Pathologic Cancer Staging by Measuring Cell Growth Energy

Emad Y. Moawad

Ain Shams University, Cairo, Egypt Dept. of Engineering
*Corresponding Author: emadmoawad@hotmail.com

Copyright © 2013 Horizon Research Publishing All rights reserved.

Abstract The aim of this research is to establish a pathologic cancer staging by measuring Cell Growth Energy (CGE) contributes to treatment management and helps to administer the appropriate low-waste dose for all cancer therapies. Regarding cancer as a cell cycle disruption disease; Nitrogen-containing bisphosphonates (NBP) Alendronate (ALN) of different concentrations were added to samples of Normal Human Epidermal Keratinocytes (NHEKs) (20,000Cell /sample) to inhibit their growth rate to model cancer effects on normal cells, [^{14}C] thymidine was added at $0.5 \mu\text{Ci/ml}$ to each of control sample and those of cell cycle arrest (with NBPs) to monitor the Cell Growth Energy (CGE) which expresses all aberrant activations of cell that lead to cancer development and simply describes the cancer stage of the cell. Radioactivity incorporated (% of control) at 37°C was determined as a measure of cell rate of growth at 24-h intervals for 3 days using a Top Count NTX micro plate scintillation counter. NHEKs rate of growth for sample with NBP of concentration $10 \mu\text{M}$ ALN was the closest to that of induced carcinomas, equivalent to 87% of that of the normal counterpart as measured by [^{14}C] thymidine incorporation ($p < 0.001$). As inhibition to rate of growth of this sample was 13% compared to the control, cell doubling time was increased consequently to 1.13 times that of cells of the control sample. By equalizing growth energy of this sample to the energy of the induced inhibition to [^{14}C] thymidine incorporation, CGE gained due to cell cycle arrest was $4862 \text{ MeV} = 0.21 \text{ Emad}$. According to Emad formula the corresponding cell doubling time is 1.12 times that of cells at the stage of Natural Background Radiation. This is 99% identical to what has been measured experimentally at 1.13 times that of control cells to confirm and provide a clear-cut criterion for accepting the CGE test for cancer staging.

Keywords Cancer Staging, Cell Growth Energy, Emad Formula

continuously. A classification scheme for cancer must encompass all attributes of the tumor that defines its life history. Stages of cancer express the extent that cancer has spread, and are usually described by numbers I to IV with IV having more progression. Such staging is considered very wide and unspecified, allows for either of over or lower estimated dose that contributes to risks of tumor regrowth and metastasis [1]. In addition, reasonable classification should be based on the premise that cancers of the same anatomic site and histology share similar patterns of growth and extension. There are two types for cancer staging, clinical and pathologic where both are considered a supplement for each other [2]. Clinical stage is based on all of the available information obtained before a surgery to remove the tumor, while pathologic stage adds additional information gained by examination of the tumor microscopically after surgery expressing the stage before therapy only [3]. E. Moawad has introduced a clinical staging by imaging techniques allow accurate cancer staging that helps to administer the appropriate low-waste dose and modify it by monitoring an earlier response to therapy which contributes besides developing dose -delivery skills to the success of all types of cancer treatments [4]. Thus, there is a need arises for innovative pathological solution to improve identification of effective diagnostic tool based on an individual's unique tumor well-tolerated with acceptably low rates of false positive and false negative results, to be parallel to what applied and achieved in the clinical staging. It is well known that in all cancer stages from early to advanced disease, cancer cells are known to have alterations in multiple cellular signaling pathways drives normal cell to carcinoma [5]. One of the most important signals is the continuous deficit in cell proliferation rate accompanied by a progressive cell cycle arrest along those stages [6]. Significant efforts have been made to understand the kinetic analysis of cell proliferation that drives cancer development and progression [7]. Basis of such efforts, there is as yet little to distinguish the cancerous cell from a variety of normal cells which have also been analyzed [6]. [^{14}C] thymidine is commonly used in vitro in cell proliferation assays. The thymidine is incorporated into dividing cells and the level of this incorporation, measured using a liquid scintillation

