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Review: Genes Associated With Radiotherapy Sensitivity In Cervical Cancer

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1. Abstract

1.1. Background: Cervical cancer is a prevalent gynecological malignancy and radiation therapy is a primary treatment approach for locally advanced cervical cancer. However, some patients with cervical cancer exhibit poor response and resistance to radiation therapy. Radioresistance is the primary cause of treatment failure. Rapid advances in molecular analysis have resulted in discussion about the genes associated with radiotherapy sensitivity in cervical cancer. This review presents the state-of-the-art for genes associated with radiotherapy sensitivity in cervical cancer.

1.2. Methods: We searched the following keywords in PubMed: cervical cancer, gene, and radioresistance for literature as of December 2022.

1.3. Results: Genes affecting radiotherapy sensitivity in cervical cancer are closely associated with DNA damage response, hypoxia, and metabolism, among other factors.

1.4. Conclusion: There are a large number of genetic mutations in radiation resistant cervical cancer.More aggressive and individualized treatment is needed for the large number of resistant cervical cancers.

2. Keywords: Cervical Cancer, Gene, Radioresistance

3. Introduction

Cervical cancer (CC) is a common gynecological malignancy and the fourth leading cause of cancer-related death in women. It was estimated that there were 604,000 new cases of CC worldwide in 2020, representing an incidence of 6.5% and a mortality rate of 7.7% [1]. Although primary prevention (vaccination) and secondary prevention (screening) have been introduced, CC remains a major threat to women's health across the globe. Radiotherapy is the main approach for treating locally advanced cervical cancer (LACC). It has been reported that LACC patients receiving radiotherapy have a 2-year overall survival (OS) rate of 72% and a 5-year OS rate of 55% [2]. However, 30% of LACC patients have a poor response to radiotherapy, as known as radioresistance, which leads to a poor prognosis with a 5-year progression-free survival (PFS) rate of 0% [3]. Radioresistance is related to hypoxia, genetic changes, cell cycle status, DNA damage and repair, apoptosis, stem cells, and tumor microenvironment.

Molecular detection is currently undergoing rapid development, enabling the prediction of a patient's treatment effectiveness by detecting specific genes. Studies have reported that three genes, ANXA2, NDRG1, and STAT1, can predict the effectiveness of radiotherapy for CC [4]. Furthermore, another study identified seven genes, including CD58, JARIC, and TRIP6, as potential indicators of radiotherapy effectiveness in CC [5]. However, the application of these genes and other radiation sensitivity-related genes in the treatment of CC remains limited, emphasizing the need for further research. This article provides a comprehensive review of genes associated with the sensitivity of radiation therapy in CC.

4. Methods

We searched the following keywords in PubMed: cervical cancer, gene, and radioresistance for literature as of December 2022.

5. Results

Genes affecting radiotherapy sensitivity in cervical cancer are closely associated with DNA damage response, hypoxia, and metabolism, among other factors.

6. Discussion

In malignancies, many genes undergo mutations and/or functional

impairments. These changes in genes also affect the radiosensitivity of tumors. In the case of cervical cancer, the genes affecting radiosensitivity are closely linked to DNA damage response, hypoxia, glycometabolism, and other related factors.

6.1. Genes Associated With DNA Damage Response

Radiation therapy causes damage to the deoxyribonucleic acid (DNA) of tumor cells, resulting in various types of DNA damage, such as base damage, crosslinking, single-strand breaks (SSBs), and double-strand breaks (DSBs). The cell cycle is divided into four phases: G1, S, G2, and M. Upon exposure to radiation, tumor cells immediately halt their cell cycle to examine and repair the DNA damage. If the damage is too severe to repair, the cell will initiate apoptosis or other death pathways. DSBs are the most frequent cause of cell death. There are two primary pathways for repairing DSBs: homologous recombination (HR) and non-homologous end joining (NHEJ). Compared with NHEJ, HR is a more complex process involving several enzymes and proteins, but it is more accurate. NHEJ, however, can occur at any point during the cell cycle, while HR only occurs in the S and G2 phases [6].

