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Review

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Update on Radiotherapy Changes of Nasopharyngeal Carcinoma Tumor Microenvironment

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Abstract

The utilization of radiotherapy (RT) serves as the principal approach for managing nasopharyngeal carcinoma (NPC). Consequently, it is imperative to investigate the correlation between the radiation microenvironment and radiation resistance in NPC. PubMed and China National Knowledge Infrastructure (CNKI) databases were accessed to perform a search utilizing the English keywords "nasopharyngeal cancer", "radiotherapy", and "microenvironment". The search time spanned from the establishment of the database until January 20, 2023. A total of 82 articles were included. The post-radiation tumor microenvironment (TME), or the radiation microenvironment, includes several components, such as the radiation-immune microenvironment and the radiation-hypoxic microenvironment. The radiation-immune microenvironment includes various factors like immune cells, signaling molecules, and extracellular matrix. RT can reshape the TME, leading to immune responses with both cytotoxic effects (T cells, B cells, natural killer (NK) cells) and immune escape mechanisms (regulatory T cells (Tregs), macrophages). RT enhances immune responses through DNA release, type I interferons, and immune cell recruitment. Radiation-hypoxic microenvironment affects metabolism and molecular changes. RT-induced hypoxia causes vascular changes, fibrosis, and vessel compression, leading to tissue hypoxia. Hypoxia activates hypoxia-inducible factor (HIF)-1α/2α, promoting angiogenesis and glycolysis in tumor cells. TME changes due to hypoxia also involve immune suppressive cells like myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and Tregs. The radiation microenvironment is involved in radiation resistance and holds a significant effect on the prognosis of patients with NPC. Exploring the radiation microenvironment provides new insights into RT and NPC research.

Keywords: Nasopharyngeal carcinoma; Radiation microenvironment; Immune microenvironment; Radiation hypoxia microenvironment

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Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy that occurs mainly in the upper and lateral regions of the nasopharyngeal cavity. Current consensus suggests that its occurrence and development are mainly associated with factors such as Epstein-Barr virus (EBV) infection, genetic susceptibility, as well as environmental factors [1]. Owing to the unique pathology, biological behavior, and anatomical structure of NPC, radiotherapy (RT) is considered the primary treatment option [2]. However, in the case of patients diagnosed with late-stage NPC, changes in the tumor microenvironment (TME) after RT can result in tumor resistance to treatment, leading to poor prognostic outcomes or tumor recurrence after treatment.

The TME encompasses a range of factors that are in close contact with tumor cells, such as neighboring blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, various signaling molecules, and extracellular matrix (ECM) [3]. RT can remodel the TME [4], which is involved in local and systemic immune regulation and influences tumor progression. This remodeled environment is termed the radiation microenvironment and includes a radiation-immune microenvironment in which RT can induce different immune responses. For example, T cells, B cells, and associated secretory factors can have a cytotoxic effect on the tumor, and macrophages, Treg cells, and Th2 cells can mediate immune escape [5]. The hypoxic radiation microenvironment is another aspect where post-radiation vascular exhaustion can exacerbate hypoxia, leading to the signaling of hypoxia-inducible factor (HIF)-1α and promoting angiogenesis through vascular endothelial growth factors (VEGFs) [6]. Furthermore, RT can affect immune cell infiltration by altering the vascular structure of the tumor tissue. Hence, RT can trigger a series of interrelated processes within the TME, leading to tumor resistance or recurrence.

Methods

PubMed and China National Knowledge Infrastructure (CNKI) databases were accessed to perform a search utilizing the English keywords "nasopharyngeal cancer", "radiotherapy", and "microenvironment". The search time spanned from the establishment of the database until January 20, 2023. A total of 7,855 English articles and 3,798 Chinese articles were retrieved. The present study employed specific inclusion

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criteria, which included 1) studies on RT progress for NPC and 2) studies on the progress of the TME. The exclusion criteria were conference abstracts, Chinese theses, and other informally published documents.

Radioimmune Microenvironment

The tumor immune microenvironment, which encompasses TME immune components while excluding other stromal and extracellular components, primarily comprises T and B lymphocytes as well as myeloid cells [7, 8]. Within this microenvironment, two functional subtypes of cells can be differentiated: one that directly exerts cytotoxic effects on tumor cells, which include T and B cells, as well as natural killer (NK) cells, and another that enables tumor immune evasion, preventing tumor destruction, including regulatory T cells (Tregs) and macrophages. There is a delicate balance between these two; therefore, RT can reshape the immune microenvironment through key mechanisms that involve the activation of immunostimulatory and inhibitory signaling pathways. This leads to tumor cell destruction and promotes immune evasion, ultimately resulting in tumor recurrence and metastasis [9].

