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EXPERT OPINION

PLASMA PROCESSES AND POLYMERS

Plasma medical oncology: Immunological interpretation of head and neck squamous cell carcinoma

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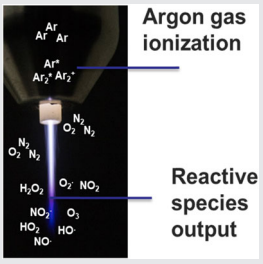
Abstract

The prognosis of patients suffering from advanced-stage head and neck squamous cell carcinoma (HNSCC) remains poor. Medical gas plasma therapy receives growing attention as a novel anticancer modality. Our recent prospective observational study on HNSCC patients suffering from contaminated tumor ulcerations without lasting remission after first-line anticancer therapy showed remarkable efficacy of gas plasma treatment, with the ulcerated tumor surface decreasing by up to 80%. However, tumor growth relapsed, and this biphasic response may be a consequence of immunological and molecular changes in the tumor microenvironment that could be caused by (a) immunosuppression, (b) tumor cell adaption, (c) loss of microbe-induced immunostimulation, and/or (d) stromal cell adaption. These considerations may be vital for the design of clinical plasma trials in the future.



KEYWORDS
cold physical plasma, HNSCC, kINPen, plasma medicine, tumor microenvironment

Abbreviations: CCND1, cyclin D1; CDKN2A, cyclin-dependent kinase inhibitor 2A; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DNA, deoxyribonucleic acid; EBM, evidence-based medicine; EGFR, epidermal growth factor receptor; FAT1, protocadherin; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IFN-γ, interferon gamma; IL, interleukin; MAMP, microbe-associated molecular pattern; MDSC, myeloid-derived suppressor cells; MUL1, mitochondrial E3 ubiquitin protein ligase 1; NK-cell, natural killer cell; p16, tumor suppressor protein p16; p53, tumor suppressor protein p53; PD-1, programmed cell death protein-1; PD-L1, programmed cell death-ligand 1; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase; PTEN, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase; R1, microscopic tumor-positive resection margins; R2, macroscopic tumor-positive resection margins; RNA, ribonucleic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; TCGA, The Cancer Genome Atlas; TP53, tumor suppressor p53; UICC, Union for International Cancer Control.

1 | HEAD AND NECK SQUAMOUS CELL CARCINOMA

1.1 | Introduction and etiology

Of all malignancies (the tendency of a medical condition to become progressively worse), squamous cell carcinoma of the head and neck (HNSCC)—particularly of the oropharynx—represents the sixth most diagnosed malignancy by incidence worldwide.[1] The tumor originates from epithelial cells of the mucosal linings of the upper aerodigestive tract (the oral cavity, oropharynx, larynx, or hypopharynx), and it is remarkably heterogeneous.[2] This means that the reason of tumor appearance, its location, the types of cells within the tumor tissue, and the recommended therapies differ significantly for the different types of head and neck cancers. The tumor is caused due to several etiological agents (substances that cause the initiation of the disease) and a variety of molecular changes. Here, excessive tobacco (e.g., smoking and chewing habits) and alcohol consumption has emerged as the most important risk factor.[3] Furthermore, there is epidemiological evidence that HNSCC can be attributed to infection by viruses.[4] About 25% of HNSCC contain high-risk human papillomavirus (HPV) DNA.[5,6] Consequently, based on the etiological risk factor and the molecular profile, HNSCC is classified into two separate entities: HNSCC caused by HPV represents the molecular entity of HPV-positive (HPV+ve) carcinomas, and HNSCC not caused by HPV, but other carcinogenic agents such as excessive alcohol and tobacco consumption, represents the molecular entity of HPV-negative (HPV−ve) carcinomas.[3] HPV status is a prognostic factor for survival because HPV+ve HNSCC is associated with better overall 3-year survival rates compared with patients suffering from HPV−ve HNSCC.[7]

The socioeconomic profile (e.g., the absence of work contract, income, and education) of advanced-stage HNSCC patients, combined with a lack of public awareness and a late presentation of patients (patient delay) in the clinics, is often associated with more advanced disease stages.[8] The overall 5-year survival rate of HNSSC is 65.9%,[9] whereas, for Stage IV, it is only 4–25%.[10] The prognosis in advanced-stage HNSCC under palliative treatment only remains poor, with a median overall survival time of 5.1 months.[11] Early-stage HNSCC is treated with surgery or radiotherapy, whereas for advanced stages, ablative tumor surgery, followed by a combination of chemo- and radiotherapy, is regarded as a gold standard treatment. Moreover, tumor infiltration depths of ≥4 mm into the mucosa are an indication to perform an elective neck dissection (the removal of the lymph nodes without any evidence that there is obvious cancer in the neck) in pT1cN0 oral squamous cell carcinomas.[12] Specifically, first-line treatment for lymph node-positive HNSCC is locoregional (restricted to a certain region of the body) postoperative (appearing after surgery) radiotherapy.[13] In addition, the treatment of distant metastases consists of postoperative chemotherapy.[14]

