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Peculiarities of Blood Circulation and Rheological Properties During the Treatment of Cancer Disease

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Abstract

Neoplasms are characterized by an abnormal, altered stroma that facilitates cancer development by providing nutritional support and establishing a barrier for host defense mechanisms. During a malignant disease all physiological processes of destruction require structural changes, that manifest at different organization levels in organs, tissues, single cells, and cellular organelles. All of these structures have specific and significantly complex rheological parameters. In a given vessel within a tumor, blood flow fluctuates with time and can reverse its direction. Elevated geometric and viscous (rheological) resistance and other molecular and mechanical factors contribute to this spatial and temporal heterogeneity. Heterogeneity contributes to both acute and chronic hypoxia in tumors—a major cause of resistance to radiation and other therapies. adsorption-rheological properties of blood prognostic significance concerning lung neoplasm course and development of complications of chemoradiation respectively. Intravascular rheological changes are one of the most important factors to explain the radiobiological principles of SBRT. Laboratory studies suggest that the radiation

response for the high-dose single fractions used in radiosurgery is predominantly related to the supporting endothelial cells. The Linear Quadratic Model (LQ Model) applies to the calculation of iso-effect doses in treating with conventional EBRT. Based on the LQ and USC model, we estimated the Biologically Effective Dose (BED) and Equivalent Dose. When the fractional dose is higher than the Transient Dose, the LQ model is inappropriate to predict the effects induced by radiation. BED is calculated by the LQ formula if the dose per fraction is below the transition dose – DT and by the USC formula if the dose per fraction is higher than DT.

KEYWORDS: Stereotactic Body Radiation Therapy (SBRT); External beam radiation therapy (EBRT); Linear Quadratic Model (LQ Model); Universal Survival Curve (USC); Biologically Effective Dose (BED); Transition Dose (DT)

Introduction

Cancer development is usually associated with a genetic mutation causing pathological alterations of the cell cycle and invasive motility. Neoplasms are characterized by an abnormal, altered stroma that facilitates cancer development by providing nutritional support and establishing a barrier for host defense mechanisms [1]. cellular intrinsic traits and molecular factors within the tumor microenvironment significantly contribute to metastatic progression.

In solid tumors, proliferating cancer cells and activated fibroblasts deform the interstitial matrix, resulting in stretched collagen fibers, compressed hyaluronan, and deformed cells-all storing solid stress, a type of mechanical force transmitted by solid tissue components. This stress compresses intratumor blood and lymphatic vessels [2,3]. cancer-associated fibroblasts (CAFs) subsume at least two distinct cell types:

1. Cells with similarities to the fibroblasts that create the structural foundation supporting most normal epithelial tissues;
2. Myofibroblasts, whose biologic roles and properties differ markedly from those of the widely distributed tissue-derived fibroblasts [4,5].

Intussusception, wherein tumor vessels enlarge and an interstitial tissue column grows in the enlarged lumen, expanding the network; vasculogenesis, wherein endo-

thelial precursor cells mobilized from the bone marrow or peripheral blood contribute to the endothelial lining of tumor vessels; “sprouting” angiogenesis, wherein the existing vascular network expands by forming sprouts or bridges; co-option (not shown), wherein tumor cells grow around existing vessels to form “perivascular” cuffs [6, 7]. Tumor vasculature consists of both vessels co-opted from the preexisting host vasculature and vessels resulting from the angiogenic response of host vessels to cancer cells [8]. The former is invested in normal contractile perivascular cells, whereas the latter lack these perivascular cells or these cells are abnormal [9,10]. Macroscopically, four spatial regions can be recognized in a tumor:

- An avascular necrotic region
- A semi-necrotic region
- A stabilized microcirculation region
- An advancing front

During the malignant disease, all physiological processes destruction require structural changes, that manifest at different organization levels in organs, tissues, single cells, and cellular organelles [11,12]. All of these structures have specific and significantly complex rheological parameters. However, the association of structural elements to mechanical properties is especially difficult within the biological microenvironment and depends on the internal cell rearrangements and cellular interactions with molecules that compose the extracellular matrix (ECM) of stroma [13-15].

Rheological Properties

Average erythrocyte velocity can be an order of magnitude lower in some tumors as compared with that of normal host tissue. In a given vessel within a tumor, blood flow fluctuates with time and can reverse its direction [16,17]. Elevated geometric and viscous (rheological) resistance and other molecular and mechanical factors contribute to this spatial and temporal heterogeneity. Heterogeneity contributes to both acute and chronic hypoxia in tumors-a major cause of resistance to radiation and other therapies [18]. Pathological changes in stroma include an increase in ECM stiffness and an accumulation of stress gradients inside the tumor mass. Abnormal mechanical stresses can increase the invasive and metastatic potential and migration of cancer cells and tissue development [19,20].

