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Review Article

Perioperative preparation for head and neck cancer patients receiving immunotherapy

Shao-Chun Wu [a,c], Kuan-Hao Liao [b,c], Pi-Chieh Lin [b], Ching-Hua Hsieh [b,*]

[a] Department of Anesthesiology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, 83301, Taiwan
[b] Department of Plastic Surgery, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University and College of Medicine, Kaohsiung, 833, Taiwan

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ABSTRACT

Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has significantly advanced the management of head and neck cancers (HNCs), and is increasingly integrated into perioperative strategies. This review addresses perioperative considerations essential for HNC patients undergoing surgery following neoadjuvant or adjuvant ICIs. Key perioperative issues include the optimal timing of surgery relative to immunotherapy, recognition and management of immune-related adverse events (irAEs), potential wound healing complications, infection risks, and anesthesia considerations. Neoadjuvant ICIs administered approximately 3–6 weeks before surgery are feasible without substantial delays or increased morbidity. Adjuvant ICIs typically begin 4–8 weeks postoperatively once adequate healing occurs, with careful integration alongside standard postoperative therapies like radiotherapy and chemotherapy. Common irAEs, including dermatologic, endocrine, pulmonary, cardiac, gastrointestinal, and renal complications, necessitate targeted preoperative screening and proactive management strategies. Multidisciplinary coordination is essential to minimize perioperative risks, with standardized protocols recommended for patient assessment, intraoperative management, and postoperative monitoring. Current evidence suggests that immunotherapy, while posing unique perioperative challenges, does not substantially elevate surgical risks if adequately managed.

1. Introduction

Head and neck cancers (HNCs) often require multimodal treatment including surgery, radiation, and chemotherapy. In recent years, immunotherapy – particularly immune checkpoint inhibitors (ICIs) targeting PD-1, PD-L1, or CTLA-4 – has emerged as a significant therapeutic advance in HNC. In recurrent/metastatic HNC, checkpoint inhibitors have improved survival in a subset of patients and are now an established treatment option.[1] These successes have prompted trials of immunotherapy in earlier stages, integrating it into the perioperative setting (neoadjuvant and adjuvant therapy).[2,3]

Integrating immunotherapy around the time of surgery introduces new perioperative considerations. Unlike traditional cytotoxic therapies, immunotherapy's unique immune-related adverse events (irAEs) and prolonged immunologic effects necessitate careful preparation and monitoring. Key issues include optimal timing of surgery relative to immunotherapy, recognition and management of irAEs, potential wound healing and infection complications, perioperative drug interactions, and coordination with other treatments.

This review provides a comprehensive overview of perioperative preparation for adult HNC patients receiving immunotherapy, with an emphasis on neoadjuvant and adjuvant settings. We discuss surgical timing strategies, anticipate and manage irAEs, address wound healing, infection, and bleeding risks, consider anesthesia implications, and highlight interactions with concurrent therapies.

2. Immunotherapy in head and neck cancer: current role and emerging paradigms

Checkpoint Inhibitors in HNC: ICIs have become integral in

* Corresponding author. No 123, Da-Pei Road, Niao-Song District, Kaohsiung, 833, Taiwan.
E-mail addresses: shaochunwu@gmail.com (S.-C. Wu), homekuanhao@gmail.com (K.-H. Liao), k99088@cgmh.org.tw (P.-C. Lin), m93chinghua@gmail.com, addy@adm.cgmh.org.tw (C.-H. Hsieh).
[c] These authors contributed equally to this work of the authorship.

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List of abbreviations

ACE-27 –	Adult Comorbidity Evaluation 27 (comorbidity index)
ACTH –	Adrenocorticotropic hormone
ALT –	Alanine aminotransferase
AST –	Aspartate aminotransferase
CKD –	Chronic kidney disease
COPD –	Chronic obstructive pulmonary disease
CTLA-4 –	Cytotoxic T-lymphocyte-associated protein 4
ECG –	Electrocardiogram
EF –	Ejection fraction
G-CSF –	Granulocyte colony-stimulating factor
HNC –	Head and neck cancer
HNSCC –	Head and neck squamous cell carcinoma
ICI –	Immune checkpoint inhibitor
IO –	Immunotherapy
irAE –	Immune-related adverse event
PD-1 –	Programmed death receptor-1
PD-L1 –	Programmed death ligand-1
pCR –	Pathologic complete response
PFT –	Pulmonary function test
TSH –	Thyroid-stimulating hormone

HNC care. PD-1 inhibitors such as pembrolizumab and nivolumab are approved for recurrent/metastatic HNSCC after demonstrating improved survival over chemotherapy.[1] These agents benefit roughly 15–30 % of unselected HNC patients with durable responses.[4,5] Combination immunotherapy and novel immunomodulators are under investigation, but single-agent PD-1/PD-L1 inhibitors remain the cornerstone of immunotherapy in HNC.