1. Introduction

Staging of cancer is not a fixed science but advancing

counter, is proportional to the amount of cell proliferation [8]. Latter have attributed the considerable variation in the percentage of labeled cells that indicates cell proliferating for similar histological cancerous tissues to errors in the technique [9]. A similar variation in tumor response to radiotherapy or chemotherapy has been observed frequently by clinicians in patients of tumors appear identical by all gross and histological parameters; in some the tumors may respond effectively, whereas in the others the tumors are unaffected by the drug and rapidly disseminate and kill them [10]. So that latter concluded that dosimetry never inherits identical results! [11]. Recently, such mysterious variations in tumor response have been explained after discovering cell growth energy (CGE) that expresses all the aberrant genetic variations that drive normal cell to carcinoma [1, 4]. As it is well known the significant correlation between the in vitro inhibition of thymidine incorporation by tumor slices and the response of patients to cancer therapy [10], current study aims to apply the same methodology used in investigating tumor response to therapy as shown by E. Moawad [1, 4], on measuring cell proliferating to distinguish the normal tissue from the cancerous one to establish an efficient cancer screening by a reasonable classification for staging of cancer.

2. Mathematical Model

The relation between cell Doubling Time (t_D) and CGE has been derived and presented by E. Moawad which is known by Emad formula as follows:

$$CGE = \ln \left[\ln \frac{\ln 2}{t_D} \right]^2 \text{ Emad} \quad (1),$$

$$\text{Emad} = 23234.59 \text{ MeV} \quad (2) [1, 4, 12-16].$$

Consequently, it is possible to determine CGE of each signal pathways from normal state to carcinoma by knowing the corresponding cell t_D of each stage through a pathologic staging. And conversely by knowing CGE stage through other clinical staging, cell t_D signatures can be predicted to distinguish all different stages of human cell. Classification of CGE stages can be settled according to studies of radiation effects at low and high doses [17-19]. These studies have posited that Natural background radiation (NBR) is the standard of the healthy stage of CGE of living organisms which corresponds to

$$E_{\text{NBR}} = 0.0000538132 \text{ Emad} / \text{Cell} \text{ or } 1.25 \text{ MeV/Cell} \quad (3) [1, 17 \text{ and } 18],$$

where this healthy stage of CGE corresponds to cell t_D according to Emad formula equivalent to

$$t_{D,\text{NBR}} = \ln 2 \times e^{\sqrt{e^{E_r}}} = \ln 2 \times e^{\sqrt{e^{0.0000538132 \text{ Emad}}}} = 1.884220083 \text{ Sec} \quad (4) [1, 17-19].$$

Accordingly, CGE stages $\leq E_{\text{NBR}}$ are considered harmless to man health. While the observational evidence for radiation-induced cancer in humans comes largely from the long term exposure to effects at Low Dose Radiation (LDR). Thus, for the setting of environmental standards and for gauging the consequences of exposures routinely received by the general public, the most important doses are relatively small doses received over long periods of time. Several official organizations e.g. the Committee on the Biological Effects of Ionizing Radiations of the National Research Council (BEIR) have settled these consequences [17]. Taking the dose-rate effectiveness factor, DREF into account, as well as other minor differences in the estimates, an overall consensus estimate for low doses and low dose rates is: risk of eventual fatal cancer: 0.05 per Sv (0.0005 per rem). This risk factor can be taken to apply to an "average person" but in its most precise form applies to a general population. Consider a population of 100,000, with a representative distribution by age and sex. Then, for example, if each person receives a 20 mSv dose, the collective exposure is 2000 person-Sv and the calculated number of excess eventual cancer deaths is 100 [17]. Accordingly the long term exposure to this LDR of 20 mSv which corresponds to

$$E_{\text{LDR}} = 0.000538132 \text{ Emad} / \text{Cell}$$

$$\text{or } 12.5 \text{ MeV/Cell} = 10 E_{\text{NBR}} \quad (5)$$

and cell $t_D \Rightarrow$

$$t_{D,\text{LDR}} = \ln 2 \times e^{\sqrt{e^{E_r}}} = \ln 2 \times e^{\sqrt{e^{0.000538132 \text{ Emad}}}} =$$

$$1.884676488 \text{ Sec} = 1.00024222 t_{D,\text{NBR}} \quad (6) [1, 17 \text{ and } 18],$$

can be settled as a beginning of the carcinogenic risk, where all living organisms would be affected if their CGE stage $\geq E_{\text{LDR}}$, and can be considered on the way to get cancer [19].

