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Review article

The immunological window in oral cancer: Integrating the progenitor exhausted T cells/terminally exhausted T cells axis and tumor-draining lymph nodes into oral and maxillofacial surgical practice

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ABSTRACT

Objective: Perioperative immune checkpoint inhibition has changed the conceptual framework of treating resectable locally advanced head and neck squamous cell carcinoma. This review aims to provide oral and maxillofacial surgeons with a practical immunological framework for interpreting perioperative immune checkpoint inhibition in oral cancer.

Methods: This narrative review summarizes and interprets recent clinical trials, guidelines, and translational studies relevant to perioperative pembrolizumab, PD-1 signaling, T-cell exhaustion, tumor-draining lymph nodes, tertiary lymphoid structures, pathological response, immune-related adverse events, and molecular residual disease.

Results: Perioperative pembrolizumab has shifted immune checkpoint inhibition from a treatment for recurrent or metastatic disease to a curative-intent strategy integrated with surgery. PD-1 signaling should be understood as a rheostat that regulates T-cell receptor and CD28 signaling rather than as a simple inhibitory brake. Durable responses to immune checkpoint inhibition are hypothesized to depend on the preservation and functional availability of the progenitor exhausted T-cell reservoir and its capacity to supply tumor-reactive progeny to the tumor microenvironment. Tumor-draining lymph nodes and tertiary lymphoid structures are therefore not only anatomical or pathological entities but also coordinated, multicellular immunological niches involving CD8-positive T-cell differentiation, CD4-positive helper subsets, B cells, and antigen-presenting cells relevant to treatment response. Surgical specimens after preoperative treatment should be interpreted as sources of pathological, spatial, immune, and molecular information.

Conclusions: Oral and maxillofacial surgeons should integrate tumor immunology into perioperative decision-making, specimen handling, adverse-event management, and translational research. This immune-aware framework may improve the interpretation of surgical treatment in the era of perioperative immunotherapy.

Abbreviations: ACTH, Adrenocorticotropic hormone; APC, Antigen-presenting cell; CtDNA, Circulating tumor DNA; CXCL13, C-X-C motif chemokine ligand 13; ENE, Extranodal extension; ICI, Immune checkpoint inhibitor; IFN-γ, Interferon-gamma; IL-12, Interleukin-12; IrAEs, Immune-related adverse events; MRD, Minimal residual disease; SLAMF6, Signaling lymphocytic activation molecule family member 6; TCF1, T-cell factor 1; TCR, T-cell receptor; TdLNs, Tumor-draining lymph nodes; TEX, Terminally exhausted T cells; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TLS, Tertiary lymphoid structures; TOX, Thymocyte selection-associated high mobility group box; TPEX, Progenitor exhausted T cells; TRM, Tissue-resident memory T cell.

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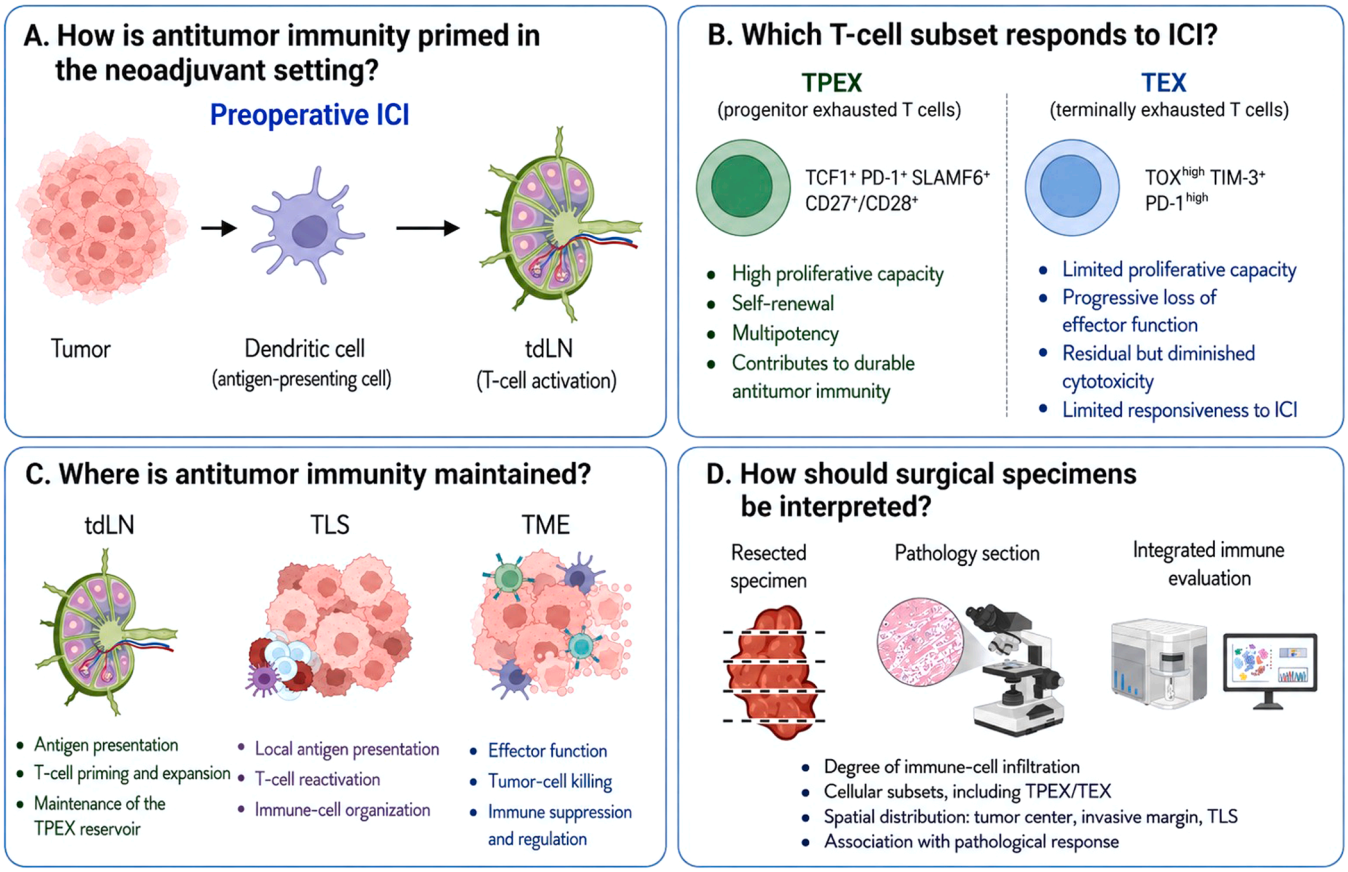