Neoadjuvant (Preoperative) Immunotherapy: Building on success in advanced disease, ICIs are being tested as neoadjuvant therapy before definitive surgery. The rationale is that treating an intact tumor may prime a stronger immune response by exposing abundant tumor antigens in situ.[1] Early trials have shown this approach to be feasible. For example, the CheckMate 358 study gave two doses of nivolumab approximately 4 weeks pre-surgery in resectable HNSCC and reported significant tumor shrinkage in about half of patients, with no surgery delays greater than 4 weeks due to treatment toxicity.[6] Pathologic tumor responses have been observed in 20–60 % of patients in various phase I/II trials of neoadjuvant anti-PD-1 therapy.[7–10] Importantly, these studies have not shown excess perioperative morbidity. In a cohort of 32 HNC patients receiving neoadjuvant pembrolizumab, postoperative complication rates were similar to matched controls who did not get immunotherapy.[11]

Adjuvant (Postoperative) Immunotherapy: ICIs are also being investigated after surgery to eradicate microscopic residual disease and modulate post-surgical immune responses. The Phase 3 KEYNOTE-689 trial showed that adding pembrolizumab in both the neoadjuvant and adjuvant settings significantly improved event-free survival in stage III/IVA resectable HNSCC.[12] In KEYNOTE-689, patients received neoadjuvant pembrolizumab, definitive surgery, and then adjuvant pembrolizumab combined with standard radiotherapy with or without cisplatin 12. The safety profile was consistent with prior studies, with immune-related toxicities manageable and no new perioperative safety signals.

Combination Approaches: ICIs are also being integrated with chemotherapy or radiotherapy. Neoadjuvant chemo-immunotherapy has shown synergistic activity – for instance, combining pembrolizumab with platinum/taxane induction chemotherapy yielded high pathological response rates (pCR) in oral cavity cancer.[13] However, although contemporary evidence indicates that cytotoxic chemotherapy remains indispensable in peri-operative HNC management, its optimal interplay with immunotherapy (IO) is still under active investigation. Two phase-II trials illustrate the current landscape. Wu et al. combined camrelizumab with nab-paclitaxel/cisplatin in resectable stage III–IVA disease and achieved a 56 % pathological complete-response rate, double the historical rate for induction chemotherapy alone, without increasing grade $\geq$3 toxicities.[14] Conversely, a 2023 multicenter study of induction camrelizumab plus TPF (docetaxel, cisplatin, 5-fluorouracil chemotherapy regimen) in hypopharyngeal cancer reported an impressive 82 % radiologic response, yet survival data remain immature and irAEs $\geq$ grade 3 occurred in 11 % of patients.[15] These studies suggest synergy but not unequivocal superiority over single-modality regimens; randomized trials are awaited to define whether "chemo-immunotherapy" will supplant chemo- or immune-therapy only strategies. Similarly, neoadjuvant immuno-radiotherapy has been tested: one phase Ib clinical trial reported a >90 % pCR rate with neoadjuvant hypofractionated radiotherapy combined with nivolumab in patients with p16-positive HNSCC, with no unexpected perioperative toxicity or surgical delays.[16]

3. Neoadjuvant immunotherapy: preoperative considerations and surgical timing

Neoadjuvant immunotherapy is administered prior to definitive surgery with the goals of tumor downsizing, early eradication of micrometastases, and immune system priming. When preparing a patient for surgery after neoadjuvant immunotherapy, several key considerations apply:

Treatment Scheduling and Surgical Timing: Optimal timing of surgery after immunotherapy is critical. ICIs have long half-lives (2–3 weeks) and durable immune effects, but in practice most trials have scheduled surgery relatively soon after neoadjuvant therapy to avoid delaying definitive treatment. In the CheckMate 358 study, surgery followed about 4 weeks after the first nivolumab dose. A multi-institutional trial of neoadjuvant pembrolizumab similarly targeted surgery approximately 3–4 weeks after the last preoperative dose.[6] In a cohort treated with pembrolizumab plus chemotherapy, the average interval was around five weeks from end of neoadjuvant therapy to surgery.[17] These intervals align with the typical 4–6 week window used after neoadjuvant chemoradiotherapy in other cancers. Crucially, studies to date report that neoadjuvant ICIs have not caused frequent surgical delays or cancellations due to toxicity.[11] In CheckMate 358, no surgery was delayed more than 4 weeks for treatment-related adverse events. Thus, with proper planning, surgeons can proceed on schedule in most cases.[6]

Preoperative Assessment: Before surgery, a thorough assessment of the patient's response and toxicity to immunotherapy is necessary. Radiologically, the primary tumor and nodal disease should be re-imaged to evaluate response; paradoxically, immunotherapy can cause pseudoprogression in rare cases,[18] so clinical correlation is important. If significant tumor shrinkage has occurred, surgical plans may be adjusted toward less extensive resection or smaller reconstruction.[13] Additionally, any immune-related adverse events that arose during neoadjuvant therapy should be identified and optimized before surgery. For example, if the patient developed immunotherapy-induced hypothyroidism, they should be started on thyroid hormone replacement preoperatively.[19] If they experienced adrenal insufficiency from hypophysitis, they must be on appropriate corticosteroid replacement

prior to surgery.[19] Active pneumonitis or colitis triggered by immunotherapy would generally warrant delaying surgery until adequately treated.