An important pathogenetic link supporting the properties of lung cancer is neoangiogenesis (the formation of new vessels). Well simultaneously, the expression of protein products that are surfactants or possess surfactant properties in patients with lung neoplasm provides the processes of neoangiogenesis and the physicochemical interfacial state of blood serum [20,21].

Based on a randomized trial involving 115 patients, a rather interesting relationship between specific characteristics of lung cancer and rheological parameters was revealed.

There is a close relationship between the biochemical components and the functional activity of the cells in the tumor microenvironment, capable of secreting surfactants/insurfactants influencing biochemical processes, and thus the adsorption-rheological properties of blood (ARPB) – surface tension (ST), serum viscosity (SV), serum elasticity (SE), serum relaxation (SR), and viscoelasticity (VE) modulus. Surface-active, viscoelastic, and relaxation properties of blood correlate with the levels of tumor markers such as VEGF, TGFβ1, C-reactive protein, and α2-macroglobulin [22]. There are direct relations between the level of VEGF, which, in addition to the prognostic factor of high aggression of LC, is an important component in the development of neoangiogenesis in such patients. [23,24].

According to the final results, it was revealed that: Indices of VV are affected by the small-cell form of LC, the presence of compression pulmonary syndrome, adrenal metastases and the ribs, the number of metastases in lymph nodes per a patient; VE is affected by metastases in the spine and non-small cell LC; SV is affected by development of exudative pleurisy, tumor invasion in the ribs and metastasis in the brain; SE is affected by metastases in subclavian lymph nodes, the sternum, the humerus and the spinal column; ST is affected by the index of differentiation of LC; SR is affected by metastases in the spine and pancreas. VV and SV possess prognostic significance concerning lung neoplasm course and development of complications of chemoradiation respectively [25,26].

Rheological principles of SBRT radiobiology

Radiotherapy is one of the main methods of lung cancer management, mainly in the chemo-radiation mode. During the treatment aimed at radical cure, the convential, hyper fractionation dosage method is mainly used [27]. in some cases of non-small cell carcinoma, stereotactic radiosurgery is the best treatment option, for instance: in inoperable patients with initial stage, during the Recurrent neoplasm and/or lung metastatic disease [28-30]. Initial clinical experiences with SBRT show impressive results in terms of local tumor control and acceptable late complications rate [31].

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), are novel and increasingly popular ways of delivering radiotherapy. This method can deliver, with high accuracy, a high dose of radiation to small and well-defined targets, utilizing either a single dose or a few fractions with a high degree of precision within the body [32,33]. High technology

modality requires a high degree of precision, accuracy, and reproducibility of the entire treatment delivery process. Maneuvers to limit the movement of the target volume and stereotactic localization of the lesion or image guidance are mandatory for target localization, minimization of margins, and dose delivery [34, 35].

Intravascular rheological changes are one of the most important factors to explain the radiobiological principles of SBRT. Laboratory studies suggest that the radiation response for the high-dose single fractions used in radiosurgery is predominantly related to the supporting endothelial cells [36]. Homeostatic factor, endothelial apoptosis regulates angiogenesis-dependent tumor growth, which only occurs at radiation doses above transition dose. High-dose radiation delivered by SABR increased vascular permeability and apoptosis through the ceramide pathway [37].

A simple way of modeling how radiation kills cells is the idea that there may be specific regions of the DNA that are important to maintaining the reproductive ability of cells.

These sensitive regions could be thought of as specific targets for radiation damage so that the survival of a cell after radiation exposure would be related to the number of targets inactivated [38]. DNA double-strand breaks (DSBs) are considered as the most lethal form of DNA damage and a primary cause of cell death and are induced by ionizing radiation during radiotherapy [39]. There are two methods of producing a double-strand break:

- One quantum of radiation damages both DNA strands (αD). This is referred to as a “double hit” because it damages two strands with one hit.
- Two quanta of radiation each breaking a single strand, produce a double-strand break (βD2). These are referred to as “single hits” because one strand is damaged with each hit.

The Linear Quadratic Model (LQ Model) applies to the calculation of iso-effect doses in treating with conventional EBRT. When the fractional dose is higher than the Transient Dose, the LQ model is inappropriate to predict the effects induced by radiation. introduced the Universal Survival Curve model (USC model), which integrated the LQ model with the multi-target model, and incorporated the effects of both low-dose and high-dose radiation [40].

The linear-quadratic (LQ) model, which derives from biological considerations of how cells could be killed by ionizing radiation, did fit the data at low doses, led to the replacement of this equation by the LQ equation as follows:

$$S(D) = e^{-(\alpha D+\beta D)}$$

D is the dose administered; S(D) is the fraction of cells to survive a given dose; αD is the probability of cell death arising from a single "double hit" producing a dou-

ble-strand break; βD2 is the probability of cell death arising from multiple "single hits," each generating single-strand breaks, close enough together to cause a double-strand break [39-42].