Fig. 1. Spatiotemporal and cellular framework of antitumor immunity in the neoadjuvant setting. (A) The induction of antitumor immunity begins with the release of tumor antigens, which are captured by dendritic cells and transported to the tumor-draining lymph node (tdLN) for T-cell priming and activation. (B) Durable responses to immune checkpoint inhibition are thought to depend mainly on progenitor exhausted T cells (TPEX), which retain proliferative capacity and self-renewal potential, rather than on terminally exhausted T cells (TEX), which show limited proliferative capacity, progressive loss of effector function, and residual but diminished cytotoxic potential. Panel B emphasizes the CD8 + TPEX/TEX axis, but the actual lymphoid and tumor niches involve a multicellular network including CD4 + helper cells, B cells, tissue-resident memory-like T cells, and antigen-presenting cells such as dendritic cells and macrophages. (C) Antitumor immunity is spatially compartmentalized: T-cell priming occurs in the tdLN, local maintenance and reactivation in tertiary lymphoid structures (TLS), and effector functions and immune regulation occur in the tumor microenvironment (TME). (D) Comprehensive evaluation of resected surgical specimens integrating histological assessment with immune profiling is essential for interpreting treatment responses. *Abbreviations: tdLN, tumor-draining lymph node; TPEX, progenitor exhausted T cell; TEX, terminally exhausted T cell; ICI, immune checkpoint inhibitor; TLS, tertiary lymphoid structure; TME, tumor microenvironment.*

1. Introduction: Why oral and maxillofacial surgeons now need tumor immunology

Oral cancer treatment has long been based on surgery-centered locoregional control. In resectable disease, primary tumor resection, neck dissection, and reconstruction are followed by postoperative radiotherapy or chemoradiotherapy according to pathological risk factors such as positive margins, extranodal extension, multiple nodal metastases, and advanced T classification. In this framework, the main responsibility of the oral and maxillofacial surgeon has been to remove macroscopic disease safely and completely, preserve function, and provide adequate pathological information for adjuvant treatment planning [1–3].

The introduction of perioperative immune checkpoint inhibitors (ICIs) changes this framework. In the KEYNOTE−689 trial, patients with resectable locally advanced head and neck squamous cell carcinoma were treated with preoperative pembrolizumab, followed by surgery, postoperative radiotherapy with or without cisplatin plus pembrolizumab, and subsequent pembrolizumab maintenance therapy. The addition of pembrolizumab significantly improved event-free survival compared with standard treatment alone [4]. Regulatory approvals in the United States and Japan further support the clinical relevance of this perioperative strategy [5,6]. Although the KEYNOTE−689 trial was not limited to oral cavity cancer, its results are directly relevant to oral cancer practice because oral cancer treatment depends heavily on primary tumor surgery, neck dissection, pathological risk assessment, and postoperative adjuvant therapy.

The important point for oral and maxillofacial surgeons is that perioperative ICI is not merely the addition of a systemic drug to conventional surgery. It changes the biological meaning of the surgical timeline. Preoperative ICI is administered while the primary tumor, tumor antigens, lymphatic drainage, and tumor-draining lymph nodes (tdLNs) remain present. Postoperative ICI is administered after gross disease has been removed, when the major clinical target is no longer visible tumor but microscopic residual disease, micrometastases, or dormant tumor cells [7–9].

To understand this new treatment sequence, oral and maxillofacial surgeons should consider four practical immunological questions: how antitumor immunity is primed in the neoadjuvant setting, which T-cell subsets respond to ICI, where antitumor immunity is maintained, and how surgical specimens should be interpreted after preoperative ICI (Fig. 1). First, preoperative ICI acts during a window in which tumor antigens, dendritic-cell trafficking, lymphatic drainage, and tdLN priming are still intact. Second, ICI efficacy depends on the differentiation state of tumor-reactive T cells, particularly the balance between T-cell factor 1 (TCF1)-positive progenitor exhausted T cells (TPEX) and

Table 1
Immunological concepts that should be connected to oral and maxillofacial surgical practice.

Immunological concept	Meaning	Relevance to oral and maxillofacial surgeons
TCR signaling	Signals received by T cells after recognition of antigen through the T-cell receptor	Determines T-cell activation, exhaustion, differentiation, and cell death
TPEX	Progenitor exhausted T cells with proliferative and self-renewal capacity	May support durable ICI responses by supplying tumor-reactive progeny, depending on preservation and functional availability of the TPEX reservoir.
TEX	Terminally exhausted T cells with limited proliferative capacity, progressive functional impairment, and residual cytotoxic potential within the tumor microenvironment	May retain residual cytotoxic potential, but have limited proliferative capacity and durability.
tdLN	Tumor-draining lymph node that receives lymphatic flow from the primary tumor	A site where antigen presentation, T-cell priming, immune regulation, TPEX maintenance, and metastatic progression may intersect
TLS	Tertiary lymphoid structure located in or near the tumor	May amplify local antitumor immune responses and contribute to treatment responsiveness
MRD	Minimal residual disease remaining after surgery below the detection limit of routine imaging or pathology	Represents a conceptual target of postoperative ICI and immune surveillance; molecular MRD assessment using ctDNA remains investigational in perioperative oral cancer.
irAE	Immune-related adverse event caused by systemic immune activation during ICI therapy	Can affect perioperative safety, surgical timing, endocrine evaluation, and multidisciplinary management
CD4 + helper T-cell–B-cell/TLS axis	Coordinated interaction among PD−1high CD4 + helper subsets (Tfh/Tph), B cells, and APCs within lymphoid structures.	May support CXCL13 production, germinal center-like reactions, TLS maturation, and indirect CD8 + T-cell priming.
Tissue-resident tumor-reactive T cells (TRM-like cells)	Locally retained intratumoral CD8 + T cells characterized by CD69/CD103 expression and cytotoxic and tissue-resident memory-like features.	May represent downstream intratumoral correlates or potential targets of perioperative ICI; their density, spatial distribution, and clonal expansion may help interpret pathological response.