Intraoperative Strategy: The surgical team should anticipate that prior immunotherapy might alter tissue characteristics. Some surgeons have anecdotally observed more fibrosis or more lymphocytic infiltrates in tissues,[16,18,20] but clinically significant effects on surgical technique are not well-documented. Notably, neoadjuvant immunotherapy can sometimes dramatically reduce tumor volume, allowing less morbid surgery. Uppaluri et al. reported cases where neoadjuvant pembrolizumab led to tumor downstaging that enabled avoidance of mandibulectomies or other extensive procedures.[20]

If a major resection with free flap reconstruction is planned, some reports have raised concern for higher flap or wound complications in patients who received preoperative ICIs. However, evidence is mixed. Single-center retrospective studies noted an association between neoadjuvant immunotherapy/targeted therapy and flap complications.[21] In contrast, the prospective pembrolizumab neoadjuvant trial found no increase in wound dehiscence, fistula, or flap loss compared to immunotherapy-naïve controls.[11]

4. Adjuvant immunotherapy: postoperative considerations and integration with surgery

Adjuvant immunotherapy refers to administering ICIs in the postoperative period, typically to eliminate microscopic residual disease or reduce recurrence risk. Preparing a patient for adjuvant immunotherapy involves both timing the initiation appropriately and managing interactions with surgery and other adjuvant treatments:

Wound Healing and Timing of Initiation: After major head and neck surgery, a period of wound healing is necessary before starting immunotherapy. In practice, recent trials have started adjuvant immunotherapy around 4–8 weeks post-surgery. For instance, in KEYNOTE-689, patients underwent standard surgery, then approximately 6–7 weeks later began radiotherapy with concurrent pembrolizumab.[12] By ~6 weeks, surgical wounds are largely healed in uncomplicated cases.

If a patient has delayed wound healing or a wound complication, immunotherapy should be postponed until adequate healing is achieved. In one trial of adjuvant tremelimumab after HNC surgery, therapy was delayed in a few patients due to slow healing, but ultimately most patients were able to start immunotherapy by 6–8 weeks postoperatively.[22] Table 1 outlines timing strategies, emphasizing that adjuvant immunotherapy typically starts within 2 months of surgery.

Concurrent Adjuvant Therapy (Radiation/Chemotherapy): A unique aspect of HNC management is that many patients receive postoperative radiation or chemoradiation for advanced disease features. Integrating immunotherapy into this paradigm requires careful planning to avoid intolerable combined toxicities. Clinical trials have explored several approaches:

- *Sequential Adjuvant Immunotherapy:* One strategy is to complete surgery and any indicated adjuvant radiation with or without chemotherapy first, then give immunotherapy sequentially for a defined period. The ongoing IMvoke010 trial tested adjuvant durvalumab after the completion of standard postoperative chemoradiation.[23] While that particular study did not show a significant disease-free survival benefit, it demonstrated that sequential PD-L1 blockade after chemoradiation was feasible without unexpected safety issues.[24] Patients were started on immunotherapy ~4–6 weeks after finishing radiation; by this time surgical wounds and radiation mucositis had sufficiently healed.
- *Concurrent Adjuvant Immunotherapy with Radiation:* An alternative approach, as in KEYNOTE-689, is to give pembrolizumab (and cisplatin for those eligible) concurrently with adjuvant radiotherapy.[12] The combination was reasonably well-tolerated. Acute mucosal toxicities were largely attributable to radiation and cisplatin, whereas immunotherapy contributed its own profile of mostly endocrine and dermatologic events.[25] Crucially, there was no increase in long-term toxicity noted with the addition of pembrolizumab.[24]
- *Steroid Use During Radiation:* One challenge of combining immunotherapy with radiation/chemotherapy is managing the frequent need for steroids. For instance, severe radiation mucositis might typically be managed with corticosteroids; however, administering prednisone or dexamethasone can dampen T-cell activity and potentially reduce immunotherapy efficacy. A balanced approach is required – judicious use of steroids for acute toxicities so as not to compromise the anti-tumor immune response.

Postoperative Complications and Adjuvant Immunotherapy: Before initiating immunotherapy post-surgery, patients should be evaluated for any surgical complications. Active infection is a contraindication to starting ICIs until controlled. Similarly, if the patient has a non-healed pharyngo-cutaneous fistula or unhealed flap, starting immunotherapy might risk exacerbating inflammation at that site. In the KEYNOTE-689 trial,[12] patients had to meet healing criteria before adjuvant therapy. In practice, a conservative rule is to ensure all incisions are well-healed, no signs of infection are present, the patient is nutritionally repleted, and any surgical drains or tracheostomies are stable, prior to commencing immunotherapy.