According to research, the utilization of RT has been found to potentially enhance the double-stranded DNA (dsDNA) release in the nucleus, elevate the permeability of the outer membrane of mitochondria, and trigger mitochondrial DNA (mtDNA) exposure in the cytoplasm, thus enhancing the immune response [10]. For instance, dsDNA and mtDNA can initiate the transcription of type I interferons (IFNs) [11]. Signals from type I IFNs can enhance cytotoxic T-cell activation, exerting a direct cytotoxic impact on tumor cells [12]. In contrast, dsDNA accumulation in tumor-derived exosomes post-RT also enhances dendritic cells (DCs) recruitment and directly triggers DC type I IFN responses, which additionally promotes $CD8^+$ T-cell recruitment [13] and provides signals to activate T cell. Therefore, RT changes the phenotype of tumor cells besides promoting the production of damage-related molecular patterns and also immune responses. Moreover, RT promotes not only the tumor cell sensitivity to T-cell-mediated anti-tumor effects but also the tumor cell recognition and elimination. The immune microenvironment of NPCs includes multiple immune cells, including T and B lymphocytes, NK cells, as well as myeloid-derived suppressor cells (MDSCs) [14].

In NPC, the most common infiltrates are EBV-negative CD3 T lymphocytes [15], which lack an effective immune response. Therefore, B lymphocytes are immune cells with potential anti-NPC properties. B lymphocytes represent the second most abundant and varied cell type within the NPC microenvironment. An increase in the abundance and diversity of B lymphocytes is associated with EBV positivity [16, 17]. According to previous studies, B cells in NPC can be recruited to tertiary lymphoid structures by $PD\text{-}1^+$ exhausted $CD4^+$ T cells of tumor origin via the CXCL13/CXCR5 axis. Additionally, a positive correlation has been observed between $CD19^+$ B cells and EBV-positive NPC patients [18]. This finding suggests that NPC-infiltrating B cells may have an anti-NPC immune function.

Along with T and B cells, NK cells were demonstrated to possess a cytotoxic impact on tumors. NK cells are a type of immune cell that holds the ability to directly trigger the death of tumor and virus-infected cells without specific immunity. RT can lead to an overexpression of stress-induced activation ligands in tumor cells, thus increasing NK cell-mediated cytotoxic effects [19]. NK cells perform various biological functions. Effective NK cell anti-tumor activity has been shown to be a prerequisite for T-cell-mediated anti-tumor immune responses [20]. NK cells, including cytotoxic T cells, exert control over tumors by secreting perforin-containing cytotoxic granules [21] or through ligands binding to death receptors in target cells, which include tumor necrosis factor (TNF)-associated apoptosis-inducing ligand (TRAIL) and Fas ligand. Moreover, NK cells also produce multiple cytokines, including those that promote inflammatory responses and immune suppression, that include interleukin (IL)-10 and TNF-α, or growth factors, including a colony-stimulating factor of macrophage granulocytes (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) [22]. Some immune mechanisms of NPCs have been shown to be downregulated, leading to immune evasion, but NK cells can secrete cytokines or directly lyse tumor cells [23]. NK cells were found to be involved in the prevention of EBV-associated malignancy progression arising from primary immunodeficiencies. These immunodeficiencies are characterized by genetic mutations that impact the function of genes contributing to NK cell differentiation and activation. A recent study has revealed that the immune features specific to NK cells in tumors are correlated to a favorable NPC prognosis. This suggests that NK cells present in the TME contribute to the regulation of the progression of EBV-associated epithelial tumors [24]. In conclusion, NK cells, including T and B cells, participate in the immune response process in different ways and undergo functional maturation to achieve cytotoxic effects on tumor cells.

In immunogenesis, tumor cells develop resistance to radiation due to the induction of anti-immune mechanisms by RT. The repetitive irradiation of tumor cells can result in the expression of IFN-stimulated genes and chronic type I IFN, which can promote radiation resistance and metastasis via inhibitory pathways [5]. IFN-γ and type I IFNs are accountable for programmed death ligand 1 (PD-L1) overexpression in tumor cells, leading to the induction of T-cell exhaustion and resistance to anti-tumor immunity [25]. Research data indicate that NPC radiosensitivity can be further enhanced by utilizing potential immunotherapy targets in conjunction with PD-1/PD-L1 blockade [26].