Experimental studies have shown that the LQ model overestimates cell killing at high single doses because it predicts a survival curve that continuously bends downward whereas the experimental data are consistent with a constant slope at high doses [43]. Therefore, there is concern that LQ model does not accurately predict tumor cell response at the higher doses per fraction used in SBRT. The response of tumors to radiation has been largely characterized in terms of factors that influence the ability of radiation to damage DNA, and that affect a population of cells in tumors to recover from such damage [44, 45]. The fundamental difference between these two models is based on five main radiobiological factors that are critical in determining the net effect of radiation therapy on tumors. These are:

- **Repair** compromises the efficiency of radiation and reduces the radiosensitivity of tumors. SABR induces more necroptosis than apoptosis
- **Repopulation** usually occurs in 2-3 weeks after conventional fractionated EBRT, depending on the fractionated radiation doses, total doses, and pathological types
- **Reoxygenation** may be reduced owing to the relatively short duration of SABR. Furthermore, tumor hypoxia may persist after vascular injury caused by SABR. Both oxygenated and hypoxic cells are ablated by high-dose radiation under SABR, resulting in highly efficient tumor-killing
- **Redistributions**: After irradiation, tumor cells at G0 stage of the cell cycle will accelerate into G2/M (radiation-induced G2/M arrest). The cell cycle is completely blocked at all stages after a single higher-dose ablation radiation
- **Radiosensitivity**: The clinical efficiency of SABR is greater than expected by the linear quadratic model and the conventional radiobiological principles of 4 Rs, may no longer be suitable to account for the killing effects of SABR. The underlying mechanisms of tumor response to radiation might also be involved in the intrinsic radiosensitivity and new radiobiological factors, e.g., vascular damage Cells differ in their intrinsic radiosensitivity. Radiosensitive cells include hematological cells and epithelial cells as well as hematological tumor cells [46,47].

Materials and Methods

The study presents the data of 9 people, of which 6 cases had residual non-small cell lung carcinoma, and 3 cases had metastatic lesions. In the residual tumor burden population, according to histological subtypes, adenocarcinoma was represented in 3 cases, squamous cell carcinoma in 2 cases, and large cell carcinoma in 1 case. The ratio of cases in men to women was 5:1. Localization of tumor was right-sided in 2 cases, left-sided – in 4, in the upper lobes of the lungs – in 2 cases, in the lower lobes-1, in the middle-upper – 2, the mediastinal – in 1. The central form of cancer occurred in 3 cases and the peripheral – in 3 cases. The maximal dimension of the tumor burden was estimated: in 1 case of squamous cell carcinoma – <3cm, 2 cases of adenocarcinoma and 1 case of large cell carcinoma – 3-4cm, and 1 case of adenocarcinoma da 1 case of squamous cell cancer – >4cm-<5cm. As for the patients with metastatic formation in the lung, in 1 case the metastases developed from rectal cancer, in 1 case from the head and neck squamous cell carcinoma, and in 1 case from breast invasive ductal carcinoma were detected. The maximal sizes of Secondary neoplasm were determined: head and neck cancer metastasis, breast and rectal were <2cm and 3-4cm respectively. The frequency of gender distribution represented: 1:2.

During the research we used 5 types single and multiple fractions SBRT dose schedules: For head and nack secondary formation (maximal size: <1,8cm) – 27 Gy in one fraction; for breast and rectal cancer cases (maximal dimension: 3-4cm) – 48 Gy in 3 fraction; for 2 upper lobe residual tumor (1 squamos cell and 1 adenocarcinoma, maximal dimension: 3-4cm) – 50Gy in 4 fraction; for lower lobe located adenocarcinoma residual cancer burden (maximal dimension 4,9cm) – 55 Gy in 5 fraction, also the same dosage for central located adenocarcinoma and large cell carcinoma (maximal size 4-5cm); for central/mediastinal located squamous cell carcinoma (maximal dimension 4,2cm) – 56 Gy in 8 fraction.

Based on the LQ model, we estimated the BED (biologically effective dose) and EQD2 (equivalent dose in 2 Gy fractions). the only parameter required to perform the calculations is the ratio.

