

REVIEW ARTICLE

Adverse effects of chemoradiotherapy on invasion and metastasis of tumor cells

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Received 30 November 2019; received in revised form 18 March 2020; accepted 3 April 2020

Available online 9 April 2020

KEYWORDS

Biological behavior;
Cancer;
Chemoradiotherapy;
Mechanism;
Invasion and
metastasis

Abstract The phenomenon of enhanced invasion and metastasis of residual tumor cells has been observed in an increasing number of patients receiving chemoradiotherapy recently, and tumor metastasis will undoubtedly limit patient prognosis. However, the key mechanism by which chemoradiotherapy affects the invasion and metastasis of tumor cells remains unclear. Studies have shown that chemoradiotherapy may directly act on tumor cells and alter the tumor microenvironment, or induce cell apoptosis and autophagy to promote tumor cell survival and metastasis. In this review, we summarize the potential mechanisms by which chemoradiotherapy may affect the biological behavior of tumor cells and open up new avenues for reducing tumor recurrence and metastasis after treatment. These insights will improve the efficacy of chemoradiotherapy.

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Peer review under responsibility of Chongqing Medical University.

Introduction

Chemoradiotherapy is the combination of radiotherapy and chemotherapy, which utilizes chemotherapy as a radiosensitizer that renders tumor cells more sensitive to radiotherapy to achieve better local control effect.^{1,2} In several cases of liver cancer, however, the therapeutic effect of chemoradiotherapy was observed as unexpected, reflected in opposite effect of chemotherapy. Tumor volume rapidly decreased in a short period after patients received a high dose of chemoradiotherapy, but metastasis would occur after discontinuation of chemoradiotherapy.³ A similar phenomenon has been observed in non-small cell lung cancer (NSCLC), where cell proliferation is accelerated after the cessation of chemotherapy and progression becomes faster than in untreated tumors.⁴ Similarly, in oropharyngeal cancer, the potential doubling time of tumors after induction of chemotherapy was shorter after treatment than before treatment. This was indicative of an increased proliferation of oropharyngeal tumor cells after poor response to chemotherapy.⁵ In extrahepatic cholangiocarcinoma, chemoradiotherapy combined with surgery is potentially beneficial to local control by improving tumor resectability and survival rate, but systemic metastases threaten patient prognosis and chemoradiotherapy needs to be considered more critically.⁶ Chemoradiotherapy also induces the metastasis of ovarian cancer cells to the bone marrow and other organs.⁷ The mechanism underlying rapid tumor metastasis after discontinuation of chemoradiotherapy is still unclear.

In a study, local treatment with 4–10 Gy radiation for oral mammary carcinoma resulted in increased lung metastasis in tumor-bearing mice compared with that in the sham irradiation control group.⁸ A similar pattern is noted in breast cancer, where even low-dose preoperative exposure can lead to increased lung metastasis.⁹ Although the Radiation Therapy Oncology Group (RTOG) noted that, in NSCLC the tolerated radiation dose can be as high as 83.8 Gy using three-dimensional conformal techniques.¹⁰ However, RTOG0617 data present different perspectives. This clinical experiment compared the prognosis of lung cancer patients receiving 74Gy and 60Gy.¹¹ The results showed that although no increased toxic side effects were observed in 74Gy radiation-treated patients, the risk of death and local failure of these patients was higher than those in 60Gy radiation-treated patients, and most of them died of metastatic recurrence. Therefore, it is speculated that high-dose radiation therapy may promote tumor invasion and metastasis.