Recent in-depth research on exosomes has also revealed their role in suppressing tumor immunity and promoting tumor growth and metastasis. Exosomes are small vesicles between 30 and 150 nm in size and are considered key factors in intercellular communication [27]. Exosomes were found to be involved in mediating the TME through the level transfer of proteins, mRNA, and miRNAs [28]. Exosomes mediate cell communication and transfer components to recipient cells. NPC cells infuse exosomes containing LMP1 (NPC-Exo) and miRNAs into the TME, leading to the evasion of the immune system from host surveillance [29]. According to a recent study, methyltransferase 3 (METTL3), methyltransferase 14 (METTL14), and WT1-associated protein (WTAP) modify the

effect of m6A on radiosensitivity and invasive metastasis of NPC. Exosome production within the NPC microenvironment may have increased, which is one possible explanation [30].

Furthermore, Tregs also affect the impact of RT on tumors. Tregs survive in RT and inhibit the proliferation of effector cells [31], and by overexpressing cytotoxic T-lymphocyte-associated protein 4 (CTLA4), they block the activation of T lymphocytes, achieving an immune suppression effect. Research has found that functional analysis at the cellular and animal levels for NPC confirms that Tregs are recruited into the TME by tumor-secreted substances, assisting tumors in escaping immune surveillance [32]. Thus, RT also induces immune resistance, leading to tumor recurrence and metastasis.

In addition to epithelial cells in the immune microenvironment, stromal cells constitute a considerable portion, mainly composed of tumor-associated macrophages (TAMs) and MDSC. MDSC directly enhances immune tolerance [33]. MDSCs, a heterogeneous group of pathologically activated myeloid cells, can enhance tumor cell metastasis by infiltrating primary tumors and suppressing immune function to accelerate tumor progression [34]. MDSCs can negate the associated immune response during RT [35]. Clinical data show that the percentage of monocytic MDSCs among the total live cells is significantly increased in high-risk groups after NPC chemotherapy, limiting the growth of MDSCs, which is vital for patient treatment [36]. TAMs are the primary components of immune infiltration in solid tumors [37]. Current research suggests that TAMs in the TME originate mainly from bone marrow-derived monocyte precursor cells recruited to tumor sites, affected by TGF-β, CCL2, IL-1/4, and other cytokines, chemokines, and even microorganisms in the tumor tissue, polarizing toward the M2 phenotype, thus inducing immune infiltration [38, 39]. Relevant reports show that TAM infiltration exhibited a close correlation to the poor prognosis of EBV-infected NPC [40], and it was experimentally proven that EBV-infected NPC cells could recruit monocytes through VEGF and activate monocytes in TAMs in a manner dependent on GM-CSF- and nuclear factor kappa B (NF-κB)-dependent manner. Gleichzeitig TAM promotes tumor metastasis and NF-κB activation [41].

In recent years, immune checkpoints have become a hotspot. These immune checkpoint molecules, such as PD-1, PD-L1, and CTLA-4, are fundamentally a component of the immune system's regulatory apparatus. They assist in maintaining equilibrium between a robust immune response when necessary and the ability to prevent typical tissue damage and destruction. Immune checkpoint inhibitors are medications used in the treatment of cancer that are developed to prevent these interactions. By obstructing the inhibitory signals given by these checkpoint molecules, the immune system is better able to target and eliminate cancer cells. However, the immune checkpoints are a significant contributor to immune tolerance [42] and radiation resistance during the onset and progression of tumors. Recent research based on different immune subtypes in NPC has demonstrated the predictive power of the immune checkpoint inhibitor (ICI) response and has increased sensitivity to RT [43]. Therefore, the application of ICIs can inhibit tumor immune evasion and enhance tumor killing by the immune system through various pathways and mechanisms, thereby increasing radiosensitivity.

In summary, RT places the body's immune microenvironment in a very delicate balance between killing tumors and immune suppression. RT has the potential to enhance the presentation of tumor antigens, trigger immunogenic cell death of tumor cells, activate pathways that mimic viral responses, and overexpress chemokines, ultimately promoting tumor cell death by T cells. Conversely, RT was found to be involved in promoting immune evasion mechanisms such as PD-L1 overexpression, immunosuppressive chemokine release, and exosome activation, thereby impeding the activation and function of T cells and similar cells.