Accordingly, the exposure to higher levels of radiation energy than that of LDR increases risks of different effects that ranged from faster tumor formation, or tissue damage lead to death or spontaneous death. Then it is important to determine the maximum tolerated dose that can be used in radiotherapy to avoid such lethal effects; O'Donoghue et al. showed that the sizes of individual administrations were set by the requirement that the whole-body burden of radioactivity must not exceed 1.1 GBq (30 mCi) [20], which corresponds to decay energy of Maximum Tolerated Dose (MTD)

$$E_{\text{MTD}} = 0.000658485 \text{ Emad} / \text{Cell} = 15.28 \text{ MeV/Cell} = 12.224 E_{\text{NBR}} \quad (7)$$

and

cell $t_D \Rightarrow$

$$t_{D,\text{MTD}} = \ln 2 \times e^{\sqrt{e^{E_r}}} = \ln 2 \times e^{\sqrt{e^{0.000658485 \text{ Emad}}}} = 1.884789939 \text{ Sec} = 1.00030244 t_{D,\text{NBR}} \quad (8) [1, 17 \text{ and } 18]$$

18]. cells/sample to derive CGE for each sample.

Thus, if CGE stage $\geq$ MTD, cell is considered cancerous. According to this staging of CGE presented by E. Moawad, tissue of CGE less than LDR effects which equal to 12.5MeV or 10 NBR is considered normal. While tissue of CGE stage higher than 10 NBR is considered on the way to get cancer expressed through initiation of aberrant genetic variation along with a slightly increase of cell cycle duration. Once tissue CGE stage reaches MTD effects which equal to 15.28 MeV or 12.224 NBR, tissue is considered malignant and patient should undergo a cancer treatment its management should take CGE in consideration. Thus, CGE stages are identified as follows: 1st Healthy stage at NBR $\rightarrow$ 10NBR, 2nd Initiation of cancerous changes stage at 10 NBR $\rightarrow$ 12.224 NBR, 3rd Cancerous stage at $\geq$ 12.224 NBR [17, 18]. Since the presented CGE staging in terms of NBR has been settled down through epidemiological studies depending on statistics to develop comprehensive cancer risk estimates from exposure to low-level ionizing radiation though at low doses (100 mSv or less) statistical limitations make it difficult to evaluate such estimates in humans [19]. Then, to strengthen confidence in these estimates that related to NBR level, the following is an experiment to check that level settled down through epidemiological studies and to provide a methodology of cancer screening through staging of CGE.

2.1. Cancer Screening through CGE Staging

Monitoring of cell cycle and its phases can be identified utilizing methods of labeled thymidine. It is well known that the thymidine is incorporated into dividing cells, where the incorporation rate increases and reaches its maximum at 48 h after which it decreases. The level of this incorporation, measured using a scintillation counter, is proportional to the amount of cell proliferation of the tissue studied. Recent clinical applications have disclosed that Nitrogen-containing bisphosphonates (NBPs) have powerful effect to induce cell cycle arrest inhibiting cell growth in a dose-dependent manner without inducing apoptosis [8]. Thus to identify stage of cancer, CGE test was performed on samples of cells of different cell cycle duration to model different stages of cancerous effects by adding different concentrations of NBPs to those samples. Cell proliferating rate for samples as a percentage of the control one (without NBPs) was measured by [^{14}C] thymidine incorporation, knowing that the rate of cell growth measured by a scintillation counter, is unaffected by the addition of thymidine to these concentrations. Accordingly, inhibition to cell proliferating rate for samples shown by the deficit of [^{14}C] thymidine incorporation as a percentage of the control one (without NBPs) represents energy gained by cells of these samples due to all genetic and aberrant activations resulted in that cell cycle arrest. Consequently, percentage of the deficit of [^{14}C] thymidine incorporation in those samples compared to the control one is equivalent to the growth energy acquired by each sample, which can be divided by number of