Abbreviations: ICI, immune checkpoint inhibitor; TCR, T-cell receptor; TPEX, progenitor exhausted T cells; TEX, terminally exhausted T cells; tdLN, tumor-draining lymph node; TLS, tertiary lymphoid structure; MRD, minimal residual disease; irAE, immune-related adverse event; APC, antigen-presenting cell; CXCL13, C-X-C motif chemokine ligand 13; Tfh, T follicular helper cell; Tph, T peripheral helper cell; TRM, tissue-resident memory.

Thymocyte selection-associated high mobility group box (TOX)-high terminally exhausted cells (TEX). Third, antitumor immunity is maintained across connected immune niches, including tdLNs, tertiary lymphoid structures (TLS), and the tumor microenvironment. Fourth, surgical specimens obtained after preoperative ICI should be interpreted not only for staging and pathological response, but also as snapshots of treatment-induced immune responses. Therefore, oral and maxillofacial surgeons need a practical understanding of tumor immunology to interpret the timing of surgery, pathological response, adverse events, and the translational value of surgical specimens. To facilitate this practical reading, Table 1 summarizes key immunological concepts that are repeatedly used in this review and explains their relevance to oral and maxillofacial surgery.

2. From a “drug after recurrence” model to an “immune induction before surgery” model

In the recurrent or metastatic setting, ICI is often understood as a drug used after disease becomes clinically apparent, as illustrated by the established role of pembrolizumab-based therapy in recurrent or metastatic head and neck cancer [10–12]. In the perioperative setting, the logic is different. ICI is introduced before surgery to activate or expand antitumor T-cell responses while tumor antigen supply and lymph node priming are still available. This creates a window in which the immune system can be stimulated before the primary lesion and regional lymphatic tissue are removed [7–9].

For oral and maxillofacial surgeons, this shift has three practical consequences. First, the interval between ICI administration and surgery is not only a scheduling issue but also an immunological window. Second, the surgical specimen after ICI is no longer only a staging specimen; it is also a snapshot of treatment-induced immune responses. Third, postoperative treatment should not be regarded simply as additional systemic therapy, but as a strategy to maintain preoperatively induced immunity and control invisible residual disease. This does not mean that surgery becomes less important. On the contrary, surgery remains the central curative modality in resectable oral cancer. However, the surgeon’s role expands from local disease removal to participation in an integrated immuno-oncological treatment sequence.

3. PD−1 is not simply a brake: a practical explanation for surgeons

PD−1 is often described as a brake on T-cell function. This metaphor is useful, but it can be misleading if interpreted too literally. PD−1 is induced after T-cell receptor (TCR) stimulation and attenuates downstream TCR and CD28 signaling through engagement with PD-L1 or PD-L2. In this sense, PD−1 acts more like a rheostat or safety valve than a simple on/off brake (Fig. 2) [11–14].

PD−1 blockade should not be interpreted simply as complete removal of an inhibitory brake. Rather, PD−1 signaling regulates the intensity of TCR and CD28-mediated activation, and this regulatory function may be important for maintaining stem-like, tumor-reactive CD8 + T cells in tdLNs. Therefore, perioperative ICI should be understood as a therapeutic retuning of the immune response rather than unrestricted T-cell activation.

Recent findings by Hor et al. further support this view [15]. They showed that the inhibitory PD−1 axis helps maintain high-avidity stem-like CD8 + T cells in tdLNs by appropriately tuning TCR signal intensity. In this model, PD−1 does not merely suppress antitumor immunity; rather, it protects highly antigen-reactive T-cell clones from excessive stimulation, terminal differentiation, or clonal loss, thereby preserving a reservoir of TPEX that can continuously supply effector progeny. The effect of PD−1 blockade depends on the immunological context, particularly the availability of a functional TPEX reservoir. Thus, the goal of ICI therapy should not be understood simply as removing the brake completely, but as optimizing the balance between T-cell activation and long-term persistence [15,16].

A useful clinical analogy is that physiological PD−1 signaling functions as an optical filter under intense antigenic stimulation: it attenuates excessive signaling and may help preserve long-term T-cell persistence. Removing sunglasses may make the view brighter, but excessive light can also make driving unstable. In a poorly lit