1.2 | Carcinogenesis of HNSCC

Histopathological examination of human tumors has provided details about the HNSCC anatomy. The tumor core has its own blood and lymphatic vessels, and it is embedded into the tumor microenvironment (TME) that consists of a network of stromal cells, infiltrating immune cells, cancer-associated fibroblasts (CAFs), cytokines, and chemokines.[15] The bidirectional communication between cells in the TME is a critical factor in normal tissue homeostasis as well as tumorigenesis. Primary tumor growth begins through the aberrant activation of oncogenic pathways and the downregulation of tumor suppressor genes, combined with aberrant immune responses and altered homeostasis in the TME that are caused by several etiological agents (e.g., tobacco, alcohol, and HPV) and genetic factors.[16,17] In 1863, Rudolf Virchow was the first researcher to propose a connection between inflammation and cancer.[18] Hence, it is critical to note that tissues experiencing chronic inflammation exhibit higher cancer incidence compared with noninflamed tissue.[19] For instance, chronic inflammatory oral mucosal diseases like oral lichen planus or oral submucous fibrosis correlate with malignant transformation rates of up to 10%.[20]

One of the hallmarks of cancer is the accumulation of driver mutations that spur carcinogenesis.[21] The prevalence of somatic mutations is highly heterogeneous among cancer types, spanning 2.5 logs from about 12 mutations per megabase DNA in melanoma to 0.02 in pilocytic astrocytoma.[22] Within this range, HNSCC ranks 12th among all types of cancers, with about 2 mutations per megabase DNA. A detailed description of frequent mutations and molecular changes in HNSCC has been summarized in extensive detail recently.[2] Modern cancer genomics identified between 50 and 100 genes that can be substantially mutated in HNSCC, which thus emerged as cancer-"driver" genes. In 2015, The Cancer Genome Atlas (TCGA) network profiled 279 HNSCC (including HPV+ve and HPV−ve) and published a comprehensive landscape of somatic genomic alterations majorly affecting signaling pathways. Highly frequent and important driver genes of HNSCC (HPV−ve) and their corresponding signaling pathways are listed in Table 1.

TABLE 1 Driver genes and pathways in HPV−ve HNSCC

Cellular process	Gene	Protein	Types of gene	Activation level in HNSCC	Activation level with gas plasma therapy
Cell cycle	CDKN2A	$p16^{INK4A}$	Tumor suppressor	Downregulation	No published data available for human HNSCC
	TP53	p53	Tumor suppressor	Downregulation	
	CCND1	G1-S-specific cyclin D1	Oncogene	Overexpression	
Growth signals	EGFR	EGFR	Oncogene	Overexpression	
Survival	PIK3CA	Catalytic p110α subunit of class 1 PI3Ks	Oncogene	Overexpression	
	PTEN	PTEN	Tumor suppressor	Downregulation	
WNT signaling	FAT1	Protocadherin (FAT1)	Tumor suppressor	Downregulation	
	AJUBA	LIM domain-containing protein AJUBA	Tumor suppressor	Downregulation	
	NOTCH1	NOTCH1	Tumor suppressor	Downregulation	
Epigenetic regulation	KMT2D	Histone-lysine-N-methyltransferase KMT2D	Tumor suppressor	Downregulation	
	NSD1	Histone-lysine-N-methyltransferase NSD1	Tumor suppressor	Downregulation	

Note: Adopted and modified from Leemans et al.[2]

Abbreviations: EGFR, epidermal growth factor receptor; HPV, human papillomavirus; HNSCC, head and neck squamous cell carcinoma.