Although preoperative chemoradiotherapy can reduce tumor burden and achieve tumor downstaging, it may increase the risk of distant metastasis and reduce disease-free survival. Tumor microenvironment of metastasis (TMEM) score and TMEM-related isoform protein expression were increased in residual breast cancer cells in patients treated with doxorubicin plus cyclophosphamide with neoadjuvant paclitaxel. This was indicative of a decrease in tumor size, but the risk of metastatic transmission also increased.¹² Analysis of the 10-year data from the German CAO/ARO/AIO-94 phase 3 trial on rectal cancer showed that the prognosis of patients after chemoradiotherapy was generally poor and the migration of tumors increased after

downstaging.¹³ An association between radiotherapy and metastases of the oropharynx and hypopharynx tumors was discovered in 1978.¹⁴ Subsequent studies have also shown that radiotherapy increases the risk of distant metastasis by increasing the number of circulating tumor cells in NSCLC and bladder cancer.¹⁵ Although the reduction of tumor burden by chemoradiotherapy is beneficial, we need to consider the impact of the associated increase in the risk of distant metastasis on patient prognosis.

While most studies in the field of tumor chemoradiotherapy focus on how to reduce tumor burden, we attempt to clarify how the key mechanisms of chemoradiotherapy affect the biological behavior of tumor cells, and explore their reasonable interventions. This may provide insights for reducing the chemoradiotherapy-related tumor recurrence and metastasis, and improve the efficacy of chemoradiotherapy.

Mechanisms of chemoradiotherapy affecting tumor cell invasion and metastasis

Chemoradiotherapy directly affects tumor cells, influencing invasion and metastasis

DNA damage affects tumor metastasis

DNA damage is an important mechanism for the understanding of the development of cancer. A consensus revealed that DNA damage induced by chemoradiotherapy is associated with cancer development.¹⁶ When DNA damage occurs, the cell is confronted with various processes, including regulation of cell cycle and programmed cell death. The micellar formulations of talazoparib and buparlisib reinforce DNA damage in breast cancer radiotherapy, causing cell apoptosis and inhibiting tumor metastasis.¹⁷ It has also been reported that radiation-induced lung DNA damage promotes breast cancer lung-metastasis.¹⁸ Some studies also show that DNA repair is related to tumor metastasis. In melanoma, DNA repair genes are upregulated in metastatic tumors compared to primary tumors.^{19,20} DNA damage repair-related proteins can enhance chemoradioresistance and alleviate DNA damage caused by chemoradiotherapy. A study showed that silencing MBD1, a DNA damage repair-related protein, reduced chemoradiotherapy resistance in pancreatic cancer.²¹ This may explain why DNA damage repair affects the recurrence and metastasis of tumors after radiotherapy and chemotherapy. DNA damage caused by chemoradiotherapy, therefore, can stimulate tumor cell metastasis, and controlling it may be beneficial to tumor therapy.

The process of DNA damage and repair is complex. The ataxia-telangiectasia mutated (ATM) protein and p53 are greatly important in DNA damage response, and once activated, they regulate many substrates for DNA damage-induced responses.²² An investigation of cell apoptosis, using different doses of chemoradiotherapy, confirmed that the ATM/p53 pathway is directly involved in DNA damage induced by chemoradiotherapy in breast cancer cell lines, and rhodamine can be used to inhibit the survival of tumor cells via the ATM/p53 pathway.²³ Radiotherapy for breast cancer induces DNA damage and p53 activation,