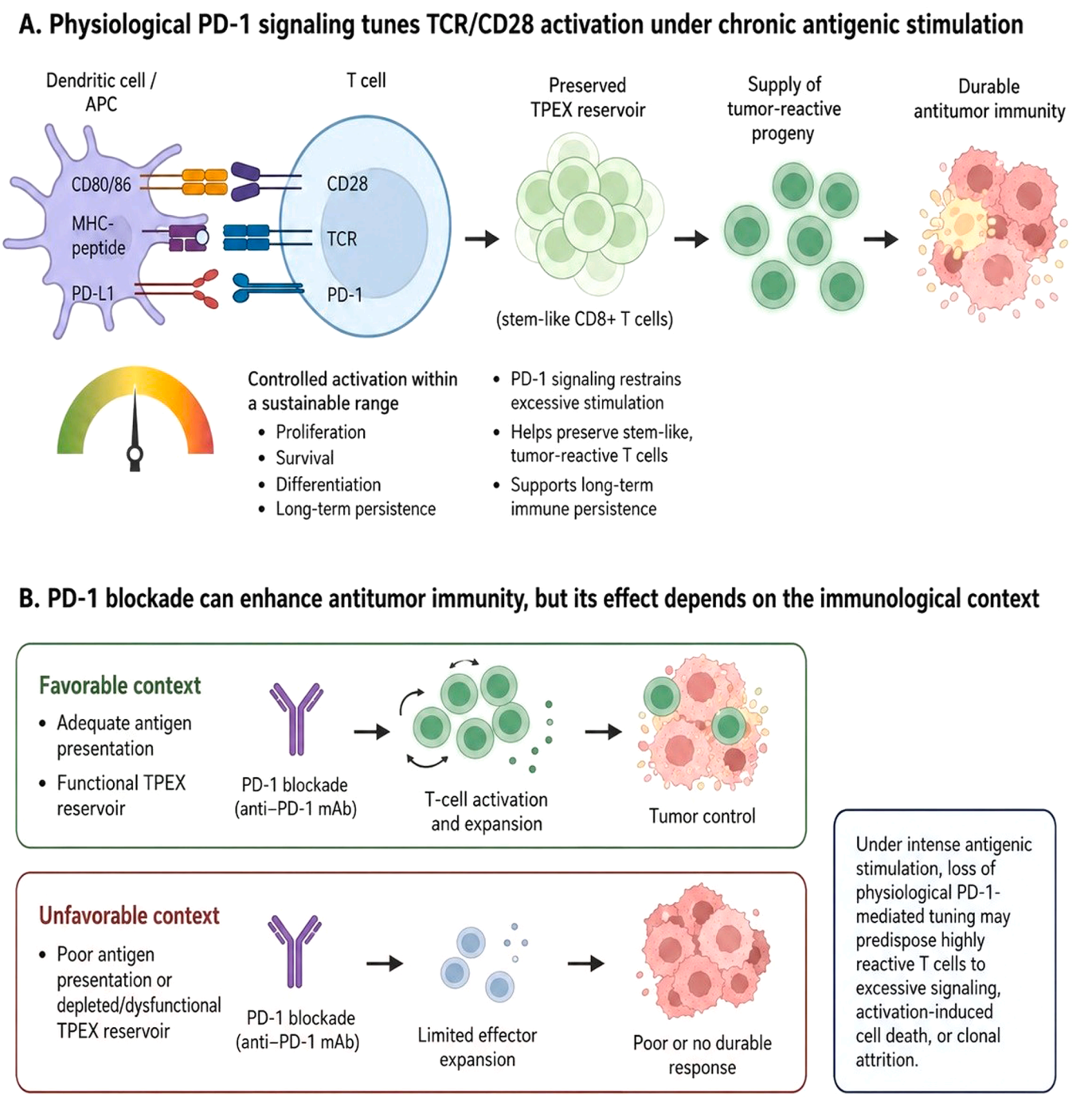

Fig. 2. PD−1 as a molecular rheostat of TCR/CD28 signaling. PD−1 signaling attenuates T-cell receptor (TCR) and CD28-mediated activation and helps maintain signaling intensity within a sustainable range. (A) Under chronic or strong antigenic stimulation, physiological PD−1 signaling may protect highly antigen-reactive, stem-like CD8-positive T cells from excessive activation, thereby contributing to the preservation of the TPEX reservoir and long-term T-cell persistence. (B) PD−1 blockade can enhance antitumor immunity, but its effect is context-dependent. In tumors with adequate antigen presentation and a functional TPEX reservoir, PD−1 blockade may promote expansion of tumor-reactive progeny and tumor control. In contrast, when antigen presentation is poor or the TPEX reservoir is depleted or dysfunctional, PD−1 blockade may generate limited effector expansion and poor durable benefit. Thus, PD−1 blockade should be understood as context-dependent immune retuning rather than universal brake release. *Abbreviations: TCR, T-cell receptor; TPEX, progenitor exhausted T cell; mAb, monoclonal antibody.*

environment, however, removing sunglasses is not sufficient; headlights are needed. Similarly, in tumors with strong antigenic stimulation, PD−1 may prevent excessive TCR signaling and protect T cells from activation-induced cell death or terminal exhaustion. In poorly immunogenic tumors, PD−1 blockade alone may be insufficient unless antigen presentation, dendritic cell function, or the immunosuppressive tumor microenvironment is also improved [15,16].

This concept helps oral and maxillofacial surgeons understand why ICI response cannot be predicted solely by the presence of PD-L1 or CD8-positive T cells [17–20]. A tumor may contain many T cells, but these cells may be bystander cells, terminally exhausted cells, or tumor-reactive cells at different stages of differentiation. A tumor may express PD-L1, but the immune supply line from tdLNs may be weak. Conversely, a tumor with modest PD-L1 expression may still respond if effective priming and functional TPEX availability are preserved [21–24].