Duration of Adjuvant Immunotherapy: If adjuvant immunotherapy is given, the duration is typically fixed (e.g., 6–12 months of therapy).[23] Pembrolizumab and nivolumab in the adjuvant setting have usually been given for up to one year of dosing. This prolonged exposure means that the healthcare team must remain vigilant for late-arising irAEs well into the survivorship period. It also means the patient will be actively under systemic therapy during much of their postoperative recovery and rehabilitation. Therefore, adjuvant immunotherapy should start only after adequate surgical recovery, typically 4–8 weeks postoperatively, and it can be combined with standard adjuvant treatments if monitored closely.[24]

5. Decision framework for clinical heterogeneity

Notably, the above generalized perioperative strategies should account for clinical heterogeneity in HNC. One-size-fits-all recommendations may obscure the wide biological and surgical diversity of HNCs. We have added a two-step clinical-decision framework table (Table 2) that guides peri-operative planning according to (i) disease attributes and (ii) host-related modifiers. Step-1 stratifies by sub-site and stage, because anatomical constraints and metastatic risk dictate both operative complexity and immune-checkpoint-inhibitor (ICI) timing. Step-2 layers host factors—Charlson/Adult Comorbidity Evaluation 27 (ACE-27) comorbidity class, human papillomavirus/PD-L1 status, and baseline autoimmune disease—onto tumor strata. This decision framework table also illustrates how the framework alters surgery timing, steroid prophylaxis and flap selection. This table is built from prospective timing data[7,24] and pooled irAE-related peri-operative risk factors reported in the 2024 neoadjuvant PD-1 meta-analysis and related cohort studies.[7,12,16,26]

Table 1
Common immune-related adverse events and perioperative implications.

irAE (Organ/System)	Frequency/Severity	Perioperative Implications & Management
Dermatologic (Rash, Pruritus)	Very common (20–30 %); usually mild	- Generally minimal surgical impact unless severe/at surgical site - For mild: topical steroids/antihistamines - For severe desquamation: postpone surgery; consult dermatology
Endocrine (Thyroid dysfunction, Hypophysitis, Adrenal insufficiency)	Hypothyroidism ~5–15 %; Hypophysitis 1–5 % (more with CTLA-4 inhibitors)	- Often permanent; can cause hemodynamic instability if uncorrected - Pre-op: Check TSH/T4, morning cortisol if suspected adrenal insufficiency - Intra-op: Stress-dose steroids for adrenal insufficiency - Post-op: Monitor electrolytes; continue hormone replacement
Pulmonary (Pneumonitis)	~3–5 % incidence with PD-1/PD-L1; grade 3–4 in ~1–2 %	- Risk of respiratory failure under anesthesia - Pre-op: Defer surgery if active; obtain chest CT for unexplained symptoms - Intra-op: Lung-protective ventilation; avoid fluid overload - Post-op: Monitor oxygen; differentiate pneumonitis vs pneumonia; start steroids if pneumonitis suspected
Cardiac (Myocarditis, Pericarditis, Arrhythmias)	Rare (~1 % for myocarditis) but potentially fatal	- Pre-op: Cardiology clearance if history of myocarditis - Intra-op: Invasive monitoring in high-risk cases; avoid myocardial depressants - Post-op: Monitor cardiac enzymes/ECG if suspicious symptoms; treat with high-dose steroids if myocarditis suspected
Gastrointestinal (Colitis, Hepatitis)	Colitis ~5 % (higher with CTLA-4); Hepatitis 1–5 %	- Colitis: Risk of dehydration/electrolyte disturbances - Hepatitis: Affects drug metabolism and coagulation - Pre-op: Postpone if active colitis or significant hepatitis - Intra-op: Avoid NSAIDs with colitis history; adjust anesthetic dosing with liver dysfunction - Post-op: Monitor stool output; test for infection with diarrhea; follow LFTs
Renal (Nephritis)	Uncommon (~1 %)	- Pre-op: Check baseline renal function; consider delay if significant elevation - Intra-op: Maintain renal perfusion; adjust renally-excreted drugs - Post-op: Monitor urine output/creatinine; avoid nephrotoxins
Neurologic (Neuropathy, Myositis, Myasthenia gravis, Encephalitis)	Rare (<1 %)	- Neuromuscular issues increase sensitivity to muscle relaxants - Pre-op: Assess for weakness; neurology consult if present - Intra-op: Avoid/minimize paralytics with myasthenia; monitor nerve function - Post-op: Close respiratory monitoring; evaluate any neurologic changes promptly

Table 2
Timing strategies for surgery and immunotherapy.

Scenario	Timing Strategy and Considerations
Neoadjuvant immunotherapy (before surgery)	- Interval to surgery: ~3–6 weeks after last ICI dose - If with chemo: Wait for count recovery/mucositis resolution (4–6 weeks) - Monitor for toxicity: irAEs should be ≤grade 1 before proceeding - No specific “washout" needed if patient is stable
Surgery between immunotherapy cycles	- For single preoperative dose: Plan surgery 2–4 weeks later - For multiple neoadjuvant doses: Surgery 1–3 weeks after final dose
Adjuvant immunotherapy (after surgery)	- Wait ≥4 weeks post-surgery and ≥2 weeks post-suture removal - With radiation ± chemo: Start concurrently (~6–7 weeks post-op) or sequentially - Delay if grade ≥2 surgical complications persist - Aim to start within 2–3 months post-op when possible
Interruption for surgery (during ongoing immunotherapy)	- Hold ICIs ≥4 weeks before elective surgery - Resume ≥4 weeks post-op once recovered

6. irAEs and perioperative implications

irAEs can involve virtually any organ system.[26,27] Recognizing and managing these toxicities in the perioperative period is a central component of preparing HNC patients on immunotherapy. Table 3 provides an overview of common irAEs and their specific perioperative implications.