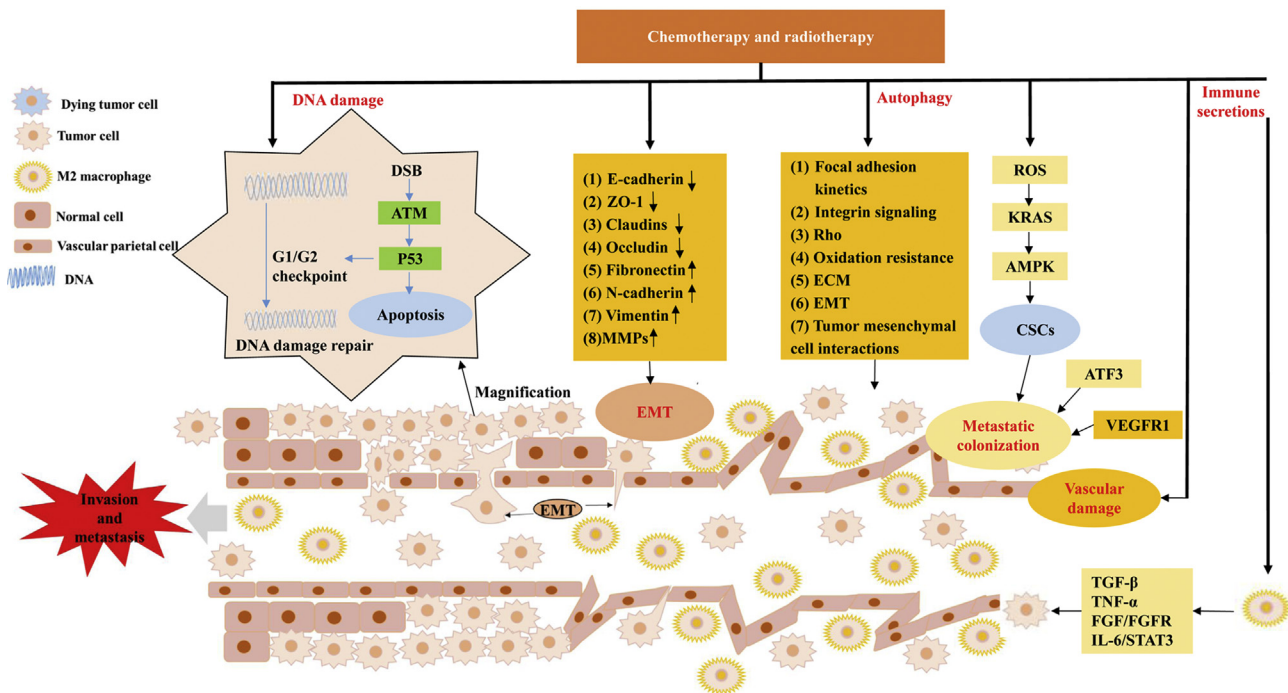


Figure 1 A highly simplified diagram shows the mechanism by which chemoradiotherapy may induce invasion and metastasis of tumor cells. DNA damage (DNA double-strand breaks, DSB) may trigger apoptosis, and necessitate the escape of tumor cells for survival. At the site of EMT, the matrix is locally degraded, intercellular connections are lost, cytoplasmic processes are protruded, and the contraction of the cytoskeleton causes the cell body to separate from its neighbors to complete ectopia. Under adverse microenvironmental conditions such as chemoradiotherapy, functional autophagy response supports the survival of tumor cells and promotes tumor invasion and metastasis. Vascular injury can directly accelerate tumor cell overflow, and the resulting dysmorphogenesis of blood vessels and macrophages is conducive for creating the TMEM and promoting tumor invasion and metastasis. Chemoradiotherapy also promotes the stem-like properties of CSCs and activates metastatic colonization. Following chemoradiotherapy, M2 macrophages release inflammatory cytokines, which trigger tumor cell metastasis. The process of promoting tumor cell invasion and metastasis by chemoradiotherapy involves many and complex molecules, but only a few representative star molecules were listed in the above diagram.

accompanied by lung injury and stimulation of lung metastasis.¹⁸ DNA repair in tumor cells of patients with brain metastases, after radiotherapy, promotes cell proliferation, survival, metastasis, and drugs that block G₂/M checkpoint under irradiation disrupt DNA damage repair and inhibit brain metastases.²⁴ Hence, DNA damage is one of the possible mechanisms, as shown in Fig. 1, that leads to tumor metastasis caused by chemoradiotherapy. Therefore, understanding DNA damage mechanisms is beneficial to the treatment of cancer, and the prevention of side effects of chemoradiotherapy.