1.3 | TME and immunology of HNSCC

It is critical to note that the immune system and composition of the TME play an essential role in the biology of HNSCC and cancer in general.[23] Paul Ehrlich was among the first researchers who postulated that under physiological conditions, the cells of the immune system are able to eradicate cancer cells and prevent primary tumor growth.[24] For example, natural killer cells (NK cells) detect and damage cancerous cells. Dendritic cells activate cytotoxic T cells and—once activated—cytotoxic T cells and NK cells release two separate cytotoxic proteins: (a) perforin permeabilizing the cellular membrane for (b) granzymes to enter and causing tumor cells to die from apoptosis. Another antitumorigenic condition is that T helper cells (T_H1) release interleukin (IL)-2 and interferon gamma (IFN-γ) to recruit and activate more NK cells. T helper cells have also been shown to activate cytotoxic T cells to eradicate cancer cells.[25] Interestingly, an impaired immune system correlates with a high cancer incidence.[17]

Immune cell types such as macrophages, mast cells, T cells, fibroblasts, and myeloid-derived suppressor cells (MDSCs) are found in the TME. It is critical to note that multiple of these cell types have a high degree of plasticity and functional diversity.[26] At both extremes, they can promote either antitumorigenic or protumorigenic effects or anything in between. Currently, tumorigenesis is explained by the model of immunoediting, based on the immunosurveillance hypothesis[27] and confirmed by investigations in vivo and clinical observations.[17,28] It is well established that solid tumors established an immunosuppressive microenvironment, partially via reprogramming of host cells such as monocytes into M2 macrophages (tumor-associated macrophages, [TAMs]) and fibroblasts into CAFs.[29,30] In clinical studies of HNSCC, mortality positively correlated to the number of CAFs in the TME.[31,32] Tumor cells also escape from adaptive immune responses by high surface expression levels of programmed cell death-ligand 1 (PD-L1). PD-L1 binds to programmed cell death protein-1 (PD-1) on cytotoxic T cells, whereby the cytotoxic T cell receives an inhibitory signal, decreasing the chances of T-cell-mediated tumor cell lysis upon the match of T-cell receptor and tumor-associated antigen (peptide loaded on significant histocompatibility class I molecules). For more details, the reader is referred to previous reviews on this topic.[33,34] Other means of immunosuppression include the recruitment of MDSCs by pericytes, leading to immunosuppression of antitumor effector cells via (a) the promotion of angiogenesis, (b) the malfunctioning of antigen presentation by dendritic cells, (c) the inhibition of NK cells, (d) the inhibition of the T-cell activation, and (e) the reduction of M1 macrophages.[17] In summary, the interaction between tumor, stromal, and immune cells in the TME

affects cancer initiation, progression, regression, and ultimately patient prognosis,[16] whereas immune-mediated eradication of tumor cells takes place if immunosuppression is not dominant.[17]

1.4 | Therapeutic modalities

Total tumor mass and the composition of the TME are two of the prognostic factors that can be actively modified by the treatment procedure. The current state of preclinical and clinical research on cancer therapy includes two different therapeutic approaches: The systemic approach, using, for instance, biochemical-molecular approaches including chemotherapy[35] and immune checkpoint inhibitors like nivolumab (immunotherapy),[36,37] and the local approach, using, for example, surgery or other novel local treatment modalities. Among the latter is medical gas plasma therapy[38] that recently has moved upward in the pyramid of evidence-based medicine (EBM), reaching EBM level III in HNSCC.[39] In the last decade, several groups have contributed to significant progress in the development of medical devices generating physical plasma that is operated at body temperature and under atmospheric pressure. Consequently, approval of first medical plasma sources was received in Germany in 2013, based on its recognized effectiveness to stimulate skin regeneration and for inactivating microbial pathogens.[40] Clinical case reports and clinical studies revealed that gas plasma therapy is effective in the treatment of infected wounds and ulcerations.[41–43] In parallel, the effectiveness of medical gas plasma as anticancer modality was confirmed by experimental studies in various types of cancer cell lines in vitro and in experimental animal models as recently summarized.[44–46] In metastatic or recurrent HNSCC, current standard anticancer modalities such as chemotherapy have a number of severe clinical side effects (e.g., myelosuppression, anemia, and renal failure).[36] In animal models, risk assessment revealed that repetitive gas plasma treatment lacks apparent side effects,[47] which was confirmed by clinical observations in HNSCC patients recently.[48] Currently, gas plasma treatment is under investigation for its ability to positively modify the biology of cancer cells, the TME, and hence tumor progression.