Many genes in CC undergo mutations and/or functional impairments. A study reported that patients with LACC who achieved complete remission (CR) after radiotherapy had multiple differentially expressed genes compared to those who did not, and BRCA1 and RAD51 were found to be the most prominent [7]. Another study identified PIK3CA, MAPK, KRAS, PTEN, and TP53 as common mutation genes in recurrent CC, with mutation rates of 14%, 8%, 8%, 6%, and 5%, respectively [8]. These genetic changes are closely related to DNA damage response (DDR), a complex regulatory system that is activated when cells' DNA is damaged. DDR involves DNA damage recognition, signal transduction, DNA repair, and other processes, with the aim of repairing DNA damage as much as possible [9]. DDR largely determines whether damaged tumor cells will survive or die.

6.1.1. DNA Damage Recognition

DNA damage sensors can detect DNA damage and recruit downstream sensors. A series of DNA damage sensors have been discovered, including γ H2AX, 53BP1, DNA-dependent protein kinase (DNA-PK) [6]. A study reported that in patients with locally advanced head and neck tumors who received radiotherapy and chemotherapy, the CR rates of patients with low and high levels of 53BP1 expression were 50% and 6.3%, respectively (P=0.0059) [10].

6.1.2 DNA Damage Signal Transduction

Mediators of DNA damage checkpoint protein 1 (MDC1), Rad24p, and others are involved in the signal transduction of DSBs. MDC1 quickly binds to DNA damage sites, promoting the recruitment of repair proteins at DNA break sites. Tumor cells with MDC insertion/deletion mutations have impaired DRR function and better radiosensitivity [11]. Rad24p plays an important role in DRR, mediating DSB signaling responses and triggering cell cycle arrest. Rad24p gene deletion increases tumor radiosensitivity [6].

6.1.3 Cell Cycle

When cells are damaged, cell cycle arrest is immediately initiated to repair the damage. Ataxia-telangiectasia mutated (ATM) and ataxia-telangiectasia and Rad3 related (ATR) are tumor suppressors that control cyclin dependent kinase activity and regulate cell cycle arrest via checkpoint kinases 1/2 (Chk1/2) [12]. ATM and ATR mutations in various malignant tumors result in more time to repair the damage and increased DNA repair pathways, thereby promoting radioresistance [13]. Rad21 plays an important role in maintaining correct chromosome separation during cell mitosis, and the absence of Rad21 increases radiation sensitivity. In CC, Rad21 knockout resulted in lower colony formation rates post-radiotherapy (P<0.1) [14]. The Kirsten rat sarcoma virus (KRAS) gene, which encodes the Ras protein, is associated with cell growth and signal transduction. KRAS mutation, a common gene mutation, leads to change of Ras protein function. In CC, patients with KRAS mutations have a worse recurrence free survival than those without mutant KRAS (P=0.03), and there is also a correlation between KRAS mutation status and distant metastasis (P=0.04) [15]. Furthermore, KRAS mutation leads to increased WEE1 kinase expression. WEE1 kinase, overexpressed in various tumors, induces G2-M cell-cycle check point arrest, providing more time for tumor cells to repair DNA damage [16]. Staphylococcal nuclease domain containing 1 (SND1) is a DDR related protein, and SND1 deficiency inhibits G2/M blockade, promoting radiation-induced cell apoptosis. SND1 deficiency significantly increases radiosensitivity in cervical cancer cells [13].

6.1.4 DNA Damage Repair

DNA damage repair is an intricate and strictly regulated mechanism that involves many genes, including ATM, BRCA1/2, and RAD51.

ATM not only induces cell cycle arrest but also promotes DNA repair through its downstream targets, thereby making it a core component of the DNA repair mechanism. Once activated, ATM initiates the HR pathway by activating BRCA1, BRCA2, PALB2, and RAD51 [9]. Studies have reported that ATM inhibitors increase the radiosensitivity of tumor cells, but further research is needed to determine their potential clinical application [12]. BRCA1 and BRCA2 are tumor suppressor genes that are activated in response to DSBs. They produce BRCA protein that bind to the DSB site and initiate the HR pathway. Therefore, they play a key role in the HR pathway. Elevated expression of BRCA1/2 improves DNA repair ability. In tumors, a negative correlation exists between the expression level of BRCA genes and radiosensitivity [17]. BRCA1/2 mutations may lead to homologous repair defects (HRD) and HRD tumors have been found to exhibit enhanced radiosensitivity [18].