Epithelial-mesenchymal transition (EMT) affects tumor invasion and metastasis

Tumor cells acquire the migration phenotype through the loss of polarity of epithelial cells and acquisition of mesenchymal characteristics, a process known as EMT.^{25,26} The mechanism of this process is complex, as cancer cell migration from original locations results from the synergy of multiple molecules that cause the decreased epithelial marker and increased mesenchymal marker.²⁷ EMT can also reduce the sensitivity of tumor cells to chemoradiotherapy.^{28,29} On the other hand, chemoradiotherapy can induce EMT, and enhance the invasion and metastasis

of tumor cells. The possible mechanisms involved in the induction of EMT by chemoradiotherapy are shown in Fig. 1. A study evaluated the relationship between EMT markers, E-cadherin, vascular endothelial growth factor and epidermal growth factor receptor, and overall survival of patients after chemoradiotherapy and intracavitary brachytherapy. The results showed that EMT markers were associated with tumor proliferation and angiogenesis after chemoradiotherapy, and overall survival of patients with cervical cancer.³⁰ Colorectal cancer cells treated with radiotherapy showed typical EMT changes, such as polarity loss, spindle cell traits, intercellular separation, pseudopod formation, enhancement of cell migration, and invasion observed at the molecular level.³¹ The EMT changes caused by chemoradiotherapy were directly observed through changes in cell morphology, hence, it may be used as a marker to determine the risk of clinical tumor metastasis. After 30 days of radiotherapy for liver cancer in nude mice, although the expression of vascular endothelial growth factor decreased to the control level, overexpression of Tmprss4 induced E-cadherin transcriptional repressor results in the loss of E-cadherin and promotes the EMT related spread and metastasis of residual tumors in mice.³² Similarly, molecular changes consistent with EMT have been

observed in oxaliplatin-treated liver cancer cells, accompanied by significantly enhanced migration and invasion.³³ Studies have found that inhibition of EMT by tyrosine kinase inhibitor decreases the invasive and metastatic potential of radiation-induced hepatocellular carcinoma.³⁴ The inhibition or promotion of EMT corresponds to a proportional inhibition or promotion of tumor metastasis. This emphasizes EMT as an important contributor to distant tumor metastasis induced after radiotherapy and chemotherapy.

Autophagy affects tumor invasion and metastasis

Macroautophagy (here called autophagy) is an intracellular degradation pathway that mediates the isolation of intracellular entities within the double-membrane sac, known as autophagosomes, and delivers them to lysosomes for degradation and recovery.³⁵ For cancer, autophagy plays a dual role in tumor cell fate: it can inhibit the occurrence of tumors via the elimination of damaged organelles in transformed cells, protect cells from oxidative stress, and prevent malignant transformation. Autophagy may also act as a tumor-supporter by triggering cancer cell survival and inhibiting apoptosis. This can promote chemoresistance and EMT mediated metastasis.³⁶ Over the past several years, emerging evidence has revealed a direct role of autophagy in inducing invasion and metastasis in cancer cells. For instance, highly expressed ATG10 in colorectal cancer is related to lymphovascular invasion and lymph node metastasis, and ATG10 may act as a potential prognostic marker in colorectal cancer.³⁷ Furthermore, advanced human tumors typically exhibit increased autophagy fluxes, which are associated with invasion/metastasis phenotypes, high nuclear grade, and poor disease outcomes.^{38,39} Autophagy regulates several mechanisms that facilitate metastasis and these include (1) focal adhesion kinetics, (2) integrin signaling and transport, (3) Rho GTPase-regulated cytoskeletal remodeling, (4) oxidation resistance, (5) ECM composition, (6) epithelial-mesenchymal transformation (EMT) signaling, and (7) tumor mesenchymal cell interactions.⁴⁰

There have also been increasing evidence in support of the activation of autophagy in tumor cells by radiation, chemotherapy, and targeted therapy.⁴¹ Multiple studies have revealed that 5-FU therapy triggers autophagy of cancer cells *in vivo*, and suppressing autophagy potentiated the anticancer effects of 5-FU.^{42,43} In colorectal cancer, chemotherapy induces genotoxic stress followed by the elevation of p53, and activated p53 regulates autophagy via the activation of AMPK and inhibition of mTOR.⁴⁴ A previous study showed that p53 promotes cell survival and chemotherapeutic resistance of liver cancer by regulating autophagy activation in the absence of nutrients.⁴⁵ Linifanib has been shown to suppress PDGFR- β and the downstream Akt/mTOR and Mek/Erk signaling, which increases autophagy in hepatocarcinoma cells, leading to their survival *in vitro* and *in vivo*.⁴⁶ Cisplatin promotes the activation of GFRA1, which induces autophagy via SRC-AMPK signaling in osteosarcoma cells.⁴⁷ Ionizing radiation triggers ROS-mediated macromolecular (mainly DNA) damage and ER stress response, resulting in autophagy.⁴⁸ Overall, autophagy triggers invasion and metastasis in cancer, and chemotherapy activates

