Review Article

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Predicting Factors of Radiosensitivity in Individual Radiotherapy

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ABSTRACT

BACKGROUND AND OBJECTIVE: Radiation dose in oncology protocols is different for each patient according to the type and grade of the tumor, as well as adjuvant therapies. In the current treatment regimens, some predicting factors of individual radiosensitivity have not been considered. Individual radiotherapy can lower side effects through radiation dose reduction with respect to tumor control. In this study, the most determining factors for predicting radiosensitivity, used for individual radiotherapy, were reviewed.

METHODS: Data were retrieved through searching Sciencedirect, PubMed, Google scholar, Iranmedex and SID databases. The titles and abstracts of Persian and English articles were searched using keywords including: radiotherapy, the rate of cell proliferation, tumoral hypoxia, inherent radiosensitivity, tumor cell cycle, inhibitor factors of tumor, cancer stem cells, field dose radiation, apoptosis and predicting factors of radiosensitivity.

FINDINGS: Out of 90 articles, 25 original articles and reviews on predicting factors of the rate of radiosensitivity were thoroughly studied. Multiple factors, such as the presence of hypoxic zone and its size, inherent radiosensitivity and apoptosis, are crucial in determining individual radiation dose. Other factors, including previous history of exposure, blood type, left-or right-handedness and physical factors, should also be considered.

CONCLUSION: With respect to the physical, chemical, and biological parameters influencing individual radiosensitivity, radiotherapy individualization can promote tumor treatment and diminish side effects of radiotherapy on normal tissue.

KEY WORDS: *Radiosensitivity, Radiotherapy, Radiation Dosage, Side Effects.*

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Introduction

Nowadays, radiotherapy plays a significant role in treating 50% of cancer patients. The recent developments in this area are mostly pertinent to treatment planning and improvement of physical and technological aspects (1), and few studies have considered individual biological aspects. So far, several predictor factors have been studied to measure tumor radiosensitivity (2). These factors

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are used to identify patients who are at great risk of long-term side effects of radiation on normal tissue (3). In addition to destroying cancer and benign cells, the healthy cells surrounding the tumor may be destroyed by radiotherapy. In the modern radiotherapy techniques, it is tried to reduce radiation dose affecting the non-tumoral tissues (3,4). Hypoxia, inherent radiosensitivity, cellular metabolism of tumor, DNA restoration, stem cells, the rate of cell proliferation, cell cycle and inhibiting factors of tumor and apoptosis play an important role in tumor control and diminishing long-term side effects (1,2,5).

Considering these factors, in case of hypersensitiveness to radiation, it is essential to reduce radiation doses as much as possible to lower the side effects in the patient, or radiation doses should be increased in patients with radiation resistance. Even with equal factors influencing the reference dose, i.e., same tumor type, grade and stage of the disease, there are still many other factors causing individual behavior. In fact, these behaviors are inherent sensitivity or resistance, and if diagnosed before treatment, they may help determine the amount of radiation dose. There are various ways to determine the effect of each of these factors, which will be discussed separately (1,2). Considering these aspects in treatment planning and administering special treatment regimens to individual patients is defined as individual treatment (1). This study aimed to determine the main effective factors for prediction of radiosensitivity, which can be used for individualization of radiotherapy, in order to adjust radiation dose so as we are able to estimate and alter the prescribed dose for individual patients.

Methods

Data were retrieved via searching Iranmedex, Sciencedirect, PubMed, Google Scholar and SID databases. Titles and abstracts of English and Persian articles were searched using keywords including: radiotherapy, the rate of cell proliferation, tumoral hypoxia, inherent radiosensitivity, tumor cell cycle, inhibitor factors of tumor, cancer stem cells (CSC), field dose radiation, apoptosis and predictor factors of radiosensitivity.

Results

Hypoxia: Today, it is proven that most solid animal tumors include hypoxic parts which can affect response to radiation therapy (6). Usually the tissue parts with oxygen tension of lower than 7 mmHg are named hypoxic zone. Studies show that lack of oxygenation cause tumor progression and its more aggressive behavior. In this state, tumor dose is expected to increase by at least 30% (7). Due to radiation and even drug (chemotherapy) resistance at the pressures below 2 mmHg, oxygenation to the tumor is suggested to increase its sensitivity to radiation (7).

To balance this effect, tumor sensitivity should be enhanced by increasing the rates of oxygen and glucose (8). One of the oxygenation methods is breathing. According to a study by Powel et al., breathing 2% CO_2 and 98% O_2 was effective in the oxygenation to tumor cells and also was tolerable for the patient (8).

Stem cells: Evidence reveal that there are numerous tumor cell populations including the types of stem cells called cancer stem cells (CSC), which are often resistant to radiation and chemotherapy and may decrease the chance of treatment with radiotherapy and promote the risk of metastasis and tumor recurrence (9-11).

In oncology, plenty of attention has been given to this issue, since the presence of CSC is associated with low prognosis (12). The cells lead to resistance to radiation in various ways such as enhancing DNA recovery and hypoxia; therefore, we should employ different molecular strategies to enhance the rate of sensitivity. Identification of markers and potential mechanisms used for

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predicting the optimal dose of radiation therapy are of utmost importance. Hence, some drugs are being manufactured to increase radiation sensitivity by connected to CSC (12, 13).

Inherent sensitivity to radiation: Radiotherapy is critical to topical tumor treatment, but it can be limited by the inherent sensitivity of tumor cells. Among all the risks threatening DNA, double-stranded damage is considered as the main responsible factor for cell death. Thus, in radiobiology, repair pathways and restoration ability of tumors can be predictive factors for therapeutic advantage of radiotherapy and chemotherapy (14).