Poly (ADP-ribose) polymerase-1 (PARP1) is a nuclear chromatin-related protein that detect SSBs. PARP1 adds poly ADP ribose (PAR) to the damage sites in SSBs and plays a crucial role in DNA repair processes. PARP1 has been found to be differentially expressed in LACC patients who are sensitive to radiotherapy and those who are resistant to radiotherapy. Elevated levels of PARP1 are significantly correlated with radiation resistance in CC (P<0.05). Signal transducer and activator of transcription 1 (STAT1), a transcriptional activation factor, has a radiosensitizing

effect. STAT1 reduces the expression of PARP1 in tumors through various mechanisms, thereby increasing radiosensitivity [19].

Inhibiting PARP1 may lead to SSB repair defects. For HRD-positive tumors, the use of PARP1 inhibitors has been shown to improve treatment efficacy, as demonstrated in ovarian cancer [9]. Furthermore, cytological tests have demonstrated that the combination of PARP1 inhibitors and radiotherapy can increase the radiosensitivity of CC [19]. Currently, the Phase I/II clinical study (NCT03644342) of PARP1 inhibitor combined with radiotherapy for advanced CC is being conducted.

Accurate DNA repair is crucial for DRR. One of the key proteins involved the HR pathway is RAD51. It facilitates the precise opening of DNA sequences to enable accurate repair of damaged DNA. It has been observed that RAD51 mutations can detrimentally affect the accuracy of DNA replication and inhibit DNA repair [20]. PARP inhibitors have been shown to increase the radiosensitivity of RAD51 mutated tumors [9]. Bromodoomain containing protein 4 (BRD4) is a transcription factor that promotes RAD51 transcription. High expression of BRD4 is associated with radiation resistance. Cell experiments have shown that inhibiting BRD4 can suppress RAD51 transcription, leading to an increase in the radiosensitivity of cervical tumors [21].

Phosphatidylinositol 3 kinase (PI-3K) mutates and amplifies in multiple malignancies. Such mutations and amplifications are the most common changes and may lead to excessive activation of the PI3K/Akt signaling pathway, which is a key downstream pathway of various protein kinases [22]. The activated PI3K/Akt signaling pathway has been shown to reduce radiation sensitivity by enhancing DNA repair, aggravating hypoxia, and increasing angiogenesis [23]. PTEN is a tumor suppressor gene that can inhibit the PI3K/Akt pathway. Loss of PTEN leads to the activation of genes such as KRAS and Akt [24]. Activated Akt promotes tumor DNA damage repair ability by improving the expression of DNA dependent protein kinases and RAD51 [25]. Akt mutations are associated with a poorer prognosis. The average progression free survival (PFS) in LACC patients who received radiotherapy and had no Akt mutations was 86 months compared to only 44 months in those with Akt mutations (P=0.008) [26].

6.1.5 Apoptosis

When cells cannot repair damage, they undergo apoptosis or other cell death pathways. Apoptosis is a common manifestation following cell damage. Retinoblastoma-associated protein 48 (RbAp48) is a radiation-sensitive gene, and its overexpression has been shown to significantly increase the expression of p53, Rb, and other proteins in cervical cancer cells, which in turn promotes cell apoptosis and improves radiation sensitivity. Conversely, silencing the RbAp48 gene reduces the response of cervical tumor cells to radiotherapy [27]. Retinoblastoma protein-interacting zinc finger gene 1 (RIZ1) is a tumor suppressor gene that is often downregulated or lost in various malignant tumors. Overexpression of RIZ1, when combined with radiotherapy, can induce more cell apoptosis and promote the efficacy of radiotherapy [28]. The TP53 gene serves a critical function in inhibiting the cell cycle and promoting cell apoptosis. However, mutation or inactivation of TP53 can counteract cell apoptosis, inhibit cell autophagy, and lead to radioresistance [29].

6.2. Genes Associated With Hypoxia

Hypoxia is a significant contributor to radioresistance. Radiation therapy damages the DNA of tumor cells through the generation of free radicals and fixates the damage through reactive oxygen species (ROS). Hypoxia reduces the number of free radicals and DNA damage, resulting in a severe decrease in the radiosensitivity of tumors. Moreover, hypoxia can alter gene expression patterns and enhance the characteristics of tumor stem cells, which further increases radioresistance [30]. Hypoxia is a common feature of solid tumors. Compared with normal tissue, the vascular system of tumor tissue is disrupted and functionally impaired, making it unable to effectively transport oxygen. In addition, the rapid growth of tumors increases their demand for oxygen, further exacerbating tumor hypoxia. While the oxygen level of normal tissue is 20%, the oxygen level of most tumors is less than 2% [31]. The radiosensitivity of tumor cells is positively correlated with the oxygen concentration in the microenvironment [32]. Tumor hypoxia is a dynamic process, and as circulating oxygen levels change, acute and chronic hypoxic areas are generated. Slow hypoxia may alternate with acute hypoxia or coexists in different regions of the tumor [33].