Incidence and Spectrum of irAEs: The most frequent irAEs with ICIs are dermatologic and endocrine. Cutaneous reactions (rash, pruritus) are the single most common category.[28] Endocrinopathies (especially thyroid dysfunction) are also common; PD-1 inhibitors often cause hypothyroidism in up to ~10–15 % of patients.[29,30] Other relatively common irAEs include pneumonitis and colitis. Meta-analysis review noted in the following order: skin toxicity, pneumonitis, hypothyroidism, and arthralgias/myalgias, with rare but severe events like myocarditis or nephritis occurring infrequently, around 1–2 % incidence or less.[28,31] Many irAEs have a delayed onset – they can occur weeks to months after starting therapy, and some (like endocrine issues) can appear even after therapy completion.[32] This means a HNC patient might present for surgery with an unrecognized irAE if not carefully screened.

Preoperative Screening for irAEs: In practice, most neoadjuvant trials have reported low rates of severe irAEs prior to surgery.[7,9,17,20] Before any surgical procedure, patients on or recently on ICIs should undergo targeted history, examination, and labs to detect irAEs. This includes asking about symptoms: cough or dyspnea (could indicate pneumonitis), diarrhea or abdominal pain (colitis), jaundice (hepatitis), fatigue, dizziness, or hypotension (adrenal insufficiency), headaches or visual changes (hypophysitis), muscle weakness (myositis or neuropathy), skin rash, etc.

Table 3
Common immune-related adverse events and perioperative implications.

irAE (Organ/System)	Frequency/Severity	Perioperative Implications & Management
Dermatologic [28, 51] (Rash, Pruritus)	Very common (20–30 %); usually mild	- Generally minimal surgical impact unless severe/at surgical site - For mild: topical steroids/antihistamines - For severe desquamation: postpone surgery; consult dermatology
Endocrine [19, 29, 30, 36] (Thyroid dysfunction, Hypophysitis, Adrenal insufficiency)	Hypothyroidism ~5–15 %; Hypophysitis 1–5 % (more with CTLA-4 inhibitors)	- Often permanent; can cause hemodynamic instability if uncorrected - Pre-op: Check TSH/T4, morning cortisol if suspected adrenal insufficiency - Intra-op: Stress-dose steroids for adrenal insufficiency - Post-op: Monitor electrolytes; continue hormone replacement
Pulmonary [28, 31] (Pneumonitis)	~3–5 % incidence with PD-1/PD-L1; grade 3–4 in ~1–2 %	- Risk of respiratory failure under anesthesia - Pre-op: Defer surgery if active; obtain chest CT for unexplained symptoms - Intra-op: Lung-protective ventilation; avoid fluid overload - Post-op: Monitor oxygen; differentiate pneumonitis vs pneumonia; start steroids if pneumonitis suspected
Cardiac [19, 33, 34, 35] (Myocarditis, Pericarditis, Arrhythmias)	Rare (~1 % for myocarditis) but potentially fatal	- Pre-op: Cardiology clearance if history of myocarditis - Intra-op: Invasive monitoring in high-risk cases; avoid myocardial depressants - Post-op: Monitor cardiac enzymes/ECG if suspicious symptoms; treat with high-dose steroids if myocarditis suspected
Gastrointestinal [28, 37, 38, 39, 40] (Colitis, Hepatitis)	Colitis ~5 % (higher with CTLA-4); Hepatitis 1–5 %	- Colitis: Risk of dehydration/electrolyte disturbances - Hepatitis: Affects drug metabolism and coagulation - Pre-op: Check baseline liver function; Postpone if active colitis or significant hepatitis - Intra-op: Avoid NSAIDs with colitis history; adjust anesthetic dosing with liver dysfunction - Post-op: Monitor stool output; test for infection with diarrhea; follow liver function tests
Renal [28, 31] (Nephritis)	Uncommon (~1 %)	- Pre-op: Check baseline renal function; consider delay if significant elevation - Intra-op: Maintain renal perfusion; adjust renally-excreted drugs - Post-op: Monitor urine output/creatinine; avoid nephrotoxins
Neurologic [26, 47, 48] (Neuropathy, Myositis, Myasthenia gravis, Encephalitis)	Rare (<1 %)	- Neuromuscular issues increase sensitivity to muscle relaxants - Pre-op: Assess for weakness; neurology consult if present - Intra-op: Avoid/minimize paralytics with myasthenia; monitor nerve function - Post-op: Close respiratory monitoring; evaluate any neurologic changes promptly

Laboratory screening is prudent: a thyroid panel (TSH, free T4) often reveals asymptomatic thyroiditis,[19] and should be checked given the high incidence of thyroid irAEs. Baseline liver enzymes (AST, ALT) and renal function can detect subclinical hepatitis or nephritis.[7,9,17,19,20] If the history suggests adrenal insufficiency or the patient required prolonged steroids, a morning cortisol or ACTH level can assess adrenal function.[19] For any prior grade $\geq$2 irAE, a specialist consult is advised preoperatively.[19]

Preoperative Management of irAE: If high-dose corticosteroids were given to manage an irAE prior to surgery, the surgical team should be aware that the patient is immunosuppressed and at higher risk of infection and poor wound healing. A plan for perioperative antibiotic prophylaxis or extended wound surveillance may be warranted. Any immunosuppressive medications should be continued as needed through the perioperative period, since controlling the irAE takes priority.[11,20] The optimal surgery window is about 3–6 weeks after immunotherapy, balancing immune activation and tumor control.[13] Encouragingly, current evidence indicates no major increase in perioperative complications from neoadjuvant ICIs.[11] If the patient is on a steroid taper, an adrenal function assessment might be done preoperatively to guide whether supplemental steroids are needed. By the time of surgery, most immune toxicities from neoadjuvant therapy are either resolved or under control.[7] Importantly, the immunotherapy history, including agent, timing, and dosages, should be properly documented, and patients should provide informed consent, including immunotherapy-specific risks.[19] In addition, specialist consultation for significant prior irAEs is needed.