2.2. For Cell Cycle Analysis

As conducted and described by Reszka et al. [8], Normal human epidermal keratinocytes (NHEKs) were seeded (100,000 cells/6 cm dish) - (20,000/well) - in KGM and grown 24 h. Treatments lasted 48 h to allow depletion of intracellular pools of isoprenoids and subsequent growth arrest. Cells were released with trypsin/EDTA (Clonetics) and then fixed in 70% ethanol at 220°C overnight. It is notable that NHEKs treated 72 h with nitrogen-containing bisphosphonates (NBPs) [alendronate (ALN)] of 5 different concentrations (0 for control sample, 10, 30, 100, and 300 μM) adhered tightly to the tissue culture plastic and could not be detached with trypsin/EDTA for analysis (data not shown). Fixed cells were treated with Rnase A (100 mg/ml in H₂O; Boehringer Mannheim, Germany) for 5 min at room temperature, and then propidium iodide (50 mg/ml; Sigma, St. Louis, MO) was added for an additional $\geq$ 30 min at room temperature. Cells (20,000 cells/sample) were sorted by FACS (FACS Calibur; Becton Dickinson, San Jose, CA), using 488 nm excitation, recording emitted fluorescence at 620 nm. [^{14}C] thymidine (NEN, Boston, MA) was added at 0.5 $\mu\text{Ci/ml}$ along with indicated pharmacological agents (all synthesized or purified at Merck and Co., Inc., West Point, PA). Radioactivity incorporated (% of control) at 37°C was determined as a measure of cell growth at 24-h intervals for 3 days using a Top Count NTX micro plate scintillation counter. Triplicate data were analyzed by ModFit LT (Verity Software House Inc., Topsham, ME) and ANOVA factorial method.

3. Results

Cell proliferation measured by [^{14}C] thymidine incorporation, did not cause apoptosis, cell detachment, or activation of stress-responsive kinases (data not shown) [8]. Inhibition of NHEKs rate of growth was observed starting from 10 μM ALN (87% of control), significant inhibition of NHEK growth was observed at 30 mM ALN (47% of control), with complete inhibition at (100 to 300) μM ALN (20% of control) where full growth rate arrest was observed, as measured by [C-14] thymidine incorporation [8].

3.1. Physical Analysis

NHEKs (20,000/well) were seeded into scintillating microplates and rate of growth was assessed after 72 h incubation with ALN [^{14}C] thymidine incorporation as a percentage of that of the control sample. As dose concentration increased gradually from 0 $\rightarrow$ 10 $\rightarrow$ 30 $\rightarrow$ (100 $\rightarrow$ 300) μM , [^{14}C] thymidine incorporation (% of control) decreased gradually from 100% $\rightarrow$ 87% $\rightarrow$ 47% $\rightarrow$ 20% respectively ($p < 0.001$). Thus, inhibition to rate of

growth increased gradually from 0% → 13% → 53% → 80 % of that of the control sample respectively. Consequently, the corresponding values of cell t_D which expresses these different CGE stages had been increased gradually from $t_{D,Control} \rightarrow 1.13 t_{D,Control} \rightarrow 1.53 t_{D,Control} \rightarrow 1.8 t_{D,Control}$ as shown in figure (1).

Figure 1. shows a comparison of the rate of growth and cell doubling time in induced cell cycle arrest samples and the control one ($p < 0.001$).