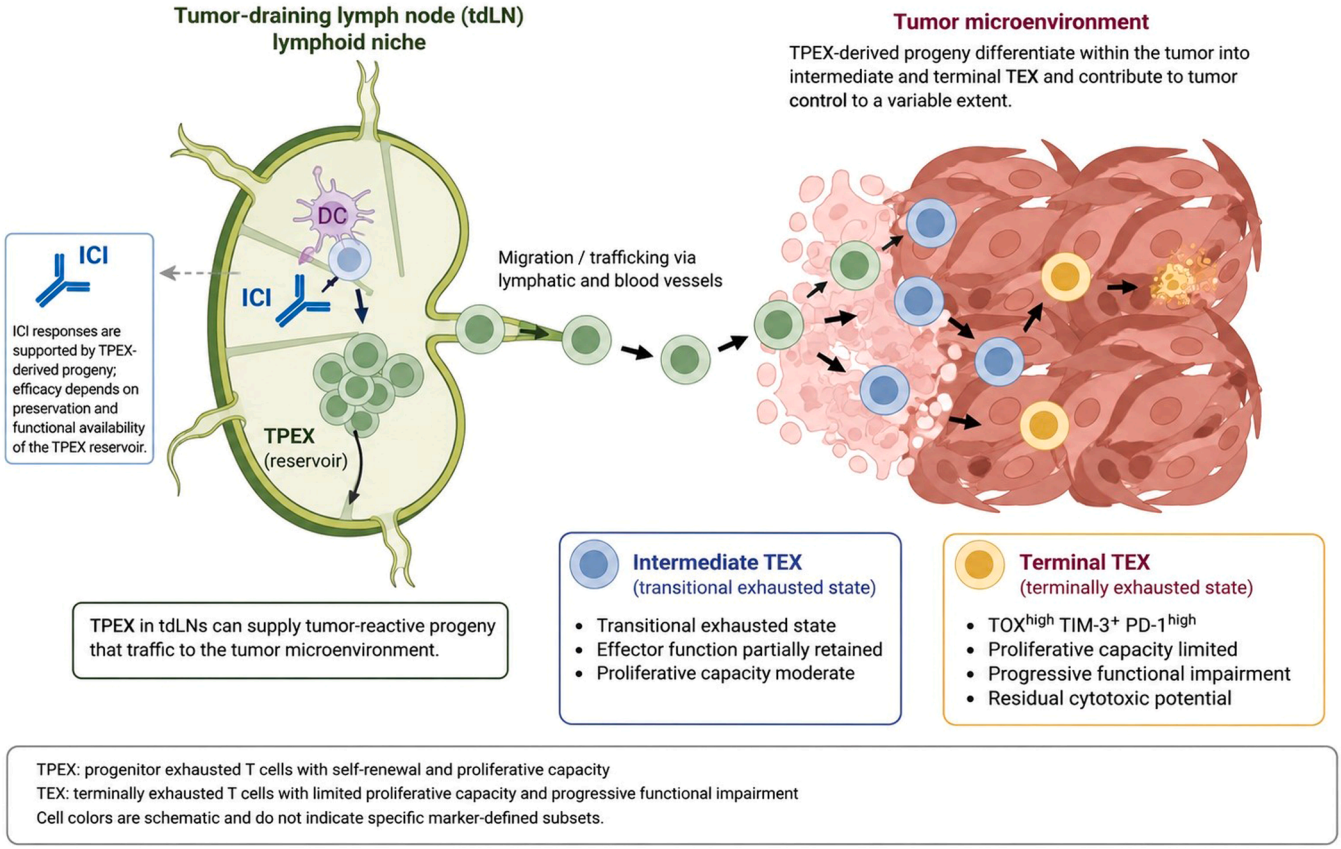

Fig. 3. Dynamic trafficking and differentiation of TPEX-derived progeny from the tumor-draining lymph nodes to the tumor microenvironment. The tumor-draining lymph node (tdLN) can function as an upstream lymphoid niche in which antigen presentation by dendritic cells supports the maintenance and functional availability of progenitor exhausted T cells (TPEX). TPEX-derived tumor-reactive progeny can migrate through lymphatic and blood vessels to the tumor microenvironment (TME). Within the tumor bed, persistent antigen stimulation and local suppressive signals promote differentiation into intermediate exhausted T cells and terminally exhausted T cells (TEX). Intermediate TEX may retain partial effector function and moderate proliferative capacity, whereas terminal TEX show limited proliferative capacity, progressive functional impairment, and residual but diminished cytotoxic potential. Durable ICI responses are thought to depend on the availability of TPEX-derived progeny and the functional integrity of the upstream TPEX reservoir, rather than direct reversal of terminal TEX. While the supply flow highlights CD8 + T-cell trafficking, the tdLN/TLS infrastructure is supported by a coordinated network of CD4 + T follicular helper/T peripheral helper-like cells, B cells, and PD-L1-positive antigen-presenting cells. *Abbreviations: tdLN, tumor-draining lymph node; TME, tumor microenvironment; TPEX, progenitor exhausted T cell; TEX, terminally exhausted T cell; DC, dendritic cell; ICI, immune checkpoint inhibitor.*

4. T-cell exhaustion as adaptation: understanding the TPEX/TEX axis

T-cell exhaustion has often been described as a state of functional failure caused by chronic antigen stimulation. Recent studies indicate that exhaustion is better understood as an adaptive differentiation program that allows T cells to persist under continuous antigen exposure. This concept is especially relevant in cancer, where tumor antigens may be present for long periods [19,25–27].

Exhausted T cells are not a single homogeneous population. TPEX express markers such as TCF1, Signaling lymphocytic activation molecule family member 6 (SLAMF6), and PD−1, and retain proliferative capacity. Intermediate exhausted T cells represent a transition state. Terminally exhausted T cells (TEX) are characterized by high expression of TOX, T-cell immunoglobulin and mucin-domain containing−3 (TIM−3), and PD−1, limited proliferative capacity, progressive loss of effector function, and residual but diminished cytotoxic potential [19, 25–30]. Durable ICI responses are thought to depend less on direct rejuvenation of terminal TEX and more on the preservation, functional availability, and differentiation capacity of the TPEX reservoir, which can supply tumor-reactive progeny to the tumor microenvironment [27–30].

Importantly, this TPEX/TEX axis should be understood as a spatially organized immune supply system (Fig. 3). TPEX are preferentially maintained in lymphoid niches such as tdLNs and, in some cases, TLS, where antigen presentation by dendritic cells supports their survival, self-renewal, and clonal expansion [22–24,31–33]. Their progeny can then migrate into the tumor microenvironment, where persistent antigen stimulation, inflammatory signals, and local suppressive pressures drive further differentiation into intermediate exhausted T cells and terminally exhausted TEX. In this sense, TEX in the tumor are not simply failed T cells; they are downstream effector-like descendants supplied from a renewable TPEX reservoir.

Furthermore, the tumor-reactive T-cell compartment within the tumor microenvironment is highly heterogeneous and is likely to be linked to this upstream supply line. Intratumoral tumor-antigen-recognizing T cells may include oligoclonally expanded populations, CD39 + CD103 + tumor-reactive CD8 + T cells, and CD8 + granzyme B + tissue-resident memory-like T cells expressing residency-associated markers such as CD69 and CD103 [34,35]. These tissue-resident populations may represent important intratumoral correlates or potential targets of ICI therapy. Rather than contradicting the tdLN/TPEX paradigm, these intratumoral tumor-reactive cells can be interpreted as part of a connected immune circuit: tdLN-derived TPEX may supply the tumor bed with functional progeny, some of which may acquire locally retained cytotoxic TRM-like features or progress along the intermediate-to-terminal exhaustion trajectory depending on local cytokine balance and chronic antigen exposure [22–24,36,37].

Overlapping tumor-reactive TCR clones may be detectable in both tdLNs and the TME; however, paired analyses of resected oral cancer specimens using single-cell transcriptomics, spatial profiling, TCR repertoire analysis, and multiplex immunohistochemistry will be essential to map these clonal dynamics and differentiation fates in surgical practice. Therefore, effective ICI therapy requires not only reactivation of intratumoral T cells but also preservation of the upstream TPEX reservoir that can continuously supply tumor-reactive progeny to the tumor microenvironment [22–24].

For oral and maxillofacial surgeons, the TPEX/TEX axis provides a way to interpret clinical patterns. A responder may have a preserved TPEX reservoir and effective supply of tumor-reactive T cells to the tumor. A non-responder may have impaired antigen presentation, lack of TPEX, or a strongly immunosuppressive tumor microenvironment. A patient who initially responds but later relapses may have residual disease, clonal escape, or exhaustion of the T-cell reservoir. These possibilities cannot be fully understood by conventional histopathology alone and will require integrated analysis of tumor tissue, lymph nodes, and blood [18,19,21].