Intraoperative and Postoperative Management of irAEs: Intraoperatively, standard practices apply, with the caveat that patients who recently received immunotherapy might be on stress-dose steroids for irAE management to prevent adrenal crisis.[19] Meticulous surgical techniques are required to minimize the duration of operation in compromised patients. After surgery, the care team must be alert to irAEs manifesting as “medical" complications. Distinguishing an irAE from a standard postoperative complication can be challenging but is crucial. For example:

Pulmonary: If a patient develops hypoxemia or bilateral infiltrates postoperatively, typical causes include pneumonia, aspiration, or fluid overload. However, in a patient on immunotherapy one must also consider immune-related pneumonitis. Immune pneumonitis can range from mild cough to acute respiratory failure.[19] It is treated with high-dose corticosteroids, not antibiotics alone. Elective surgery should ideally be delayed in anyone with active pneumonitis until it is resolved.
Cardiac: Immune-related myocarditis is a rare (<2 %) but life-threatening toxicity, characterized by myocardial inflammation that can present as arrhythmias, heart failure, or cardiogenic shock.[19,33] In the perioperative setting, unexplained hypotension, troponin elevation, or arrhythmias in a patient on ICIs should prompt consideration of myocarditis.[34,35] This diagnosis would require holding immunotherapy and initiating intensive immunosuppression.
Endocrine: Endocrine irAEs, especially primary adrenal insufficiency (from adrenalitis) or secondary adrenal insufficiency (from hypophysitis), are of great relevance perioperatively.

Patients with adrenal insufficiency cannot mount a stress cortisol response and are at high risk of refractory hypotension under anesthesia or with surgical stress.[19,36] If a patient is known to have ICI-induced adrenal insufficiency, they must receive stress-dose glucocorticoids during the perioperative period.[19]

Gastrointestinal: Immune-mediated colitis typically presents with diarrhea, cramping, or bleeding. In the perioperative context, severe colitis could lead to dehydration, electrolyte imbalances, and even sepsis if there is mucosal ulceration.[37,38] If a patient has active colitis, it is generally advisable to postpone elective surgery until it's under control.

Hepatic: Immune-related hepatitis is usually asymptomatic, noted by elevated AST/ALT on labs,[39] though severe cases can cause jaundice.[40] If significant hepatic dysfunction is present, it can affect metabolism of anesthetic agents and coagulation. Surgery should ideally wait until hepatitis improves.

Postoperative Monitoring: After surgery, it's important to differentiate expected post-surgical issues from irAEs. For instance, postoperative ileus and diarrhea are common after bowel manipulation or antibiotic use, but one must keep immune colitis on the differential if the patient is on immunotherapy and has persistent diarrhea unresponsive to conventional measures.[28] Similarly, fatigue and hypotension might be from anesthesia or blood loss - but in an immunotherapy patient, check cortisol to ensure adrenal insufficiency isn't contributing.[41,42] Use multimodal analgesia and minimize the use of opioids if possible.[19] Close collaboration between the surgical team and medical oncology is important. A higher level of monitoring for those patients with significant preoperative irAEs should be considered.

7. Wound healing, infection, and bleeding risks

The interplay between immunotherapy and surgical outcomes such as wound healing, infection, and bleeding is an important consideration, though current evidence is mostly reassuring:

Wound Healing: Surgery in HNC often involves extensive incisions, flaps, or grafts, so proper wound healing is paramount. There was initial theoretical concern that immunotherapy might impair wound healing by disrupting the coordinated immune/inflammatory response that healing requires. However, clinical data so far do not show a major detrimental effect of ICIs on wound healing in humans. In the largest cohort study available, neoadjuvant pembrolizumab did not increase rates of wound dehiscence, fistula, or flap loss compared to controls.[11] Another trial reported delayed wound healing in 22.7 % of patients who received neoadjuvant chemo-immunotherapy.[13] These were typically minor delays – all were managed conservatively, and there were no wound-related surgical re-interventions or failures.[13] This suggests that while healing might be modestly prolonged in some cases, serious wound complications are not significantly elevated by immunotherapy itself.

