

## Research Progress on the effect of radiotherapy on immune function of tumor patients

WENXIN LI<sup>1</sup>, XIAOLEI YU<sup>1</sup>, QINGSHAN LI<sup>1</sup>, FAN XU<sup>1</sup>, SHENG LIN ZHANG<sup>1</sup>, XIAO LI<sup>2</sup>

Departments of <sup>1</sup>Oncology and <sup>2</sup>Radiology, Affiliated Hospital of Chengde Medical College

### Abstract

With the cure rate of 21%, radiotherapy is one of the most effective methods for tumor treatment, and about 70% of solid tumors need radiotherapy. With the in-depth study of human impact by radiotherapy and immune system and tumor microenvironment, radiotherapy is no longer used as a local treatment. It is found that irradiation of tumor can activate body immunity. There exist two different views: one is that radiotherapy inhibits immunity, because it can kill tumor cells and normal cells at the same time. The other is that radiotherapy promotes immunity, causing tumor cell necrosis or apoptosis, releasing immune cytokines or promoting immune cell activation, and bystander effect. In recent years, the idea of radiotherapy promoting immunity has been more and more supported by literatures. Whether radiotherapy promotes or inhibits immunity is a research hot spot in recent years. This paper reviews the research progress of the effect of radiotherapy on immune function of tumor patients.

**Key words:** Radiotherapy ; Immune function ; Malignant

### Introduction:

The treatment of malignant tumors is a thorny problem in the world, with increasing incidence and mortality year by year and obvious trend of disease in younger population. Traditional treatment methods of cancer include surgery, radiotherapy and chemotherapy. The main function of all the methods are to remove or kill tumor cells. Because the malignant tumor showed invasive growth, it is difficult to completely remove or eliminate.<sup>1</sup> Due to the lack of specificity and long-term effectiveness of these treatments, tumor cells and normal cells are killed at the same time,

and treatment failure is often caused by recurrence and metastasis. In addition, due to the serious toxic and side effects of radiotherapy and chemotherapy, patients are often unable to tolerate and are forced to terminate treatment. Emerging targeted therapies control tumor growth by inhibiting tumor carcinogenic sites, causing ineffectiveness and long-term drug resistance. This situation urges people to try to find new treatments.<sup>2</sup>

Radiotherapy is a local treatment for malignant tumors, and its main biological effect is to damage DNA,

*Corresponding Author:*

Xiaolei Yu, Departments of Oncology, Affiliated Hospital of Chengde Medical College, 36 Nanyingzi Street, Shuangqiao, Chengde, Hebei 067000, P.R. China. E-mail: [28574060@qq.com](mailto:28574060@qq.com)

regulate signal transduction pathway, so as to change the tumor microenvironment.<sup>3</sup> Radiotherapy can kill or destroy tumor cells and immune cells simultaneously. Leading to immunosuppression.<sup>4</sup> Below, I will elaborate the impact of radiotherapy on immune function from two aspects.

1. Effects of radiotherapy on immune cells and related factors: Effect of radiotherapy on tumor microenvironment. The immune microenvironment of tumor patients can be divided into four categories: Inhibitory microenvironment, inflammatory microenvironment, migration microenvironment and angiogenesis microenvironment. Radiotherapy promotes the continuous exchange of a large number of immune cells and immune cytokines in the tumor microenvironment, and play a two-way role in tumor growth and metastasis.

1.1 Effect of radiotherapy on DC cells: As the most powerful antigen-presenting cells in vivo, DC cells play a key role in the process of antitumor. Ullrich et al<sup>5</sup> found that tumor cells are difficult to be recognized by peripheral T cells, and the tumor antigen signal presented is not enough to activate DC cells. In addition, the tumor microenvironment inhibits the maturation of DC. Studies have found that malignant tumors undergo programmed death after radiotherapy, release a large number of tumor antigens and interact with immune cells. Among them the specific immunity of DC cells is the key to activate the immune function of the body.<sup>6</sup> Zhao Chongwei et al<sup>7</sup> have confirmed that radiotherapy can promote DC maturation, migration and phagocytosis. Its mechanism is : (1) radiotherapy can induce and promote the production of PEG-2 and COX-2

inflammatory factors, and then activate DC; (2) Radiotherapy can induce the translocation of troponin to the cell membrane, activate the body specific signal pathway, and promote the recognition and phagocytosis of tumor cells by DC cells; (3) Radiotherapy causes tumor cells to release chemokines such as SDF-2, stimulate DC chemotaxis to the radiotherapy site and promote DC activation; (4) Radiotherapy can up regulate the expression of MHC I molecules on the surface of tumor cells and promote the presentation of MHC I. At the dose of non lethal tumor radiotherapy, it can produce a dose-dependent enhancement of MHC I presentation, which shows that radiotherapy promotes the maturation of DC cells and then activates immunity.