2 | MEDICAL GAS PLASMA AND HNSCC

2.1 | Molecular basis of plasma cancer treatment

Cold physical plasma that is generated with medical gas plasma devices essentially is a multicomponent system, consisting of electrons, ions, electric fields, visible and UV as well as near-infrared radiation, and reactive oxygen (ROS) and nitrogen species (RNS).[49] As all RNS also contain oxygen, with the exception of a few species such as atomic and metastable nitrogen, we find the abbreviation ROS more suitable than RONS.[46] Therefore, the term ROS is used throughout the text. The unique feature of plasma technology over other types of medical technologies or ROS-producing agents is the multiplicity of ROS being generated at the same time.[50,51] This way, many types of ROS can act on cells and tissues, introducing ROS-mediated damaging and signaling.[46,52] Intriguingly, physical plasma generated via gas plasma jets can also be modified in terms of ROS composition and concentration, yielding different biological effects.[53,54] This creates possibility of application-specific tuning and optimization of each plasma source and feed gas composition in a disease-specific manner.[55] In cancer, ROS have the ability to modify the redox state and activity of signaling pathways as well.[56] A selectivity of plasma-derived ROS inactivating tumor cells over nonmalignant cells has been debated.[57] For example, gas plasma treatment induces cellular senescence and apoptosis in melanoma cell lines with minimal effects on normal melanocytes in vitro.[58] Similar findings have been made investigating selective effects in pancreatic cancer in comparison to nonmalignant fibroblasts.[59] Several reports have found antitumor efficacy of gas plasma treatment with HNSCC.[60–64] So far, studies investigating the effect of gas plasma treatment on the activation level of signaling pathways in human HNSCC are scarce. Gas plasma-induced apoptosis in HNSCC in vitro was linked to AKT1 ubiquitination and degradation initiated by the mitochondrial protein MUL1, an E3 ligase known to regulate cell growth and death.[63] It seems that ROS, either directly from plasma treatment of HNSCC or secondary mitochondrial ROS generated after plasma treatment,[65] alters mitochondrial membrane potential and triggers mitophagy and decelerated growth in vitro and in vivo.[64] With patient-derived HNSCC tumor tissue punch biopsies, ex vivo gas plasma treatment led to an increase of mitochondria-derived cytochrome *c* and cell death.[62] For a comprehensive overview on the physics of the kINPen[55] and the biomedical effects of plasma-derived ROS,[46] the reader is kindly referred to the respective reviews.

2.2 | Clinical results of plasma medical oncology in HNSCC

Our recent prospective observational study[66] investigated the therapeutic effect of plasma treatment on

locally advanced HNSCC (Union for International Cancer Control [UICC] IV) patients who suffered from contaminated tumor ulcerations and who experienced a lack of lasting remission after first-line anticancer treatment. All patients received a standardized medical gas plasma treatment with the kINPen MED (neoplas tools GmbH, Greifswald, Germany). The jet was operated using three standard liters per minute of argon gas. Argon was excited within the active plasma zone in the head of the kINPen, and excited argon species were subsequently driven out to the ambient air where they reacted with oxygen and nitrogen to form ROS and RNS.[67] One cycle of therapy lasted 1 week that included three individual single-gas plasma applications, followed by 1 week without plasma therapy. For one single-gas plasma application, the area of the ulcerated tumor was repeatedly exposed to the visible tip of plasma effluent for approximately 1 min/cm^2. The effluent's length was 12 mm, and the vertical distance from the plasma jet nozzle to the naturally moist tumor tissue was 8 mm. Palliative care including the use of wound dressings was continued throughout the medical gas plasma therapy. The patients had a history of tumor-positive resection margins (R1, R2) or recurrent disease. Of the six patients who entered the observational study, one-third showed partial tumor remission with medical gas plasma treatment. With regard to this therapy, all patients were confidently identified as responders or nonresponders within the first 2 weeks after starting the therapeutic intervention. In the group of gas plasma responder patients, the ulcerated tumor area decreased by up to 80% in size within 7 months (regression phase, Figure 1c) when compared with tumor size before (Figure 1a) and several weeks after (Figure 1b) gas plasma therapy. After an initial regression phase, however, the antitumor efficacy of plasma treatment gradually decreased after at least a 1-month lasting *plateau phase*. Eventually, the tumor returned to the *progressive phase* and continued growth until fatality.[66] These existing results are now put in context to several hypotheses generated by us on their mechanistic basis.