Hypoxia can induce the expression of hypoxia-inducible factor 1 (HIF-1). Under normal oxygen conditions, HIF-1 is rapidly degraded, but hypoxia leads to its stabilization and accumulation [32]. HIF-1 regulates the expression of multiple genes, including vascular endothelial-derived growth factor (VEGF) and human N-Myc downstream-regulated gene 2 (NDRG2), which impact tumor radiation sensitivity. VEGF plays an important role in regulating angiogenesis and vascular regeneration, processes that are crucial for tumor growth and development. The expression of VEGF is increased in various tumors. However, tumor vascular reconstruction after radiotherapy is also one of the main reasons for radioresistance. Although radiotherapy damages some tumor blood vessels, VEGF can stimulate angiogenesis and vascular reconstruction, providing the necessary nutrients for tumor recurrence after radiotherapy [35]. Additionally, tumor vascular endothelial cells are highly resistant to radiotherapy and are an important factor affecting the efficacy of radiotherapy [36]. Inhibiting VEGF has a radiosensitizing effect. When combined with radiotherapy, VEGF inhibition increase to 23.06% in the apoptosis rate of tumor cells, compared to the 12.08% apoptosis rate of cells treated with radiotherapy alone [30].

NDRG2 is a target gene for HIF-1 and its expression is upregulated under hypoxic conditions. NDRG2 can inhibit radiation-induced apoptosis of cervical cancer cells, thereby promoting radiation therapy. Studies have shown that overexpression of NDRG2 results in a decrease while silencing NDRG2 leads to an increase in the radiosensitivity of cervical tumor cells [34]. Furthermore, HIF1, as a key regulatory factor of glycolysis, promotes glycolysis, enhances tumor antioxidant capacity of tumors, leading to increased radioresistance. HIF1 induces overexpression of

hexokinase 2 (HK2) and dehydrogenase kinase 1, which further contribute to radioresistance [37].

6.3. Genes Associated With Metabolism

The metabolism of reactive oxygen species and glucose in tumors has been found to be closely linked to radioresistance.

6.3.1 Glycometabolism

Normal tissues produce energy by metabolizing glycose through oxidative phosphorylation (OXPHOS) in the presence of oxygen and by the glycolytic pathway only under hypoxic conditions. Tumor tissue, on the other hand, relies more on aerobic glycolysis to generate energy, even in the presence of sufficient oxygen. This phenomenon is known as the Warburg effect [38]. The Warburg effect enables tumors to synthesize a large number of nutrients to support their growth and proliferation, and adapt to a hypoxic environment. The Warburg effect is also closely related to radioresistance. It produces substances such as pyruvate and lactate. These substances have antioxidant properties and can effectively eliminate free radicals and ROS, thereby reducing free radical-mediated damage [39]. HK2, a key metabolic enzyme in the glycolytic pathway, is often overexpressed in tumors. HK2 reduces tumor cell apoptosis by direct interacting with mitochondria, thereby reducing the efficacy of radiotherapy [40].

70% of human tumors have been found to have overexpression of genes related to glycolysis [38]. In CC, the upregulation of glycolytic genes is associated with worse OS (P=0.015) [7]. In addition, cervical tumor cells that are radioresistant have shown increased sensitivity to radiation therapy after the use of glycolytic inhibitors [41]. Many genes are involved in the metabolic shift from OXPHOS to glycolysis in tumor cells. HIF-1 promotes the Wahlberg effect by inducing the overexpression of glucose transporters [42]. The oncogene c-Myc promotes the Warburg effect in CC by enhancing the expression of HK2 [37]. ETS-related gene (ERG), a proto-oncogene, is overexpressed in malignant tumors. ERG may be a key regulatory factor for the Wahlberg effect in CC. ERG promotes the expression of HK2 and phosphoglycerate kinase 1 (PGK1) by directly binding to their promoters, thereby enhancing the Warburg effect [42]. The SET and MYND domain-containing protein 2 (SMYD2) is a carcinogenic gene and promotes the glycolysis of tumor cells. Overexpression of SMYD2 is associated with poor prognosis in patients with CC [43]. 6.3.2 Reactive oxygen metabolism.