Radiation-Hypoxic Microenvironment

During tumor growth, tumor vessels provide tumor cells with abundant nutrients and oxygen and remove metabolic waste, which enables the tumor to grow rapidly and potentially invade and metastasize [44]. However, tumor cells have high metabolic activity and require considerable energy. When demand exceeds supply, hypoxic areas form, altering metabolic capacity [45]. Furthermore, when tumor cells are stimulated by hypoxia, a series of changes occur at the molecular and cellular levels. Acid waste produced by anaerobic glycolysis can improve tolerance to hypoxia and resistance to external damage, thus disrupting the TME [46]. RT, a key measure against tumors, has been shown to elicit stress responses, repair damage, and restores cellular homeostasis [47]. Radioactive hypoxia is a part of the microenvironment after RT in tumor cells. The tumor cell resistance to RT can be attributed to their capacity for DNA damage repair and tolerance. Therefore, the impact of a hypoxic microenvironment on radiation resistance is a significant environmental factor. The etiology of hypoxia can be succinctly categorized into two components: a decrease in tumor angiogenesis and an increase in destruction.

Substantial research has been conducted on the mechanisms of angiogenesis. VEGF specifically enhances endothelial cell growth and increases the permeability of newly formed vessels [48]. VEGF overexpression is common in NPC [49], and VEGF secretion is highly correlated with NPC angiogenesis, metastasis, and poor prognosis. One study emphasized the relationship between JAK2, STAT3, and VEGF expression and NPC development and progression [50]. Recently, a method of angiogenesis that is different from endothelial-derived angiogenesis, namely vascular mimicry (VM), has been discovered. VM is a vascular network pattern that is formed by highly invasive tumor cells and replaces endothelial cells and has been confirmed in various tumors [51], including lung, stomach, and ovarian cancers [52-54]. However, there is little research on NPC, with only a few studies reporting that Foxq1 can regulate VM to promote NPC metastasis [55] and the synergistic effect of anti-VM and anti-VEGF treatment in NPC [56]. To summarize, the hypoxic environment of solid tumors is strongly related to the synergistic action of VEGF and VM [56]. RT can induce endothelial cell apoptosis, leading to vessel destruction and endothelial cell aging. Aging endothelial cells cause en-

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dothelial dysfunction, thus inhibiting angiogenesis and inducing oxidative stress and inflammation [57], ultimately leading to the formation of a hypoxic microenvironment.

Furthermore, non-tumor cell components and functions in the tumor region were validated to also undergo significant changes, especially the activation and proliferation of matrix cells (such as cancer-associated fibroblasts (CAFs)) and an increase in matrix components (such as fibrin), leading to morphological tumor remodeling [58]. As a result, vessels are compressed or aggregated, and fibrin clots block vessels [59], causing damage to blood circulation, insufficient oxygen supply, and increased tissue hypoxia. In a recent study, a degradable magnesium alloy (Mg) with anticancer activity was designed by reducing cancer cell proliferation. This experiment verified that the physiological functions of elements such as Mg can change with changes in the hypoxic environment. Magnesium has been observed to promote angiogenesis in normoxic conditions, while conversely, it has been found to impede angiogenesis in hypoxic conditions [60]. Many factors can lead to the formation of a hypoxic microenvironment. Hypoxia has a close correlation cancer cell proliferation, migration, invasion, and angiogenesis, interacts with other cells and pathways, and has a significant impact on the TME.

Research has found that hypoxia and HIF-1α/2α play important roles in tumor angiogenesis [61]. Post-RT vascular injury can lead to significant activation of HIFs [62]. Under hypoxic conditions, enzymes involved in HIF degradation are deactivated, allowing HIF to enter the cell nucleus, where it participates in angiogenesis, anaerobic glycolysis, inhibition of apoptosis, and transcription of other genes. This increases oxygen delivery and normalizes tumor vessels [63]. Additionally, the endogenous PI3K-AKT-mTOR pathway activation induces an increase in the HIF pathway, resulting in a comparable hypoxic microenvironment [64]. Both exogenous and endogenous hypoxia disrupt autophagy mechanisms by upregulating metabolic processes, DNA repair, and anti-apoptotic pathways, thereby enhancing the radiation resistance of tumor cells. Clinical studies revealed that 100% of primary NPC cases and 58% of neck lymph node metastases contain hypoxic areas and HIF-1α overexpression and risks of metastasis and eventual death [65]. Thus, HIF-1α has emerged as a significant prognostic factor for NPC and a promising therapeutic target. Moreover, research has shown that hypoxia can regulate CAFs, which are spindle-shaped cells that can synthesize collagen in connective tissues and also contribute to wound healing, tissue fibrosis, and inflammatory processes [66]. HIF was suggested to be involved in the metabolic reprogramming of CAFs and mediates their tumor-promoting effects [67]. It has been found that CAFs induce radiation resistance and promote the survival of NPC cells post-RT through the IL-8/NF-κB pathway to decrease radiation-induced DNA damage. The administration of trabectedin, a CAF inhibitor, has the potential to restrict the survival of NPC cells induced by CAF and mitigate the impact of radiation [68].