Infection Risk: The relationship between ICIs and infection is complex. Unlike chemotherapy, ICIs do not directly cause neutropenia or break down mucosal barriers, so they are not broadly immunosuppressive in the traditional sense. However, irAEs themselves can create vulnerable situations and the use of high-dose steroids or other immunosuppressants can predispose to infection. In surgical patients, typical risks for surgical site infection include diabetes, poor nutrition, long operative time, etc., and immunotherapy does not obviously add to these.[43] In the Cincinnati neoadjuvant trial, infections were reported in 33 out of 92 patients, representing a 36 % incidence rate.[7] Another retrospective analysis found similar SSI rates between ICI-exposed and unexposed patients undergoing various cancer surgeries.[44]

Bleeding and Thrombosis: Immunotherapy has no known direct effects on coagulation factors or platelets in most patients. Rarely, immune thrombocytopenia or acquired clotting inhibitors can occur under ICI therapy.[19,45,46] If a patient has unusual bleeding or bruising on immunotherapy, a workup for immune thrombocytopenia is warranted. In the perioperative setting, one study noted no difference in intraoperative blood loss or transfusion needs between ICI-exposed versus unexposed patients.[44]

Interaction with Radiation on Tissues: Many HNC patients will have had prior radiation or will receive radiation after surgery. Some preclinical data suggest combining immunotherapy with radiation can increase inflammation in normal tissue,[19] which theoretically might worsen healing or increase fibrosis long-term. Clinically, however, trials combining ICIs with radiation did not report significantly worse acute wound or mucosal complications.[24]

Collectively, immunotherapy alone does not significantly heighten infection or bleeding risk in surgical HNC patients, and its effect on wound healing appears minimal aside from cases complicated by immunosuppressive medications.[11,13]

8. Anesthetic and perioperative medication considerations

Patients receiving immunotherapy may present unique challenges for the anesthesia team, though with proper precautions they can be managed safely. Collectively, managing an HNC patient receiving immunotherapy through the perioperative period benefits from standardized protocols to ensure no aspect is overlooked.

Preoperative Evaluation by Anesthesiology: The anesthesiologist should review all organ systems; emphasis on cardiopulmonary and endocrine function is crucial. Any history of myocarditis or pneumonitis should be flagged. Baseline tests often include electrocardiogram for all patients; in ICI-treated patients, one might also consider an echocardiogram if there are risk factors or past cardiac irAEs.[19] From an endocrine perspective, anesthesiologists often check that steroid-dependent patients have received their dose or will receive stress coverage. They may also check morning labs (cortisol, thyroid) if not already done. An endocrinologist consultation preoperatively is recommended for any patient with immunotherapy-induced hypophysitis or adrenal issues.[19]

Intraoperative Management: There are no known direct pharmacokinetic interactions between checkpoint inhibitors and anesthetic drugs. Therefore, standard anesthetic agents can be used. However, the physiologic perturbations caused by irAEs require adjustments:

Hemodynamics: Patients on long-term steroids should get IV hydrocortisone at induction to prevent refractory hypotension.[19,36] Anesthesiologists should have vasopressors ready, especially if the patient has any history of autoimmune myocarditis or autonomic neuropathy from immunotherapy. In one retrospective study, immunotherapy-exposed patients had a slightly higher rate of needing vasopressor support during surgery.[44]

Airway and Ventilation: Surgeries for HNC often involve difficult airways. Immunotherapy generally doesn't change airway management. For ventilation, if lung involvement (pneumonitis) is present or was present, use lung-protective ventilation strategies to avoid exacerbating any inflammatory lung injury.

Neuromuscular Blockade: If there is any suspicion of myasthenic syndrome or polyneuropathy from ICIs, the anesthesia plan

might involve either avoiding neuromuscular blockers or using minimal doses with strict monitoring.[47,48]

Drug Choices: Anesthesiologists sometimes use dexamethasone intraoperatively for nausea prophylaxis in immunotherapy patients. A single low dose (4–8 mg) is unlikely to cause harm and might even help if adrenal function is borderline.[49,50]

Postoperative Pain and Nausea Management: Treat pain adequately, as uncontrolled pain can raise stress hormones. There is no contraindication to patient-controlled analgesia, regional catheters, or acetaminophen. For antiemetics, aside from dexamethasone, 5-HT3 antagonists (ondansetron) and other standard antiemetics are appropriate.

Monitoring and Disposition: Given the possibility of immune-mediated organ involvement, anesthesiologists may opt for a higher level of postoperative monitoring for ICI patients. For example, an overnight ICU or step-down unit stay might be chosen for a patient with prior pneumonitis, to monitor respiratory status closely.

9. Interactions with chemotherapy and radiotherapy in the perioperative setting

Many HNC patients receiving immunotherapy will also receive chemotherapy and/or radiotherapy as part of multimodal therapy. It is important to consider how these treatments interact around the time of surgery:

Chemotherapy + Immunotherapy (Induction or Adjuvant): When chemotherapy and immunotherapy are combined before surgery (induction chemo-immunotherapy), patients may experience additive toxicities from both. High-grade neutropenia from chemotherapy could increase infection risk, but interestingly, some studies have shown that adding ICIs to chemotherapy did not dramatically increase severe toxicities beyond those expected from chemotherapy alone. For example, rates of grade$\geq$3 events were similar between chemotherapy alone versus chemotherapy plus PD-1 inhibitor in small trials.

Induction chemotherapy can cause mucositis, weight loss, and organ toxicities that must resolve before surgery, so the immunotherapy is layered on an already intense regimen. In the peri-op period, managing such patients includes all steps above plus the usual care for chemotherapy toxicities (e.g., giving G-CSF if neutropenic, ensuring blood counts are adequate before operating, and waiting at least 3–4 weeks from last chemotherapy dose to allow mucosa and marrow recovery).