As cell t_D of these stages have been expressed as ratios of that of the control stage, then such staging of CGE can be checked to prove efficacy of cancer staging by proving conformity of $t_{D,Control}$ and $t_{D,NBR}$ that settled by E. Moawad for the NBR and shown in Eqt (4), by measuring CGE of the closest sample model to cancer effects of cell cycle arrest shown in Eqt (4), Eqt (6) and Eqt (8), and then determining its corresponding cell t_D using Emad formula

shown in Eqt(1) to check $t_{D,Control}$ compared by $t_{D,NBR}$ shown in Eqt (4) as will be shown in the following: In the experiment previously reported, $[^{14}C]$ thymidine was employed in the growth medium at a concentration of $0.5 \mu Ci/ml$, then the initial radioactivity of each sample was equivalent to $\Rightarrow E_{Each.Sample} = 0.5 \times 10^{-6} \times 3.7 \times 10^{10} \times$

$$\frac{5730 \times 3.16 \times 10^7}{\ln 2} \times 0.156 = 7.539 \times 10^{14} \text{ MeV. Knowing}$$

that NHEKs (20,000/sample) growth was assessed after 72 h incubation with the ALN then the released energy per

$$72h/cell \Rightarrow \text{Released Energy}_{/Cell} = \frac{7.539 \times 10^{14}}{20000}$$

$$\times (1 - e^{\frac{-\ln 2 \times 72 \times 60 \times 60}{5730 \times 3.16 \times 10^7}}) = 37402.5 \text{ MeV. Thus CGE for each}$$

sample can be identified. The sample of the closest CGE to what previously classified for staging of CGE was the sample of concentration $10 \mu M$ ALN. Thus, the CGE of the cancerous model sample was $37402.5 \times 0.13 = 4,862 \text{ MeV} = 0.21 \text{ Emad}$, using Emad formula the cell t_D of this sample

$$\text{was } t_D = \ln 2 \times e^{\sqrt{e^{E_r}}} = \ln 2 \times e^{\sqrt{e^{0.21 \text{ Emad}}}} = 2.105 \text{ Sec} = 1.12$$

$t_{D,NBR}$ which is 99% identical to what has been identified experimentally at $1.13 t_{D,Control}$ to confirm the conformity of $t_{D,Control}$ and $t_{D,NBR}$, efficacy of classification of CGE stages assessed on NBR basis settled down by E. Moawad and BEIR [1, 17-19] and to provide a clear-cut criterion for accepting the CGE test for cancer staging.

4. Discussion

Cancer screening by monitoring the variations in the kinetics of cell proliferation of normal tissue and that of malignant one give a complete figure for cancer incidence as a result of energy balances. As cell cycle arrest associated with a failure in apoptosis is commonly shared by all types of malignant cells [17, 18], NBP (ALN) was added to samples of normal cells with different concentrations to model cancerous cells of different stages. This was because of recent clinical applications having disclosed that NBPs have powerful effect to inhibit cell growth in a dose-dependent manner without inducing apoptosis [8]. Since the tumor cell and normal cell have usually been measured independently and seldom derive from corresponding tissues, possible differences between tumor and normal may be obscured by larger differences between distinctive cell types. Therefore current approach distinguishes the kinetics of a carcinogenically induced tumor and a normal tissue in an instance where the correspondence of these tissues is reasonably assured. The kinetic analysis is based on measurements of the incorporation of $[^{14}C]$ thymidine in vitro in the normal tissue and that of induced rate of growth inhibition. Our results are consistent with the hypothesized equalization between inhibition to cell proliferating rate which represents energy gained by cells of these samples due to all genetic and aberrant activations resulted in that cell cycle arrest and the deficit of $[^{14}C]$ thymidine incorporation. Motives behind this hypothesis are the symmetry of the tested tissue samples, besides to the principle of work and energy which states that the energy necessary to affect kinetics is of a sufficient level to induce that effect [4]. Conformity of the results of the provided experiment to estimates of cancer risks settled down through epidemiological studies strengthens the confidence in these estimates and confirms such hypothesis for the mechanism of cancer incidence in the same time. Much evidence also supports such mechanism for cancer incidence which explains many mysterious issues. For instance, despite that radiation is a potential cause of cancer [21- 26], radiation therapy has been in use as a cancer treatment for more than 100 years. Then there are two radiation levels for two different effects, one led to tumor formation, while other for tumor cure according to CGE of the exposed tissue [1]. Another finding supports the strong direct correlation between growth rate inhibition and the CGE which is the greater resistance to all types of cancer therapies of the hypoxic tumor cells for its higher CGE due to lower nutrient