It is well known that under cellular hypoxia, cells reduce their dependence on mitochondrial oxidative phosphorylation and preferentially use the anaerobic glycolysis pathway, which does not rely on oxygen consumption, to maintain sufficient ATP production to meet body energy needs [69]. Consequently, the metabolic feature of most tumors is increased glycolysis, which is caused by hypoxia, forcing tumor cells to switch from oxidative phosphorylation to glycolysis. These changes are mediated by HIF-1α-driven transcription, resulting in upregulating glucose transporter proteins and glycolysis-involved genes [70]. This phenomenon promotes tumor cell survival and metastasis under hypoxic conditions. This glycolysis is observed in various cells, and recent research has discovered a new circular RNA that can directly bind and stabilize ubiquitinated mRNA, thereby inhibiting the glycolysis process and NPC proliferation and migration through ubiquitination and upregulation of protein levels [71], thus demonstrating the impact of glycolysis on NPC proliferation and migration.

Hypoxia also has a significant impact on alterations in the immune microenvironment. This is because hypoxia can improve the immune attack resistance of tumor cells, resulting in immune evasion [72]. Research has shown that hypoxic regions in solid tumors are infiltrated by high levels of immune suppressive cells, including MDSCs, TAMs, and Treg cells [73]. As mentioned previously, MDSCs can directly promote immune tolerance, making them one of the main components of the immunosuppressive network that leads to tumor T-cell defects, with direct evidence that HIF-1α can regulate MDSC function and differentiation in a hypoxic microenvironment. TAMs, a significant constituent of immune infiltration in solid tumors [37], were found to tend to be situated primarily in hypoxic regions, and HIF-1α-induced under hypoxic conditions has an inhibitory effect on cytotoxic T cells [74]. Treg cells can also be driven by HIF-1α-dependent transcription factors (FoxP3) or attracted by the cytokine spectrum in the tumor bed microenvironment [75]. Recent research suggests that ICI not only causes T-cell attacks on tumor cells but might also regulate the TME through the normalization of tumor vessels [76, 77]. The novel interaction has the potential to offer opportunities for immunotherapies aimed at decreasing tumor hypoxia and enhancing radiosensitivity. Unfortunately, there is no strong evidence that biomarkers for ICIs in NPC have been identified.

Conclusion and Future Perspectives

Numerous studies have shown that, despite continued improvements in the efficacy and safety of RT, tumor recurrence after RT remains an issue, and the TME plays a critical role in this process. The activation of the immune system and the immune suppression induced by RT are delicately balanced. The process of metabolic reprogramming and the induction of angiogenesis within the TME is crucial for the effective elimination of tumor cells by cytotoxic T cells and other immune cells. The composition of multiple cells and the ECM within this particular environment has demonstrated a capacity to mitigate the immune responses of the host toward malignant neoplastic cells. The proliferation of tumors is facilitated by various mechanisms, including the secretion of immunosuppressive cytokines, metabolic alterations, and other factors. Conversely, TMEs that are hypoxic and acidic have been observed to provide radioresistance by impeding the prolifera-

tion of anti-tumor cells, including CD8 T lymphocytes and NK cells, while promoting the proliferation of tumor-tolerant cells such as MDSCs and Treg cells [78].

These characteristics of the TME may be helpful in NPC treatment. For example, potential immune therapy targets could be used in combination with the PD-1/PD-L1 blockade to further increase the radiosensitivity of NPC [79]. The heterogeneity of the NPC TME can identify biologically different immune subtypes, predict prognosis, and predict immune therapy responses [43]. EBV-infected NPC cells can secrete cytokines and exosomes containing viral products to modulate the function of matrix cells in the TME, thus promoting NPC progression and avoiding host immune attack [80].

In summary, RT induces remodeling of the TME, with hypoxia and immunity being the two most critical aspects. The two are interrelated and inseparable. Most malignant tumors create a hypoxic microenvironment that is conducive to their development, thus suppressing immune responses. Currently, the immune stimulation process is inseparable from the stimulation of HIFs, thereby immunogenically activating key progressions.

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Conflict of Interest

None to declare.

Author Contributions

Dao Qi Zhu: conceptualization, writing - original draft, literature review, funding acquisition; Chao Su: writing - review and editing; Jing Jun Li: writing - review and editing, compilation of references; Ai Wu Li: writing - review and editing, overall structure and organization; Ying Luv: writing - review and editing, final proofreading, funding acquisition; Qin Fan: supervision, project administration, funding acquisition.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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