenwoolde Y, Kampinga HH *et al.* (2004). Significance of plasma transforming growth factor-beta levels in radiotherapy for non-smallcell lung cancer. Int. J. Radiat. Oncol. Biol. Phys., 58 :1378-1387.
11. Arpin D, Perol D, Blay JY *et al.* (2005). Early variations of circulating interleukin- 6 and interleukin-10 levels during thoracic radiotherapy are predictive for radiation pneumonitis. J. Clin. Oncol., 23: 8748-8756.
12. Williams J, Chen Y, Rubin P, Finkelstein J and Okunieff P (2003). The biological basis of a comprehensive grading system for the adverse effects of cancer treatment. Semin. Rad. Oncol., 13: 182-188.
13. Borska L, Andrys C, Krejsek J, Hamakova K, Kremlacek J, Ettler K and Fiala Z (2008). Serum levels of the pro-inflammatory cytokine interleukin-12 and the anti-inflammatory cytokine interleukin-10 in patients with psoriasis treated by the Goeckerman regimen. Int. J. Dermatol., 47 (8): 800-805.
14. Hart JP, Broadwater G, Rabbani Z, Moeller BJ, Clough R, Huang D *et al.* (2005). Cytokine profiling for prediction of symptomatic radiation-induced lung injury. Int. J. Radiat. Oncol. Biol. Phys., 63:1448-1454.
15. Ishii Y and Kitamura S (1999). Soluble intercellular adhesion molecule-1 as an early detection marker for radiation pneumonitis. Eur. Respir. J., 13: 733-738.
16. Sasaki R, Soejima T, Matsumoto A *et al.* (2001). Clinical significance of serum pulmonary surfactant proteins A and D for the early detection of radiation pneumonitis. Int. J. Radiat. Oncol. Biol. Phys., 50:301-307.
17. Wutzler S, Lehnert T, Laurer H, Lehnert M, Becker M, Henrich D, Vogl T and Marzi I (2011). Circulating levels of Clara cell protein 16 but not surfactant protein D identify and quantify lung damage in patients with multiple injuries. J. Trauma, 71(2):E31-6.
18. Anscher MS, Marks LB, Shafman TD *et al.* (2003). Risk of long-term complications after TGF-beta1-guided very-high-dose thoracic radiotherapy. Int. J. Radiat. Oncol. Biol. Phys., 56: 988-995.
19. Hauer-Jensen M, Kong FM, Fink LM and Anscher MS (1999). Circulating thrombomodulin during radiation therapy of lung cancer. Radiat. Oncol. Investig., 7 (4): 238-42.
20. Dainiak N and Sorba S (2009). Early identification of radiation accident victims for therapy of bone marrow failure. Stem Cells, 15 (4) :275-285.
21. Walden TL and Farzaneh NK (1991). Biochemical response of normal tissues to ionizing radiation. In: Gutin, PH.; Liebel, SA.; Sheline, GE., editors. Radiation Injury to the Nervous System. New York: Raven; Pp. 17-36.
22. Dainiak N, Waselenko JK, Armitage JO, Mac TJ and Farese AM(2003). The hematologist and radiation casualties. Hematol. Am. Soc. Hematol. Educ. Program, 473-96.
23. Farooque A**,** Singh N**,** Adhikari JS**,** Afrin F and Dwarakanath BS (2014). Enhanced antitumor immunity contributes to the radio-sensitization of ehrlich ascites tumor by the glycolytic inhibitor 2-deoxy-d-glucose in mice. Los One. Sep., 23(9): 108-121.
24. Gorin NC, Fliedner TM, Gourmelon P, Ganser A, Meineke V, Sirohi B *et al.* (2006). Consensus conference on European preparedness for haematological and other medical management of mass radiation accidents. Ann. Hematol., 85: 671-9.
25. Roy L, Bertho JM, Souidi M, Vozenin MC, Voisin P and Benderitter M (2005). Biochemic approach to prediction of multiple organ dysfunction syndromes. BJR, Suppl., 27:146-51.
26. Akashi M, Hirama T, Tanosaki S, Kuroiwa N, Nakagawa K, Tsuji H *et al.* (2001). Initial symptoms of acute radiation syndrome in the JCO criticality accident in Tokai-mura. J. Rad. Res., 42(Suppl): S157-66.
27. Cen L, Carlson BL, Schroeder MA, Ostrem JL, Kitange GJ, Mladek AC *et al.* (2012). p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. Neuro Oncol., Jul., 14(7):870-81.
28. Henriquez HLA, Lara PC, Pinar B *et al.* (2009). Constitutive gene expression profile segregates toxicity in locally advanced breast cancer patients treated with high-dose hyperfractionated radical radiotherapy. Radiat Oncol, 4:17.
29. Quarmby S, West C, Magee B, Stewart A, Hunter R and Kumar S (2002). Differential expression of cytokine genes in fibroblasts derived from skin biopsies of patients who developed minimal or severe normal tissue damage after radiotherapy. Radiat. Res., 157(3):243–248.
30. Rieger KE, Hong WJ, Tusher VG, Tang J, Tibshirani R and Chu G (2004). Toxicity from radiation therapy associated with abnormal transcriptional responses to DNA damage. Proc. Nat. Acad. Sci. U S A., 101 (17): 6635–6640.