1.2 Effect of radiotherapy on early rapid cytokines TNF- $\alpha$  and IFN- $\gamma$ : TNF- $\alpha$  and IFN- $\gamma$ , as early immediate cytokines in vivo, are necessary cytokines for radiotherapy and play an important role in the early stage of anti-tumor.<sup>8</sup> Zheng Fang et al, confirmed that TNF- $\alpha$  is an important immuno-modulatory factor, which can kill and inhibit tumor cells.<sup>9</sup> TNF- $\alpha$  can kill several tumor cells and dissolve tumor cells, but it has no effect on normal tissue cells and has no species specificity.<sup>10</sup> It was found that the cytotoxic effect of TNF- $\alpha$  on tumor cells was accompanied by DNA breakage. Shi Wenfang et al,<sup>11</sup> confirmed that the cytotoxic effect of TNF- $\alpha$  can cause necrosis and apoptosis. Irradiation of cells with X-rays causes DNA damage and activation of DNA damage repair response, and then activates NF- $\kappa$ B. Radiation mediated NF- $\kappa$ B activation can directly induce the expression of TNF- $\alpha$ . TNF- $\alpha$  can up regulate the expression of tumor endothelial adhesion molecules and promote MDSC

adhesion capture and infiltration. IFN- $\gamma$  factor is the only member of water-soluble dimer cell factor type II interferon, which was originally macrophage activating factor.<sup>12</sup> Perez et al,<sup>13</sup> found that IFN- $\gamma$  was up-regulated after irradiation of melanoma, which has the effects of direct anti-tumor and stimulating anti-tumor immune response in order to inhibit tumor development. In recent years, a large number of domestic and foreign scholars have given low-dose irradiation to mice and found that low-dose radiotherapy can promote the expression of IFN- $\gamma$  and TNF- $\alpha$ .<sup>14</sup>

1.3 Effect of radiotherapy on advanced cytokine HMGB-1: HMGB-1 is an advanced cytokine, mainly existing in eukaryotic nucleus. Some scholars believe that HMGB-1 is involved in the transmission of endogenous signals and is a dangerous signal of cell necrosis.<sup>15</sup> Wang xinjuan et al,<sup>16</sup> confirmed that HMGB-1 is closely related to tumor occurrence, growth, invasion and metastasis, and participates in cell differentiation, migration and regeneration. Radiotherapy causes tumor cell necrosis releases HMGB-1, that binds to TLR4 and promotes the processing and presentation of tumor antigen by MHC-1.<sup>17</sup> It has been found that radiotherapy promotes the activation and maturation of DC and T cells by promoting the release of HMGB-1.<sup>18</sup> Radiotherapy can induce tumor cells to release HMGB-1, improve the immunogenicity of tumor cells, simultaneously regulate the expression of MHC-I, ICAM-1 and VCAM-1, then chemotactic immune cells and activate the host innate immune response.<sup>19</sup> Yanai H et al,<sup>20</sup> found that HMGB-1 in postoperative radiotherapy group was significantly higher than that in preoperative non

radiotherapy group. Muller S et al,<sup>21</sup> found that HMGB-1 activates MAPK, p38, JNK, p42/p44 and other signal pathways by binding with RAGE, and then causes the activation of MMP-2 and -9, so as to promote tumor cell infiltration and metastasis.

2. Clinical study on the effect of radiotherapy on immunity: Except that radiotherapy is not required for tumors insensitive to radiotherapy, such as ovarian teratoma, fibrosarcoma and melanoma, most tumors need to be treated with radiotherapy, such as nasopharyngeal carcinoma, esophageal cancer, lung cancer, breast cancer, rectal cancer and cervical cancer. The main function of radiotherapy is to kill tumor cells, and it also has the effects of analgesia and hemostasis. There are disputes the effect of radiotherapy on the immune system in the process of anti-tumor. In recent years, a large number of scholars have used CD3<sup>+</sup>T cells, CD4<sup>+</sup>T cells, NK cells and CD4/CD8 ratio as indicators to evaluate the effect of radiotherapy on immune function, to observe the dynamic expression of the above indexes before and after radiotherapy, and to investigate the effect of radiotherapy on immune function.