Radiotherapy needs ROS, a group of oxygen-containing molecules, to induce DNA damage. However, compared with radiation-sensitive tumor cells, radiation-resistant tumor cells exhibit an enhanced ability to eliminate ROS [44]. Glutamine Synthetase (GS) is significantly elevated in radiation-resistant tumor cells. GS participates in the synthesis of reduced glutathione (GSH), which can clear ROS and reduce the DNA damage caused by radiotherapy [45]. Inhibiting GS can improve the efficacy of radiotherapy. Recent studies have reported that glutaminase inhibitors have increased the efficacy of radiotherapy in CaSki and SiHa cells, with a Dose Modifying Factor (DMF) of 1.9 and 1.2, respectively [46]. Moreover, nuclear factor erythroid-related factor 2 (NRF2) is a transcription factor that regulates the generation of ROS. NRF2 upregulates the expression of antioxidant-related enzymes, leading to a decrease in ROS levels. Additionally, NRF2 upregulates the expression of the anti-apoptotic protein Bcl-2, preventing cell apoptosis and promoting radiation resistance [44]. NRF2 gene overexpression has been found in 7% of cervical cancer and is associated with poor outcomes [47]. Liver kinase B1 (LKB1) is a tumor suppressor gene, and LKB1 deficiency has been found associated with treatment resistance in lung cancer [48]. LKB1 is involved in the metabolic regulation of cells. LKB1 mutation leads to a decrease in intracellular GSH and an increase in ROS [49]. In recurrent CC, LKB1 mutations have been identified in 4% of recurrent CC cases [8].

6.4. Treatment Options For Radioresistant Cervical Cancer

Radioresistance remains an important cause of LACC treatment failure [3]. Radioresistance can be attributed to many factors such as gene mutation, hypoxia, and the tumor microenvironment. To improve treatment outcomes of radioresistant CC, it is crucial to explore and employ alternative treatment modalities and enhance radiotherapy sensitivity.

6.4.1 Immunotherapy

Immunotherapy has been used to treat various malignant tumors. The tumor microenvironment (TME), consisting of tumor cells, fibroblasts, blood and lymphatic vessels, immune cells, and immune factors, plays a critical role in tumor occurrence and progress. Tumor immune microenvironment (TIME) refers to all immune cells and immune factors in the TME [50]. In TIME, two immune components can either inhibit or promote tumor growth, and their interactions dictate the development of tumors. Tumors eventually suppress the immune system through multiple pathways [51]. Immunotherapy reactivates the inhibitory tumor immune response in the immune system. Currently, the most common form of immunotherapy involves the use of immune checkpoint inhibitors (ICIs). ICIs work by binding to immune checkpoint proteins, which can suppress tumor immunity, thereby increasing the immune system's ability to identify and attack tumor cells [52]. The most well-known immune checkpoint proteins are programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte antigen (CTLA-4).

Unfortunately, the current effectiveness of immunotherapy is not yet satisfactory. In the KEYNOTE-158 study, the PD-1 inhibitor Pembrolizumab was used to treat CC that had previously failed treatment, with an objective remission rate (ORR) of 12.2% (95% CI, 6.5% to 20.4%) [53]. Another study showed that the combination of PD-1 inhibitor and CTLA-4 inhibitor in the treatment of advanced CC resulted in an ORR of 25.6% (95% CI, 18.8 to 33.9) [54]. The number of anti-tumor immune cells, the spatial distance between immune cells, and hypoxia may all affect the efficacy of immunotherapy [50].

6.4.2 Addressing Hypoxia

Hypoxia not only causes radioresistance but also significantly reduces the effectiveness of immunotherapy [55]. Addressing hypoxia can effectively

solve radioresistance and enhance the efficacy of immunotherapy. Anemia is one of the causes of tumor hypoxia [56]. For cervical cancer patients, anemia is often associated with poor treatment outcomes. Correcting anemia through blood transfusions can improve the efficacy of radiotherapy [57]. However, some studies have suggested that blood transfusions and erythropoietin treatment have a limited impact on tumor hypoxia and do not lead to survival benefits [58].