Individual response to ionizing radiation enhances therapeutic use and prevents damage to healthy tissue. It can be argued that even tumors' radiosensitivity is different in various tissues and organs (15). There are a variety of strategies to hamper DNA repair and radiation resistance in tumors. Nitric oxide is one of the substances released under the effect of radiation in hypoxic conditions and leads to increased single- and double-strand DNA breakage. In case this mechanism is accompanied with a pre-drug with the ability to release more nitric oxide, it might promote tumor radiosensitivity (16).

Apoptosis: Among all the radiosensitivity prediction methods, radiation-induced apoptosis of CD4 and CD8 T-lymphocytes is the fastest method (about 24 hours) (17). Prediction of long-term effects of radiation in patients treated with radiotherapy is very effective by evaluation of these lymphocytes in individual radiotherapy. In a study, Ozsashin et al. showed that after an 8-Gy dose, lymphocytes are predictable for representing long-term side effects of radiation (18).

Tumor inhibitors: Cell death is one of the most significant end points in radiotherapy. Tumor antigen P53 (Trp53-1) has an important role in apoptosis regulation, but it can also influence autophagy mechanism. This inhibitor enhances radiosensitivity through activating apoptosis and deactivating autophagy radiation (19, 20). In fact, a mutation in this gene can cause the opposite effect by reducing protein function. According to a study conducted by Couture et al., Ki-67 and P53 are predictors of response to treatment of head and neck cancer with advanced squamous in chemoradiation (21).

Rate of cell proliferation: Uncontrolled cell proliferation is one of the hallmarks of malignant tumor growth (22, 23). In many organs, cells have two modes: active and off. Therefore, it could be said that the effect of radiation is different in the two types. The rate of cell proliferation is the most important parameter in prediction of radiosensitivity. As mentioned above, P53 plays an essential role in increasing radiosensitivity; however, it is found that increased expression of this protein promotes radiosensitivity and leads to a decrease in tumor proliferation rate (24). In a study by Lavertu et al., Ki67 protein expression followed by high-speed proliferation of cells caused radiosensitivity in patients with oral cancer (squamous cell) (22).

Cell cycle: Activation of check points of each cell cycle is one of the most common responses of cells to damage. Tumoral cells may show different sensitivities to radiation, depending on the phase and cycle the cells are located in. External stimuli such as drugs and radiation can coordinate various cells in one phase and, in turn, create a resistance or sensitivity at all levels of the same tumor. This effect is observable in chemotherapy (25-27). In a study done by Kaufmann et al., radiation stopped cells in the G2 phase and eventually, caused radiation resistance in stem cells (28).

DNA restoration: There is a relationship between DNA repair ability and risk of cancer and radiosensitivity. DNA repair ability demonstrates resistance to radiation (29). Some studies on malignant cells showed that radiation leads to regulation of telomerase activity and increased involvement of DNA in restoration and thus, it enhances resistance to radiation (20).

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Other factors:

Exposure history: Adaptive response and hormesis are two natural phenomena that have been studied in the recent years (31, 32). In adaptive response, resistance to higher and more doses is brought about by exposure to sublethal doses (33-35). In hormesis phenomenon, low and high doses of radiation have opposite effects suggesting beneficial effect of radiation in low-doses. Even in some areas with high natural radioactivity no evidence of increased risk have been reported (31, 36-39). Except for natural radiation, these phenomena have been reported in medical exposure (35-40) and their existence is rejected by some other reports (31, 35). The annual dose allowed for natural resources is 4.2 mSv per year and the dose allowed for radiation workers is 20 mSv per year. It is 260 mSv per year in one of the cities in Iran (Ramsar) (34). Recent studies indicate that, contrary to popular beliefs, high field dose had no pathogenic effects. The effect of high field dose on cancer, which might affect resistance or radiosensitivity of people in the area, still remains a challenging issue (32,33,39).

Left- or right-handedness: Aside from all these factors, at equal doses, people still show different biological effects including acute effects of radiation. Some reports indicate that breast cancer and some autoimmune diseases are more common in left-handed people. This effect can be observed in radiosensitivity rates of these people. We can state that radiosensitivity of left-handed patients is higher than right-handed ones; however, further studies are required in this area (41,42).

Blood type: Increased risk of some types of cancer is more in some blood types. According to a study carried out by Elahimanesh et al., radiosensitivity in different blood types was reported (43).

Radiation materials causing sensitivity and resistance: Some of the chemicals in the environment or cells can be effective on radiosensitivity (44). History of using some of these materials, which have an effect similar to oxygen, date back to 70 years ago. Sulfur and cysteine are the most important of them. Involvement of other substances, which sweep up free radicals, and even the effects of some vitamins on the electromagnetic waves have been reported (44, 45, 46).

Other physical factors: Other factors such as radiation field size, depth and radiation energy influence the amount and intensity of exposure, which should be considered in administration of radiation doses to individual patients (47). Extensive research has been carried out on hyperthermia or increase in tumor temperature. This method should be considered as a physical factor during radiotherapy.

Conclusion: Reference dosages are obtained and used based on the aforementioned factors. However, these factors are different in individual patients, and in many patients with the same tumor, gender and conditions, varying degrees of side effects such as skin burns are observed, which might be due to differences in individual sensitivity to radiation. In this study, physical, chemical and biological parameters influencing the dose and intensity of radiation were evaluated to determine the factors predicting individual sensitivity. Moreover, a specific dose for each individual was administered, which can increase the probability of tumor control in radiotherapy and also reduce the side effects caused by radiation on normal tissue.

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