autophagy. Therefore, chemoradiotherapy may contribute to the invasion and metastasis via activating autophagy (Fig. 1). Further research of autophagy in the tumor microenvironment may help develop new inhibitors and clinical trial strategies.

Chemoradiotherapy induces metastatic colonization of cancer cells

The formation of premetastatic niche and colonization of cancer cells are important programs for metastasis. Emerging evidence has shown that chemoradiotherapy may facilitate premetastatic niche formation and cancer cell colonization at distant sites. Paclitaxel demonstrates the pro-metastatic effect of chemotherapy by facilitating tumor diffusion and metastasis formation via the generation of a pro-metastatic niche and enhancement of metastatic colonization.⁴⁹ Chang et al revealed that paclitaxel and cyclophosphamide can trigger tumor cell dissemination and metastatic colonization via the recruitment of myeloid progenitors to the primary, as well as secondary, sites in a pattern that relies on stress-inducible gene Atf3.⁵⁰ Paclitaxel and cisplatin promote the retention of tumor cells in pulmonary vessels of mice, leading to metastasis and colonization. A possible mechanism is that chemotherapy induces the activity of vascular endothelial growth factor receptor 1 (VEGFR1), which enhances the adhesion of endothelial cell and tumor cell, as well as the paracrine interactions.⁵¹ Radiation following 10 days of subcutaneous implantation in mice can stimulate tumor cell colonization via capillaries. This phenomenon was confirmed by the increased infiltration of CD31 positive cells, following local irradiation in mice with Lewis lung cancer.⁵² Overall, chemoradiotherapy may facilitate cancer cell seeding and colonization, resulting in tumor metastasis.

Chemoradiotherapy enhances the stem-like properties of cancer stem cells (CSCs)

Active metastatic colonization is contingent upon the dissemination of CSCs that can re-initiate tumor growth. CSCs are a small subset of tumors that can self-renew and proliferate, and play crucial roles in tumor progression and recurrence. Although chemotherapy and radiotherapy can kill most tumor cells, they do not affect CSCs, leading to their enrichment and development into more refractory tumors.⁵³ A previous study showed that typical CSCs account for about 1–10% of the total number of cells in head and neck cancer, whereas this proportion may elevate with the increase of therapeutic radiation dose.⁵⁴ Eradication of CSCs is essential for effective therapy of cancer, as CSCs can promote regrowth of the cancer cells and lead to tumor recurrence. Nevertheless, it is difficult to eliminate CSCs as they are usually resistant to therapy. The stem-like characteristics of CSCs are potentially necessary for successful metastatic colonization, and increasing evidence support the claim that chemoradiotherapy enhances the stem-like characteristics of CSCs.⁵¹ A previous study showed that chemotherapy stress reinforced the sphere-forming ability of CSCs in breast cancer, and induced the change of cell morphology and EMT-related genes at the mRNA level.

Meanwhile, the migration capacity of CSCs was not affected.⁵⁵ Cancer cells that develop EMT have been claimed to obtain stemness and experience metabolic alterations, although these ideas are controversial. Irradiation is known to stimulate the characteristics of CSCs, including dedifferentiation and self-renewal, and enhance oncogenic metabolism via activating the EMT-inducing signaling pathways.⁵⁶ It has been shown that Gemcitabine may induce the stem-like cell properties in pancreatic cancer via the involvement of ROS/KRAS/AMPK signaling pathway.⁵⁷ These findings suggest that chemoradiotherapy enhances the stem-like properties of CSCs and the resultant active metastatic colonization.