Bevacizumab has been shown to improve the disordered distribution of tumor blood vessels, normalize tumor blood vessels, and address hypoxia. In breast cancer, it was observed that after the use of bevacizumab, the tumor oxygen supply increased [59]. For patients with metastatic, persistent, or recurrent CC, combining chemotherapy with bevacizumab leads to a more favorable therapeutic outcome than chemotherapy alone, resulting in an OS of 16.8 months compared to 13.3 months (95% CI, 0.62 to 0.95; P=0.007) [60]. A self-oxidizing and degradable nanosystem has been developed to address tumor hypoxia. This nanosystem includes calcium peroxide (CaO_2), manganese dioxide (MnO_2), and the chemotherapy drug doxorubicin. CaO_2 can efficiently transport hydrogen peroxide, and MnO_2 reacts with hydrogen peroxide to generate oxygen continuously and effectively, thus improving the oxygen deficiency in TME [55].

Radiation sensitizers enhance the killing effect of radiotherapy on tumor cells by accelerating DNA damage and indirectly generating free radicals. The ideal radiosensitizer, which can enhance the radiosensitivity of tumor tissue while reducing the toxicity of normal tissue, is still under research [61]. Some studies have linked the use of radiotherapy sensitizers with the alleviation of hypoxia. One example is the use of Au nano particle−hemoglobin complex nanoparticle loaded platelets (Au-Hb@PLT). When activated by tumor cells, Au-Hb@PLT can penetrate into tumor tissue. Hemoglobin alleviates hypoxia, and Au nanoparticles serve as radiation sensitizers, making tumor cells more sensitive to radiation therapy. In mouse experiments, Au-Hb@PLT combined with even low-dose radiation was found to improve the efficacy of radiotherapy for tumors [62]. Currently, the nanosystem and Au-Hb@PLT are still being experimented, and blood transfusions and bevacizumab have not been found to bring significant survival benefits. Further exploration is needed in addressing hypoxia and radiation sensitization.

6.4.3 Radiation Dose

At present, the radiation dose is still being given uniformly and has not been adjusted according to the biological differences of tumors. Electron Paramagnetic Resonance Oxygen Imaging (EPR O2 imaging) can accurately display the extent and location of hypoxia within tumors [63]. By identifying areas with severe hypoxia, higher doses can be administered to enhance treatment efficacy, while areas with better oxygenation may need lower radiation doses. In a clinical trial (NCT03163979) initiated in 2017, high-dose radiation therapy was administered to areas of tumors that were found to be insensitive to radiation therapy based on positron emission tomography (PET). The study is still ongoing, and we await its results.

6.4.4 HPV Treatment

Most cervical cancer cases are associated with human papillomavirus (HPV), with non-HPV-related cervical tumors accounting for only 5.5-11% of cases [64]. HPV-related tumors express the E6 and E7 oncoproteins, and E6/E7 is not present in nontumor tissues. Therefore, E6/E7 has emerged as a good therapeutic target. In cell experiments, researchers have used small interfering ribonucleic acid (siRNA) to specifically block the expression of the E6/E7 oncoproteins. Combining siRNA with radiotherapy has been found to effectively inhibit tumor growth in mice transplanted with cervical cancer cells [65]. There are therapeutic HPV DNA vaccine0s available for HPV-related tumors. In a single-arm?; Phase II clinical study, a combination of HPV DNA therapeutic vaccine and pembrolizumab was used to treat patients with recurrent or advanced CC. Out of 26 patients, 11 (42%; 95% CI, 23-63) achieved overall remission, and no serious side effects were reported [66].

Genetically engineered T cells have shown remarkable clinical efficacy in tumors that have failed previous immunotherapy. T cells have been engineered to bind to the T cell receptor (TCR) targeting HPV-16 E6/E7 for the treatment of HPV-related tumors. In the study of E6 TCR-T cells, 12 HPV-related tumor patients who had previously failed treatment were treated with E6 TCR-T cells, and 2 of them showed objective tumor responses [67]. Similarly, in the study of E7 TCR-T cells, 12 patients with HPV-related tumors that had failed previous treatment, including 8 cases of failed immunotherapy, were treated with E7 TCR-T cells. After the treatment, 6 patients demonstrated significant tumor regression [68]. The treatments for HPV discussed above are still in the research stage and we look forward to the research results.

7. Conclusion

Radioresistance remains a major cause of LACC treatment failure [3], and it can be attributed to various factors, including genetic mutations. Therefore, there has been extensive research exploring genes related to radiosensitivity in cervical cancer. By identifying the genes associated with radiation sensitivity, it may be possible to accurately distinguish patients who are more likely to be radioresistant and provide them with personalized radiotherapy and other treatments to improve treatment efficacy and patient outcomes.

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