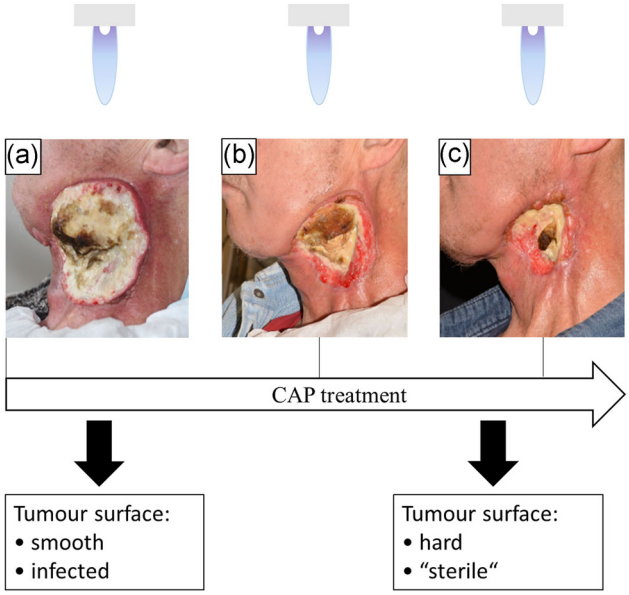


FIGURE 1 Timeline of tumor characteristics during palliative cancer care with gas plasma treatment showing tumor surface development in a responder patient with a well to moderately differentiated head and neck squamous cell carcinoma. (a) Tumor without gas plasma treatment; (b) 3-month and (c) 5-month follow-up of the tumor surface after several sessions of gas plasma treatment. Images adapted from Metelmann et al.[39] CAP, cold atmospheric pressure plasmas

2.3 | Role of immunity in plasma treatment of HNSCC?

Current literature gives evidence that plasma treatment affects both immune cells (Table 2) and the immunogenicity of tumor cells. Regarding the former, plasma treatment not only affects the viability of different leukocyte subpopulations differentially,[75] but it also induces molecular and phenotypic alterations in lymphocyte[77,81] as well as myeloid subsets.[68,74,82–86] Regarding the latter, plasma treatment has been shown to induce immunogenic cancer cell death in vitro[65,87,88] and in vivo.[71,80,89] It has be reported that this type of cell death supports the formation of antitumor immunity,[90] a potent effector as evidence with Nobel Prize-winning checkpoint inhibitor therapy has provided.[91] The concept of plasma assistance in anticancer immunity has been summarized recently.[92] Moreover, we have unpublished and published evidence of alterations in immune cell infiltrates in plasma-treated tumor tissue of patients.[66] At the same time, it needs to be appreciated that end-stage HNSCC patients often experience excessive microbial growth on tumors, possibly providing a plethora of stimuli to the immune system via microbe-associated molecular patterns (MAMPs). In light of an initial tumor regression phase with plasma treatment, followed by a steady-state growth and eventually progressive disease concomitant with desmoplastic reaction (growth of fibrous or connective tissue secondary to an insult), one or several mechanisms may be at play to explain the biphasic tumor response to medical gas plasma therapy in HNSCC Stage IV patients:

1. Tumor adaption: Tumor-eradicating agents put micro-evolutionary pressure on cancer cells, ultimately promoting the growth of cells that are inherently less

TABLE 2 Plasma effects on immune cell populations in vitro

Cell type	Function	Plasma effect	References
Myeloid lineages			
Macrophages	M1 antitumorigenic, secrete T_H1 cytokines M2 protumorigenic	Upregulation of M1 macrophages, downregulation of M2 macrophages	[68–70]
Dendritic cells	Antigen-presenting cells from the bone marrow, initiate innate and adaptive immune responses for tumor regression; activate cytotoxic T cells	Recruitment of antigen-presenting cells into tumors	[71]
		No change in intratumoral dendritic cells	[72]
		DC maturation with plasma-treated tumor cells	[73]
Neutrophils	Phenotypically plastic, opposing functions in tumor progression	Induction of neutrophil extracellular trap formation with a resulting increase of IL-8 release	[74]
Mast cells	Recruited to the tumor to promote tumor angiogenesis	No published data available	–
Myeloid-derived suppressor cells	Suppression of the host immune system	No published data available	–
Lymphoid lineages			
Natural killer cells	Antitumorigenic, detect and eradicate tumor cells	Nonstimulated cells are sensitive; mitogen-activated cells are robust	[75]
Cytotoxic T cells	Bind to the MHC-I receptor of cells, release granzymes and initiate (tumor) cell apoptosis	Nonstimulated cells are sensitive; mitogen-activated cells are robust	[75]
		Enhancement of cytotoxic T-cell infiltration into tumors	[76]
T helper cells	Subgroups T_H1 (antitumorigenic) and T_H2 (protumorigenic) ratio of both lineages correlates with tumor stage and grade	Nonstimulated cells are sensitive; mitogen-activated cells are robust	[75]
		T_{emra} cells are most robust to plasma treatment	[77]
		Proliferation of activated cells is not selectively inhibited by plasma; plasma treatment does not lead to proliferation	[78]
		Changes in the redox balance after plasma treatment	[79]
		Increased influx in tumor tissue exposed to plasma	[80]
Regulatory T cells	Primarily protumorigenic by suppressing mechanisms of immunosurveillance; divergent role	No published data available	–
B cells	Humoral immunity, promote tumor progression by releasing protumorigenic cytokines and altering T_H1 (antitumorigenic) and T_H2 (protumorigenic) ratio	Nonstimulated cells are sensitive; mitogen-activated cells are robust	[75]