1. $BED_{(\alpha/\beta)} = D \cdot (1 + d/\alpha/\beta)$ $\quad BED_{10} = 27 \cdot (1 + 27/10) = 99.9$ Gy
   $EQD2 = D \cdot (d+\alpha/\beta)/(2+\alpha/\beta)$ $\quad EQD2 = 27 \cdot (27+10/2+10) = 83.25$ Gy
   $d=2{,}2$Gy $\alpha/\beta=10$Gy
2. $BED_{10} = 51 \cdot (1 + 17/10) = 137.50$ Gy $\quad EQD2 = 51 \cdot (17+10/2+10) = 114.75$ Gy
   $d=15$ Gy $\alpha/\beta=17$ Gy

3. BED_{10} = 50 · (1 + 12.5/10) = 112.5 Gy EQD2 = 50 · (12.5+10/2+10) = 93.75 Gy
   d=12.5Gy α/β=10 Gy
4. BED_{10} = 55 · (1 + 11/10) = 115.5 Gy EQD2 = 55 · (11+10/2+10) = 96.25 Gy
   d=11Gy α/β=10 Gy
5. BED_{10} = 56 · (1 + 7/10) = 95.2 Gy EQD2 = 56 · (7+10/2+10) = 79.33 Gy
   d=7 Gy α/β=10 Gy

Many authors believe that the use of the LQ model is inappropriate because it does not accurately explain the observed clinical data and ignores the impact of radioresistant subpopulations of cells. Also, the calculated equivalent doses are much higher than the actual effects.

Universal survival curve (USC) model was constructed to provide a superior approximation of the experimentally measured survival curve data in the high-dose range by hybridizing the LQ model survival curve for the low-dose range (the shoulder) and the multitarget model asymptote for the high-dose range. According to the USC model, DT is the transition dose from the LQ model to the multitarget model. The USC model depends on five radiobiological parameters: α, β, D_0, Dq, and D_T. According to the USC model, we calculated the (Biologically Effective Dose) BED_{USC}, (Single Fraction Equivalent Dose) SFED, and (Standard Effective Dose) SED. Estimated radiobiological parameters: α =0.33 Gy-1; D0 =1.25 Gy; D_q=1.80 Gy; D_T =6.2 Gy; α/β=10 Gy

$BED_{USC} = 1/(\alpha \cdot D_0) \cdot (D - n \cdot D_q)$ $SFED = D - (n - 1) \cdot Dq$
$SED = (1/(\alpha \cdot D_0)) \cdot (D_{sbrt} - n_{sbrt} \cdot D_q) / (1 + 2/\alpha/\beta)$

1. BED_{USC} = (1/0,33 · 1.25) · (27 – 1.8) = 61.09 SFED = 27 SED = 1/ (0.33 · 1.25)) · (27 − 1 · 1.8)/(1 + 2/10) = 50.91
2. BED_{USC} = (1/0,33 · 1.25) · (51 – 3 · 1.8) = 110.55 SFED = 51 − (3 − 1) · 1.8 = 47.4 SED = (1/ (0.33 · 1.25)) · (51 − 3 · 1.8)/ (1 + 2/10) = 92.12
3. BED_{USC} = (1/0,33 · 1.25) · (50 – 4 · 1.8) = 103.76 SFED = 50 − (4 − 1) · 1.8 = 44.6 SED = (1/ (0.33 · 1.25)) · (50 − 4 · 1.8)/ (1 + 2/10) = 86.46
4. BED_{USC} = (1/0,33 · 1.25) · (55 – 5 · 1.8) = 111.52 SFED = 55 − (5− 1) · 1.8 = 47.8 SED = (1/ (0.33 · 1.25)) · (55 − 5 · 1.8)/ (1 + 2/10) = 92.93
5. BED_{USC} = (1/0,33 · 1.25) · (56 – 8 · 1.8) = 100.85 SFED = 56 − (8− 1) · 1.8 = 43.4 SED = (1/ (0.33 · 1.25)) · (56 − 8 · 1.8)/ (1 + 2/10) = 84.04

In all SBRT schemes, the fractional dose was higher than the transit dose (>6,2 Gy). At high single fractional dose exposures (eg 27 Gray, 17 Gray) a very large difference between the effective and equivalent doses is noticeable.

Discussion

The prerequisite of LQ model application is complete oxygenation of tumor cells during radiation with a fractional dose of lower than 1–6 Gy. BED is calculated by the LQ formula if the dose per fraction is below the transition dose DT and by USC formula if the dose per fraction is higher than DT. SFED is defined as the dose delivered in one fraction that has the same biological effect as the tested dose-fractionation scheme. It should be noted that the closer the fractional dose is to the transition dose, the radiobiological parameters calculated by the LQ and the USC model are less differentiated from each other. Numerous experimental studies found obvious vascular injury under high-dose radiation, especially above 10 Gy, which induced hypoxia, acidification of tumor microenvironment, and indirect death of tumor cells [26,39,48]. High-dose radiation-induced blood vessel injury and ischemia, further leading to tumor necrosis. Radiobiological values estimated with high accuracy plays an important role for clinicians to effectively determine both clinical outcome and radiation-induced adverse events.

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