5. Tumor-draining lymph nodes and tertiary lymphoid structures: immune sites that surgeons remove and observe

Oral and maxillofacial surgeons routinely remove or sample lymph nodes, but these tissues have traditionally been interpreted mainly as sites of metastasis and pathological staging [1–3,38–43]. In the ICI era, tdLNs should also be understood as immunological organs. Tumor antigens released from the primary tumor are captured by dendritic cells and transported through lymphatic drainage to tdLNs. There, antigen presentation, T-cell priming, clonal expansion, differentiation, and immune suppression may occur simultaneously [22–24,44].

TLS near the tumor may also contribute to antitumor immunity.

Crucially, the immunological landscape of these lymphoid niches is not restricted to the CD8 + T-cell lineage. A broader, multicellular lymphoid-niche model is required to understand PD−1/PD-L1 biology within tdLNs and TLS. PD−1 ^{high} CD4 + helper subsets, particularly T follicular helper cells, may contribute to B-cell help, CXCL13 production, and germinal center-like organization [45]. T peripheral helper-like cells and other CD4 + helper populations may also participate in local B-cell–oriented immune responses within TLS-like niches, although their precise role in oral cancer requires further clarification [46]. In addition, antigen-presenting cells, including dendritic cells and macrophages, are important functional components of this niche. Dendritic cell–T-cell crosstalk, involving cytokines such as IFN-γ and IL−12, has been implicated in successful anti-PD−1 responses [47]. Thus, perioperative ICI responses in oral cancer should be interpreted as coordinated responses across a multicellular network rather than as an isolated CD8 + T-cell pathway. TLS can contain T-cell areas, B-cell follicles, dendritic cells, and high endothelial venule-like structures. They may act as local sites where T-cell responses are restimulated and amplified close to the tumor [31–33]. Therefore, a practical way to view the immune landscape is to consider the tumor as the front line, TLS as local immune hubs, and tdLNs as upstream supply bases. From this perspective, tdLNs are not only sites of metastatic spread but also potential reservoirs where TPEX are maintained and remain functionally available before their progeny enter the tumor and differentiate into effector-like TEX [22–24].

This review does not propose that the extent of neck dissection should be immediately changed on the basis of immunological theory alone [38–43]. However, it emphasizes that lymph nodes removed during surgery are not merely anatomical or pathological units. They are valuable specimens for evaluating how antitumor immunity is initiated, amplified, suppressed, or redirected after perioperative ICI. Importantly, the immunological value of lymph nodes should not be used as a justification for leaving clinically or radiologically suspicious nodal disease untreated. At present, there is no direct evidence in oral cancer showing that preservation of a potentially metastatic lymph node improves ICI efficacy.

In conventional surgical oncology, the extent of neck dissection has been determined by the probability of occult or clinically evident nodal metastasis. In the perioperative ICI era, this question gains an additional immunological dimension. TdLNs may contain both metastatic deposits and immune niches that support antigen presentation, T-cell priming, and TPEX maintenance. However, this concept of a functional sentinel lymph node should therefore be treated as a translational hypothesis, not as a current surgical indication for de-escalation. Rather, it provides a rationale for future prospective studies that map metastatic risk and immune function according to nodal level, especially in clinically N1 oral cancer.

6. What should oral and maxillofacial surgeons look for after preoperative ICI?

The introduction of preoperative ICI makes the surgical specimen more informative. Pathological response, including major pathological response and pathological complete response, is clinically important. However, oral and maxillofacial surgeons should also recognize that the specimen may contain information about immune mechanisms. Important questions include whether the tumor bed contains dense immune infiltration, whether viable tumor remains at the invasive front, whether immune exclusion is present, whether CD4 + T-cell–B-cell aggregates or germinal center-like reactions are present, whether PD-L1 + antigen-presenting cells are enriched, and whether lymph nodes show signs of multicellular immune activation or suppression [8,9]. Furthermore, evaluating the density and clonal expansion of intratumoral CD8 + tissue-resident memory-like cells can provide useful insights into local mechanisms of response or resistance to immunotherapy.

In collaboration with pathologists and translational researchers, surgical teams can help design specimen workflows. Preoperative biopsy, resected primary tumor, metastatic and non-metastatic lymph nodes, adjacent mucosa, and peripheral blood may all provide complementary information. When feasible, fresh tissue collection for flow cytometry, single-cell RNA sequencing, TCR repertoire analysis, spatial transcriptomics, or multiplex immunohistochemistry should be planned before surgery [19,21,48]. Such planning cannot be improvised after resection; it requires communication among surgeons, pathologists, oncologists, immunologists, and research staff.

7. Practical perioperative considerations: timing, immune-related adverse events, and multidisciplinary communication

Perioperative ICI introduces management issues that are particularly relevant to surgeons. The timing of surgery should balance the need to allow immune activation with the need to avoid disease progression or treatment-related delays [8,9]. In the KEYNOTE−689 trial, surgery was planned after the preoperative pembrolizumab phase according to the trial protocol [4]. In real-world practice, coordination among surgery, medical oncology, anesthesiology, pathology, and radiotherapy is essential.

Immune-related adverse events (irAEs) must also be incorporated into perioperative planning. Endocrine irAEs such as thyroid dysfunction, hypophysitis, adrenal insufficiency, and immune-related diabetes can affect perioperative risk [49,50]. In particular, adrenal insufficiency may impair stress responses during surgery. Therefore, preoperative evaluation should include symptom review and appropriate laboratory screening, such as thyroid function, glucose, electrolytes, morning cortisol, and adrenocorticotropic hormone (ACTH) when clinically indicated. Surgeons should not regard irAEs as issues managed only by medical oncologists; some irAEs directly affect surgical safety [49,50].

A second practical issue is interpretation of nodal status after ICI. ICI may induce pathological regression in the primary tumor or lymph nodes. Therefore, negative or regressed lesions after treatment should be

Table 2
Common misconceptions about immune checkpoint inhibition and practical reinterpretations for oral and maxillofacial surgeons.