and oxygen supply to these cells for a long term cause them to divide more slowly [27], their cell t_D would be longer and hence their CGE would be higher as shown from Eq (1). Moreover, it is recommended in radiotherapy to measure the CGE of cancerous tumors prior the treatment to administer the equivalent decay energy of the radioactive dose [1, 4, 12-16]. And as is usually the case, current thesis suggests approving a new histogram for Dose-Tumor energy instead of the current one for Dose-Tumor volume to settle down a new protocol for cancer treatments. This recommendation explains why the fast growing tumor responds efficiently, compared by the slow growing one of same size to same dose of cancer therapy due to its comparable lower growth energy for its shorter doubling time [1, 4, 12-18]. Thus, it is clear from this much evidence that stage of CGE is the best expression of the stage of cancer. Wide classification of CGE into three stages is primarily focusing on detecting presence of cancer and administering the appropriate low-waste dose for all cancer therapies as well. Nevertheless, further studies are strongly warranted for investigating the evolution of the CGE along man's life from birth till death, to target intensive classification to CGE stages that helps in predicting and controlling man health. Despite [^{14}C] thymidine has been used by latter in vitro in cell proliferation assays 50 years ago and may be more, they haven't attributed variations in [^{14}C] thymidine incorporation in similar histological tissues to variations in CGE of those tissues. This revealed the importance of Emad formula, which calculates the growth energy of the growing systems that follows the exponential growth by knowing its growth constant. This is allowed for the first time to measure the biological growth energy in MeV or Joules, to asses the stages of energy that allow the kinetic cellular alteration process accompanied to the genetic variation that derive the normal tissue to carcinoma.

5. Conclusion

Validity of CGE staging results as a diagnostic tool recommends to be considered as more reliable test with promising efficacy and low costs to obtain a more accurate assessment as to whether cancer is present besides to staging it. Therefore, strategies that directly query signaling pathway activation via CGE assays in individual cancer are expected to provide important insights into the molecular "logic" that distinguishes cancer and normal tissue on one hand, and enables personalized intervention means on the other.

Conflict of Interest

The author declares that there is no conflict of interest concerning this paper.

REFERENCES

- [1] Emad Y. Moawad Radiotherapy and risks of tumor regrowth or inducing second cancer. *Cancer Nanotechnology* (2011) 2:81–93
- [2] Eric Lucas (2006-01-31). "FIGO staging of cervical carcinomas". Screening.iarc.fr. <http://screening.iarc.fr/viavili/appendix1.php>. Retrieved 2010-10-14
- [3] Gøtzsche, Peter C; Nielsen, Margrethe (2011). "Screening for breast cancer with mammography". *Cochrane database of systematic reviews* (1): CD001877. doi:10.1002/14651858.CD001877.pub4. PMID 21249649.
- [4] Emad Moawad. Isolated System Towards A Successful Radiotherapy Treatment, *Nuclear Medicine and Molecular Imaging* (2010) 44:123–136
- [5] Wu C-J, Cai T, Rikova K, Merberg D, Kasif S, et al. (2009) A Predictive Phosphorylation Signature of Lung Cancer. *PLoS ONE* 4(11): e7994. doi:10.1371/journal.pone.0007994
- [6] Allan B. Reiskin and Mortimer L. Mendelsohn, A Comparison of the Cell Cycle in Induced Carcinomas and Their Normal Counters, *Cancer Res* 1964;24:1131-1136.
- [7] W. Jeffrey Allard, Jeri Matera, M. Craig Miller, et al. (October 2004). "Tumor Cells Circulate in the Peripheral Blood of All Major Carcinomas but not in Healthy Subjects or Patients with Nonmalignant Diseases". *Clin. Cancer Research* 10 (20): 6897–6904.
- [8] Reszka et al. Nitrogen-Bisphosphonates Block Retinoblastoma Phosphorylation and Cell Growth by Inhibiting the Cholesterol Biosynthetic Pathway in a Keratinocyte Model for Esophageal Irritation, *Mol Pharmacol* 59:193–202, 2001
- [9] Johnson HA, Rubini JR, Cronkite EP, Bond VP (1960). "Labeling of human tumor cells in vivo by tritiated thymidine". *Lab. Invest.* 9: 460–5.
- [10] William H. Wolberg and Raymond R. Brown, Autoradiographic Studies of in Vitro Incorporation of Uridine and Thymidine by Human Tumor Tissue, *Cancer Res* 1962;22:1113-1119
- [11] Katherine K. Matthay, Colleen Panina, Correlation of Tumor and Whole-Body Dosimetry with Tumor Response and Toxicity in Refractory Neuroblastoma Treated with ^{131}I -MIBG, *Journal of Nuclear Medicine* Vol. 42 No. 11 1713-1721
- [12] Emad Y. Moawad, Clinical and pathological staging of the cancer at the nanoscale, *Cancer Nano* (2012) 3:37–46.
- [13] Emad Y. Moawad, Reconciliation between the clinical and pathological staging of cancer. *Comp Clin Pathol.* 2012; DOI: 10.1007/s00580-012-1603-6.
- [14] Emad Y. Moawad, Optimizing Bioethanol production through regulating Yeast Growth Energy, *Syst Synth Biol* (2012) 6:61–68
- [15] Emad Y. Moawad (2013). Safe Doses and Cancer Treatment Evaluation. *Cancer and Oncology Research*, 1, 6 - 11. doi: 10.13189/cor.2013.010102.
- [16] Emad Y. Moawad, Administering the optimum dose of L-Arginine in regional tumor therapy. *Ind J Clin Biochem.*