sensitive to the treatment or fostering new genetic variants (acquired resistance) that withstand the treatment. Such a mechanism is well known in tumor drug resistance,[93] and it may be at play in the decrease of efficacy observed in antitumor plasma therapy too. A possibility to circumvent this issue would be using a combination of drug and plasma therapy.[86,94]

2. "Microbial assistance": Plasma treatment effectively decreased the microbial burden on tumors. MAMPs released during this process and binding pattern recognition receptors can activate macrophages and dendritic cells, which in turn can positively contribute to an efficient antitumor TME. Tumor antigens phagocytosed by these myeloid cells and presented to T cells in the draining lymph node may foster antitumor T-cell responses. Once the microbial contamination is eradicated due to the plasma treatment, a critical immunostimulant may be lost, tilting the proimmunogenic and inflammatory conditions to suppressive conditions.

3. Desmoplastic reaction and wound healing response: Considering the relatively soft and infected tumor tissue before plasma treatment and in comparison to the hard and noninfected tumor tissue after many cycles of plasma treatment, an analogy to fibrotic and wound healing responses becomes apparent, both being anti-inflammatory at final stages. Stroma-rich tumors are a negative prognostic factor in gastric cancer,[95] for example. A large number of fibroblasts significantly contribute to a barrier against antitumor immune cells and chemotherapy by decreasing blood flow and angiogenesis.[96] It is clear that such a response is not provoked due to temperature-dependent tissue necrosis, as the plasma of the kINPen does not induce tissue damage.[97]

2.4 | Outlook

A larger number of patient biopsies are needed at several stages during treatment to elucidate the cellular and molecular changes taking place during the course of medical gas plasma therapy. Moreover, a correlation between microbial contamination and the efficacy of plasma therapy could be tested. Likewise, tissue sampling and tumor cell DNA sequencing (or RNA sequencing) would allow following either genetic or transcriptional adaptions of tumor cells over the course of plasma treatment. Tissue sectioning and enumeration of tumor-infiltrating lymphocytes and macrophages would identify whether the antitumor efficacy of plasma is directly linked with intratumoral leukocytes. If so, and if high levels of immunosuppressive molecules are detected in the tumor (e.g., PD-L1, cytotoxic T-lymphocyte-associated protein 4 [CTLA4]), checkpoint therapy may be an option to combine with gas plasma treatment. To prevent desmoplastic reactions, novel agents such as PEGPH20 (a Phase II trial on this drug, NCT01839487, has been completed in 2018 Stage IV pancreatic cancer) may be used in combination with plasma treatment. Synchronizing the tumor characterization (e.g., contamination, desmoplastic reaction, and immune infiltrate) with the appropriate medication may also further tailor oncological therapy toward precision medicine.[98] Furthermore, clarifying the molecular and TME differences between gas plasma responders and nonresponders in HNSCC patients may generate patient selection criteria for gas plasma therapy in the future. Another topic of future research is whether HNSCC cells can become resistant to gas plasma treatment or whether immunological aspects can predominate, or both.

3 | CONCLUSION

This is an exciting time for the field of plasma medical oncology, as illustrated by the examples discussed here in this article, which has revealed a therapeutic concept, the treatment phases, and an immunological interpretation of the clinical data. Nonetheless, it currently remains a challenge to identify treatment regimens capable of preventing the specific changes from regressive to the progressive phase when using gas plasma therapy in the clinic, motivating further translational research to move plasma medical oncology forward as a novel anticancer treatment modality. Irrespective of that, providing a novel gas plasma-based palliative treatment to head and neck cancer patients is significantly improving their quality of life during their final stages by decreasing microbial burden on tumors and enhancing social interaction—an aspect that by itself should be a motivator to scientists in the field of plasma oncotherapy.

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