Topic	Simplified understanding	Practical immunological understanding	Practical implications for oral and maxillofacial surgeons
PD−1	A harmful brake that suppresses T cells	A rheostat that fine-tunes TCR/CD28 signaling	Plan perioperative ICI with awareness that excessive immune activation may cause irAEs, whereas insufficient activation may limit antitumor efficacy.
PD-L1	A definitive predictive marker of ICI response	One component of the broader immune context	Use PD-L1 expression as a decision-support factor, not as a stand-alone determinant of perioperative ICI selection or expected response.
CD8-positive T cells	More CD8-positive T cells are always better	Tumor specificity, spatial distribution, clonality, and differentiation state are critical; intratumoral tissue-resident memory (TRM)-like phenotypes and oligoclonal expansion must be evaluated.	When reviewing biopsy or surgical specimens, interpret CD8-positive infiltration together with spatial distribution, TPEX/TEX phenotype, TRM-like features, and TCR clonality.
T-cell exhaustion	Irreversible T-cell dysfunction	A dynamic differentiation process under chronic antigen stimulation	Do not interpret exhausted T-cell markers as simple treatment failure; consider whether a functionally available TPEX reservoir may support durable ICI benefit.
tdLN	A site of metastasis	A site where antigen presentation, T-cell priming, immune regulation, TPEX maintenance, and metastatic progression may intersect	During neck dissection, treat lymph nodes as staging specimens and potential immune-profiling specimens; record nodal level and preserve tissue for analysis of multiple immune-cell subsets, including CD8 + T cells, CD4 + helper cells, B cells, and APCs, when feasible.
Surgery	Removal of visible tumor	Locoregional tumor control plus an opportunity to evaluate treatment-induced pathological, spatial, immune, and molecular responses	Use resection and neck dissection specimens to guide postoperative RT/CRT/ICI decisions based on margins, ENE, nodal burden, MPR/pCR, and treatment response.

Abbreviations: CD8, cluster of differentiation 8; CRT, chemoradiotherapy; ENE, extranodal extension; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MPR, major pathological response; pCR, pathological complete response; PD−1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RT, radiotherapy; TCR, T-cell receptor; tdLN, tumor-draining lymph node; TEX, terminally exhausted T cell; TPEX, progenitor exhausted T cell.

interpreted in the context of prior imaging, clinical nodal status, treatment timing, and pathological examination. This is particularly important when considering sentinel lymph node biopsy or limited nodal sampling after systemic immune modulation. Direct evidence remains limited, so careful interpretation and documentation are required [38–43].

In clinical practice, the timing of surgery after preoperative pembrolizumab should follow the approved regimen and multidisciplinary planning. The immunological window should not be interpreted as a reason to delay definitive surgery beyond the planned schedule, particularly when tumor progression, airway compromise, infection, bleeding, or nutritional decline is a concern.

8. Minimal residual disease and the meaning of postoperative ICI

After surgery, the primary tumor is removed and tumor antigen load is reduced. Nevertheless, microscopic residual disease, disseminated tumor cells, or dormant tumor cells may persist below the detection limit of imaging and routine pathology. Postoperative ICI can be understood as a strategy to maintain the antitumor immunity induced preoperatively and to provide immune surveillance against such invisible disease [7,51–54].

In oral cancer, the lymphatic pathway has a dual biological significance. On the one hand, tumor-derived antigens and antigen-bearing conventional dendritic cells can travel through afferent lymphatic vessels to tdLNs, where antigen presentation and T-cell priming occur. This pathway supports the generation and maintenance of tumor-reactive T-cell responses. On the other hand, the same lymphatic route can also allow tumor cells to reach regional lymph nodes. Once tumor cells establish nodal metastases, they may further disseminate through efferent lymphatic flow, nodal blood vessels, or systemic circulation, thereby contributing to distant relapse [55–57]. Thus, the lymphatic system is both an immune-induction route and a metastatic dissemination route [58]. Postoperative ICI can therefore be viewed as a strategy to maintain antitumor immunity against residual disease that may persist along, or beyond, this lymphatic-metastatic pathway.

For surgeons, this concept is important because a robust locoregional response does not necessarily eliminate systemic risk. Pathological response should be interpreted together with margin status, extranodal extension, nodal burden, lymphovascular invasion, perineural invasion, and emerging biomarkers such as circulating tumor DNA (ctDNA). Future perioperative treatment may be individualized according to both pathological risk and immune or molecular indicators of residual disease [51–53,59]. Taken together, these concepts require oral and maxillofacial surgeons to connect tumor immunology with surgical decision-making, specimen interpretation, perioperative safety, and postoperative surveillance. Common misconceptions about immune checkpoint inhibition and their practical reinterpretations for oral and maxillofacial surgeons are summarized in Table 2.

ctDNA is a promising tool for molecular residual disease assessment in head and neck cancer, but it remains investigational in perioperative oral cancer immunotherapy. Therefore, ctDNA should be discussed as a future risk-stratification tool rather than as a current standard determinant of postoperative ICI duration or treatment intensity.

9. What changes in daily thinking for oral and maxillofacial surgeons?

The main change is not that surgeons must become immunologists. Rather, oral and maxillofacial surgeons should become immune-literate clinicians who can ask the right questions at the right time. In the perioperative ICI era, surgery is no longer interpreted only as a locoregional treatment, but as one component of an immuno-oncological sequence that begins before resection and continues after surgery [7–9].

Before treatment, the surgeon should ask whether the patient is a candidate for perioperative ICI, whether the tumor and nodal disease should be biopsied or sampled for immune analysis, and whether baseline endocrine or autoimmune risks have been evaluated. This pretreatment phase is also the time to coordinate imaging, pathological confirmation, tissue collection, and multidisciplinary planning, because preoperative ICI acts while the primary tumor, tumor antigens, lymphatic drainage, and tdLNs remain present [4,7,22–24].