2.1 Lung cancer: a large number of studies have confirmed that non-small cell lung cancer is most sensitive to radiotherapy. Peng Xiao xiang et al,<sup>22</sup> found that the CD4/CD8 ratio of lung cancer patients after radiotherapy decreased significantly compared with the previous, indicating that radiotherapy inhibits the immune function of the body. Guo Zhan wen et al,<sup>23</sup> studied the dynamic changes of peripheral blood CD3<sup>+</sup>T cells, CD4/CD8 ratio, B cell percentage and IgG in

patients with lung cancer before and after radiotherapy. Finally, it is concluded that radiotherapy reduces the immune function of lung cancer patients.

2.2 Nasopharyngeal carcinoma: radiotherapy is the primary treatment for nasopharyngeal carcinoma. Radical dose radiotherapy can achieve radical effect in early patients. Liu Li et al,<sup>24</sup> found that CD4<sup>+</sup>T cells, CD3<sup>+</sup>T cells and CD4/CD8 ratio in peripheral blood of patients with nasopharyngeal carcinoma after radiotherapy were significantly lower than those before radiotherapy.

2.3 Esophageal cancer: radiotherapy is the main treatment for esophageal squamous cell carcinoma. Zhou Jie et al<sup>[25]</sup> found that CD4<sup>+</sup>T cells, CD3<sup>+</sup>T cells, CD4/CD8 ratio and NK cells in peripheral blood of esophageal cancer patients after radiotherapy decreased significantly compared with those before radiotherapy, indicating that radiotherapy inhibits the immune function of esophageal cancer patients. By studying the changes of T cell subsets after operation and after radiotherapy, Wang Yue wei et al,<sup>26</sup> found that the dysfunction of T cell subsets in the radiotherapy group was more serious than that in the operation group, but the normal immune function could be restored through the body's self-repair. It shows that the damage of immune function in patients with esophageal cancer by radiotherapy is short-term.

2.4 Breast cancer: it has been confirmed that breast conserving surgery plus radiotherapy has a similar effect on radical surgery, breast cancer patients with the following indications after modified radical surgery also need radiotherapy: (1) The maximum diameter of the primary tumor is  $\geq 5$ cm,

or the tumor invades the breast skin and chest wall. (2) Patients with positive axillary lymph nodes  $\geq 4$ . (3) For patients with 1-3 axillary lymph nodes positive, according to the high-risk factors of recurrence and metastasis (age  $\leq 40$  years old, hormone receptor positive, incomplete number of lymph node dissections or metastasis proportion  $> 20\%$ , HER-2/neu over-expression, etc). At present, radiotherapy has little effect on the immune function of breast cancer patients. Li Xinli et al,<sup>27</sup> studied the dynamic changes of CD3<sup>+</sup> and CD4<sup>+</sup>T cells in peripheral blood of patients with breast cancer before and after radiotherapy. It was found that these indexes were significantly lower than those before radiotherapy ( $P < 0.05$ ), indicating that radiotherapy inhibited the immune function of breast cancer patients.

### Expectation

As one of the important means of malignant tumor treatment, radiotherapy challenges how to prolong the survival time of tumor patients. The traditional treatment of malignant tumors has reached the bottle neck. With the more and more in-depth research on the mechanism of radiotherapy on immune function, radiotherapy combined with immunotherapy has become a new starting point for tumor treatment. Preclinical trials have achieved encouraging results, but the mechanism of radiotherapy on immune function is complex, and the time, location, mode and dose of radiotherapy have different effects on immune function. At present, many studies are in vitro cell experiments or animal experiments, and there is a lack of corresponding clinical experimental data. At present, the implementation of the new scheme of

radiotherapy combined with immunotherapy urgently needs a clear research direction, including the optimal radiotherapy dose, the time point of immunotherapy in the process of radiotherapy, the split dose of radiotherapy and the mechanism of combined therapy. With more clarity on the above problems, we can more effectively use radiotherapy as adjuvant of immunotherapy and break through the difficult problem of tumor treatment.

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