Chemoradiotherapy affects invasion and metastasis through the TMEM

Tumor metastasis depends on the TMEM, and it is not independent of the direct contact of three cell types: tumor cell, endothelial cell and macrophage.⁵⁸ The effects of radiotherapy and chemotherapy on tumor metastasis, from the tumor microenvironment, associated with endothelial and immune cells.

Chemoradiotherapy affects tumor invasion and metastasis by facilitating vascular damage

Chemoradiotherapy induced modifications of the host, including immunosuppression and vascular damage, can facilitate invasion and metastasis.^{59,60} For instance, a single fraction dose of 5–10 Gy can cause minor vascular damage, and more than 10 Gy can induce more severe vascular damage.⁶¹ Recent studies have shown that chemoradiotherapy may produce acute and late, local and systemic side effects including vascular damage.^{62,63} In chemotherapy, bleomycin administration can result in damage to the endothelial cells lining the common pulmonary arteries and veins.^{64,65} This bleomycin-induced endothelial cell retraction, with increased lung endothelial permeability, is related to increased retention of I.V. injected tumor cells and enhancement of lung nodule formation.⁶⁶ After X-irradiation, the enhancement of experimental metastasis has been attributed to the vascular damage associated with this treatment.^{67,68} Radiotherapy, therefore, causes damage to the DNA of NSCLC cells and increases the number of circulating tumor cells in the blood, which may result from damage to the vessels by radiation. Thus, tumor cells can easily break the barrier and enter the blood circulation to complete distant migration.⁶⁹ Compared with untreated mice with cancer cells that were stationary in blood vessels, mice treated with the cyclophosphamide showed proliferation, extravasation, and extravascular colony formation of cancer cells in the vessels.⁷⁰ These suggest that normal vascular injury caused by chemoradiotherapy possibly provides an outlet for tumor metastasis and promotes angiogenesis, and this may be the precondition for tumor metastasis. Additionally, several markers associated with vascular damage have been identified.⁷¹ Therefore, after chemoradiotherapy, preventing or reversing vascular damage may reduce the recurrence of tumor metastasis.

Notably, the structure and function of vessels in solid tumors are abnormal, and anti-angiogenesis therapy promotes tumor metastasis. In a study on sorafenib-treated mice, tumor growth was accelerated, mouse survival was decreased, lung metastasis was increased, and sorafenib downregulated the expression of HIV-1 Tat interactive protein 2 (HTATIP2) through the JAK-STAT3 signaling pathway. This, in turn, promoted the invasive and metastatic potential of orthotopic tumors of hepatocellular carcinoma cells in the mice.⁷² In another study, aspirin minimized the pro-metastasis effect of sorafenib by mediating the inhibition of COX2 to upregulate tumor suppressor HTATIP2.⁷³ VEGFR-2 tyrosine kinase inhibitor AZD2171 was also found to inhibit tumor growth, both in vivo and in vitro, and promote tumor sensitivity to radiation, limiting metastasis.⁷⁴ The upregulation of fibroblast growth factor-2, a pleiotropic angiogenesis inducer, is thought to be the mechanism by which tumors evade anti-VEGF therapy.⁶⁹

Immune secretions affect tumor cell invasion and metastasis

Immune cells, including macrophages and platelets, promote tumor metastasis after stimulation by chemoradiotherapy, and the possible mechanisms are shown in Fig. 1. Condeelis et al believe that macrophages are located at the center of the TMEM and have six characteristics for promoting malignant tumors: tumor cell invasion, inflammation, matrix remodeling, angiogenesis, seeding at distant sites and intravasation.⁷⁵ Chemoradiotherapy promotes the release of inflammatory cytokines by macrophages, such as tumor necrosis factor- α (TNF- α) and transforming growth factor- β 1 (TGF- β), which aggravates tumor injury.⁷⁶ Tumor-associated macrophages are the main cells for the expression of immunoreactive C-X-C chemokine receptor 4 in mouse tumor cells, whereas M2-related macrophages, especially those in direct contact with vessels, may stimulate tumor recurrence and metastasis after chemotherapy induction.⁷⁷ FGF and their receptor (FGFR) regulate a variety of cellular processes, including proliferation, survival and motility, and in a study, FGF2 was highly expressed in recurrent cancer tissues, after chemoradiation in esophageal cancer patients. The 2-year and 5-year local recurrence-free survival rates of patients with high expression of FGF-2 were 15.4% and 0% respectively, while those of patients low expression of FGF-2 were 45.8% and 33.3% respectively.⁷⁸ FGF2 and its related signaling pathway can promote tumor metastasis in various sites including breast cancer, lung cancer, colorectal cancer, melanoma, etc.^{70,71,79,80}