- 2013; DOI: 10.1007/s12291-013-0379-z
- [17] Emad Y. Moawad (2013). Nuclear Transmutation and Cancer in the Biological Cell. *International Journal of Biochemistry and Biophysics*, 1, 1 - 8. doi: 10.13189/ijbb.2013.010101. http://www.hrpub.org/journals/article_info.php?aid=139
- [18] Emad Y. Moawad (2013). Cell Growth Energy Represents a Measure for Man Health; Regulates Nuclear Transmutations and Aberrant Activation in Human Cell. *Universal Journal of Medical Science*, 1, 27 - 35. doi: 10.13189/ujmsj.2013.010203. http://www.hrpub.org/journals/article_info.php?aid=414
- [19] Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2 (Free Executive Summary) <http://www.nap.edu/catalog/11340.html>
- [20] O'Donoghue JA, Sgouros G, Divgi CR, Humm JL. Single-dose versus fractionated radioimmunotherapy: model comparisons for uniform tumor dosimetry. *J Nucl Med*. 2000; 41: 538–47.[Abstract/Free Full Text]
- [21] Brenner DJ, Shuryak I, Russo S, Sachs RK (2007) Reducing second breast cancers: a potential role for prophylactic mammary irradiation. *J Clin Oncol* 25:4868–4872
- [22] Brenner DJ, Curtis RE, Hall EJ, Ron E (2000) Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer* 88:398–406
- [23] Ron E (2006) Childhood cancer–treatment at a cost. *J Natl Cancer Inst* 98:1510–1511
- [24] Harlan LC, Potosky A, Gilliland FD, et al. Factors associated with initial therapy for clinically localized prostate cancer: Prostate cancer outcomes study. *J Natl Cancer Inst* 2001;93:1864–1871.
- [25] Pollack A, Zagars GK, Starkschall G, et al. Conventional vs. conformal radiotherapy for prostate cancer: Preliminary results of dosimetry and acute toxicity. *Int J Radiat Oncol Biol Phys* 1996;34:555–564.
- [26] Lee CT, Dong L, Ahamad AW, et al. Comparison of treatment volumes and techniques in prostate cancer radiation therapy. *Am J Clin Oncol* 2005; 28:618-625.
- [27] Castello PR, David PS Mitochondrial cytochrome oxidase produces nitric oxide under hypoxic conditions: implications for oxygen sensing and hypoxic signaling in eukaryotes. *Cell Metab*. 2006; 3:277–87