During surgery, the surgeon's conventional responsibilities remain essential: complete tumor resection, safe margins, appropriate neck management, functional reconstruction, and complication prevention. At the same time, the resected specimen should be understood as more than a staging specimen. It can provide information on pathological response, residual viable tumor, extranodal extension, nodal burden, immune-cell infiltration, spatial immune organization, and mechanisms

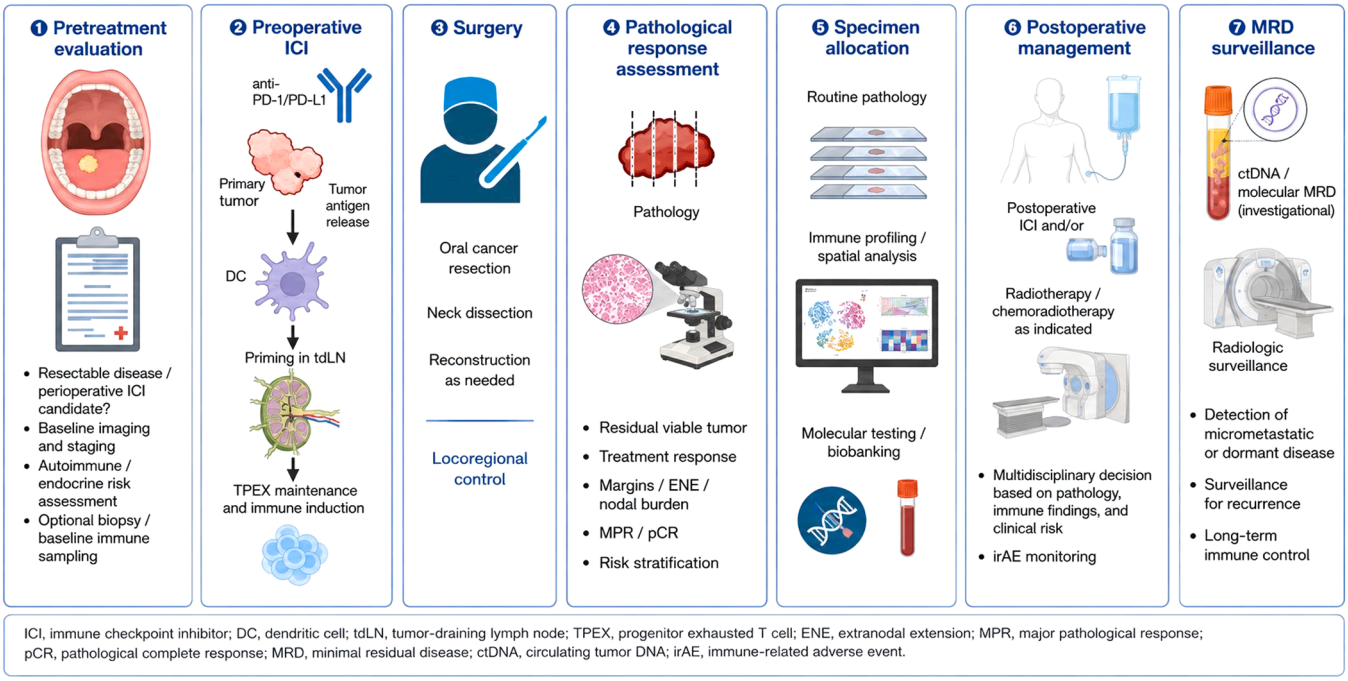

Fig. 4. Comprehensive clinical and translational roadmap for perioperative immune checkpoint inhibitor therapy in oral cancer. The integrated management paradigm combines locoregional control with systemic immune surveillance. (1) Pretreatment evaluation identifies patients who may be candidates for perioperative immune checkpoint inhibition (ICI). (2) Preoperative ICI is administered while the primary tumor, tumor antigens, lymphatic drainage, and tumor-draining lymph nodes (tdLNs) remain present. (3) Surgery provides definitive locoregional control through oral cancer resection, neck dissection, and reconstruction when needed. (4) Pathological response assessment evaluates residual viable tumor, treatment response, margin status, extranodal extension (ENE), nodal burden, major pathological response (MPR), pathological complete response (pCR), and risk stratification. (5) Specimen allocation enables routine pathology, immune profiling, spatial analysis, molecular testing, and biobanking. (6) Postoperative management integrates ICI, radiotherapy, chemoradiotherapy, immune-related adverse event monitoring, and multidisciplinary decision-making. (7) MRD surveillance combines standard radiologic follow-up with investigational molecular approaches such as circulating tumor DNA (ctDNA) analysis to detect molecular residual disease or early recurrence. *Abbreviations: ICI, immune checkpoint inhibitor; DC, dendritic cell; tdLN, tumor-draining lymph node; TPEX, progenitor exhausted T cell; ENE, extranodal extension; MRD, minimal residual disease; ctDNA, circulating tumor DNA.*

of response or resistance. Therefore, specimen handling and allocation for routine pathology, immune profiling, spatial analysis, molecular testing, or biobanking should be planned before resection whenever feasible [19,21,48].

After surgery, pathology should be interpreted not only as a report of locoregional disease control, but also as a guide to postoperative ICI, radiotherapy, chemoradiotherapy, and surveillance. Postoperative management should consider both conventional pathological risk factors and emerging immune or molecular indicators, including circulating tumor DNA and other markers of minimal residual disease [51–54,59]. In this way, oral and maxillofacial surgeons can contribute not only to tumor removal, but also to immune-aware treatment planning and long-term recurrence prevention.

This practical workflow is summarized in Fig. 4. The goal is not to reduce the importance of established surgical principles, but to place them within a broader perioperative strategy in which immune induction, surgical control, pathological interpretation, specimen-based analysis, postoperative therapy, and minimal residual disease (MRD) surveillance are connected.

10. Conclusion

PD−1 signaling should be understood as a rheostat that regulates T-cell activation and persistence, and the effect of PD−1 blockade depends on the immunological context, particularly the availability of a functional TPEX reservoir. Perioperative ICI has expanded the conceptual framework of oral cancer treatment. For oral and maxillofacial surgeons, the key issue is not only how to remove the tumor, but also how to understand the immune response that occurs before and after surgery. PD−1 should be viewed as a regulator of TCR signaling, T-cell exhaustion as an adaptive differentiation program, TPEX as a renewable source of antitumor T-cell responses, tdLNs and TLS as immunological sites of priming and amplification, and postoperative ICI as a strategy for maintaining immune surveillance against residual disease.

This review provides a practical immunological framework for oral and maxillofacial surgeons treating oral cancer in the perioperative ICI era. As immunotherapy becomes integrated into curative-intent treatment, oral and maxillofacial surgeons will play an increasingly important role not only in local tumor control but also in immune-aware treatment planning, specimen interpretation, and multidisciplinary translational research.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT to assist with language editing and organization. The authors reviewed and edited the content as needed and take full responsibility for the content of the manuscript. No generative AI was used to create or alter the figures. All schematic figures were created with BioRender.com under an appropriate publication license.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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