Chemotherapy also induces tumor cell senescence, which irreversibly prevents cell proliferation and suppresses tumors. It also induces normal cell senescence, which leads to local and systemic inflammation and increases tumor growth and metastasis.⁸¹ In a study, IL-6/STAT3 signaling loop and platelet-derived growth factor-BB/PDGF receptor pathway were upregulated in a conditioned medium (CM) from senescent cells; besides, CM can promote angiogenesis in the chicken chorioallantoic membrane by endothelial cell invasion.⁸² The effect of macrophages on tumor cell metastasis is systematic and

comprehensive. Thus, numerous immune cell secretions affect the invasion and metastasis of cells via TMEM alteration after induction of chemoradiotherapy.

Accumulating evidence shows that under certain conditions, radiation can be used in combination with immune checkpoint inhibitors to enhance the efficacy.⁸³ Anti-CTLA4 alone fails to suppress tumor growth or increase survival, while radiotherapy alone could delay the growth of primary lesions. The combination of Anti-CTLA4 therapy and radiotherapy, however, can significantly increase the overall survival and reduce lung metastasis.⁸⁴ PD-1 blockers also increase the anti-tumor response. Combination radiotherapy/ α PD-L1 mAb therapy generated efficacious CD8 (+) T-cell responses that increased long-term survival and prevented tumor recurrence in a study.⁸⁵ Immune secretions affect tumor cell invasion and metastasis, and the combination of radiation and immunotherapy that targets them presents a potential novel therapeutic approach.

Summary and outlook

The beneficial effects of chemoradiotherapy on cancer treatment has been emphasized, however, cancer recurrence and metastasis of tumor cells after chemoradiotherapy should not be overlooked. Tumor metastasis is influenced by several factors, and the effect of chemoradiotherapy on tumor cells is not simply a trade-off effect. We conclude that chemoradiotherapy may directly affect tumor cells and promote tumor cell survival and metastasis by altering the TMEM or cell apoptosis and autophagy. Understanding the mechanism of action linking tumor metastasis and chemoradiotherapy will help us develop more effective therapeutic drugs and increase treatment options. This can reduce patient burden and improve prognosis.

For a follow-up study, the following recommendations should provide direction for improving cancer chemoradiotherapy. First, an in-depth study of the molecular mechanism of chemoradiotherapy in promoting tumor cell invasion and metastasis should be undertaken. This is required to provide a theoretical basis for clinical control of tumor metastasis. Second, appropriate drugs should be developed to be used in combination with chemoradiotherapy to inhibit the invasion and metastasis of tumor cells and improve the efficiency of chemoradiotherapy. Finally, the minimum dosage of chemoradiotherapy associated with the lowest rate of residual tumor metastasis and strong tumor-suppressive ability needs to be determined. This has practical significance for improving the survival of patients. The realization of the above recommendations will promote the effective application of chemoradiotherapy, and improve patient survival. This study highlighted the side effects, and summarized the possible mechanisms, of chemoradiotherapy in promoting invasion and metastasis of tumor cells. It also highlighted the side effects of chemoradiotherapy and deepened the understanding of the relationship between chemoradiotherapy and cancer. Consequently, new insights for clinically improving the effectiveness of chemoradiotherapy, and

controlling cancer metastasis and recurrence, were demonstrated.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by the Top Yong Talents of Ten Thousand Talent Program of Yunnan Province.

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