When adjuvant chemotherapy, typically cisplatin, is given concurrently with radiation and immunotherapy, toxicity management becomes challenging: mucositis, dysphagia, cytopenias from cisplatin will occur. Such patients absolutely need multidisciplinary supportive care, including nutrition, hydration, and hematologic support. There is some indication that intense triple therapy (chemoradioimmunotherapy) can be administered with careful monitoring. For instance, interim safety analyses from trials like Javelin HN and KEYNOTE-689 did not show prohibitive toxicities.[24]

Radiotherapy + Immunotherapy: Radiation to the head and neck causes acute effects (mucositis, dermatitis, xerostomia, odynophagia) and chronic effects (fibrosis, hypothyroidism, etc.). Immunotherapy given concurrently might exacerbate some inflammatory symptoms. Clinicians have observed, for example, that radiation dermatitis might be more severe when a PD-1 inhibitor is on board.[51,52] However, severe synergistic toxicity has not been definitively shown in trials.[24]

An interesting phenomenon is the abscopal effect, where radiation combined with immunotherapy can induce immune-mediated tumor regression outside the radiation field.[13,53] While desirable oncologically, it implies a systemic immune activation that theoretically could increase irAE risk[54,55]; indeed, some studies report slightly higher incidence of certain irAEs when radiation is combined.[55,56]

In perioperative preparation, if adjuvant radiation is planned with immunotherapy, one should anticipate severe mucositis and need for a feeding tube in many cases. From a surgical standpoint, prior radiation poses wound challenges; adding immunotherapy after salvage surgery might increase the risk of wound breakdown in an irradiated field, so extreme diligence in wound care is warranted. If postoperative radiation is being given with immunotherapy, wound healing must be complete before starting, as radiation will further impair healing if started too early.

Radiation also causes lymphopenia by affecting circulating lymphocytes, which could theoretically reduce immunotherapy efficacy (since ICIs need T-cells to work).[56,57] Timing radiation in relation to immunotherapy is an area of ongoing research to maximize synergy and minimize harm.[19]

In conclusion, the combination of surgery, immunotherapy, chemotherapy, and radiotherapy necessitates meticulous care. Each modality's side effects can exacerbate others (for example, dehydration from mucositis may aggravate renal perfusion in someone with ICI nephritis). A defined timeframe and backup strategies for dose holds or decreases are critical. Clinical trials are still underway to determine how best to merge different modalities, but preliminary results show that it is feasible and can enhance outcomes with careful supervision.

10. Conclusions

The integration of immunotherapy into perioperative management for HNC patients necessitates a detailed and coordinated approach involving surgeons, anesthesiologists, oncologists, and supportive care specialists. Immunotherapy, particularly ICIs, presents unique challenges including the management of irAEs, which can significantly impact perioperative outcomes if not identified and managed promptly. Proper timing of surgical interventions, typically scheduled 3–6 weeks after neoadjuvant immunotherapy and adjuvant immunotherapy initiated within 4–8 weeks postoperatively, is critical to maximizing therapeutic efficacy and minimizing complications.

Perioperative care requires meticulous screening and management of irAEs, with common complications affecting dermatologic, endocrine, pulmonary, cardiac, gastrointestinal, and renal systems. Preoperative assessments must include thorough clinical evaluations, laboratory screenings, and specialist consultations to optimize patient safety and surgical outcomes. Intraoperatively, standard anesthetic practices are generally safe, yet vigilance is required to manage potential complications such as adrenal insufficiency, pneumonitis, or myocarditis effectively. Postoperative care mandates heightened monitoring, distinguishing between common surgical complications and potential irAEs, which can manifest subtly and require specialized treatment strategies.

The multidisciplinary coordination ensures comprehensive care, integrating immunotherapy seamlessly with other standard treatments like chemotherapy and radiotherapy, thus enhancing patient outcomes. Current clinical evidence supports that with appropriate protocols and proactive management strategies, perioperative risks associated with ICIs are manageable, allowing most patients to undergo surgery without significant delays or increased morbidity. Further research and ongoing clinical trials will refine these perioperative strategies, potentially improving patient safety, recovery rates, and overall survival outcomes in HNC patients receiving immunotherapy.

Informed consent statement

Not applicable.

Institutional review board statement

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Conflicts of interest

The authors affirm that they do not have any competing interests.

References

1. Shibata H, Saito S, Uppaluri R. Immunotherapy for head and neck cancer: a paradigm shift from induction chemotherapy to neoadjuvant immunotherapy. *Front Oncol*. 2021;11:727433.
2. Sim E, Nguyen H, Hanna G, Uppaluri R. Current progress and future directions of immunotherapy in head and neck squamous cell carcinoma: a narrative review. *JAMA Otolaryngol Head Neck Surg*. 2025;151(5):521–528.
3. Gross N, Ferrarotto R, Amit M, et al. Long-term outcomes of a phase II trial of neoadjuvant immunotherapy for advanced, resectable cutaneous squamous cell carcinoma of the head and neck (CSCC-HN). *J Clin Oncol*. 2022;40(16_suppl):9519.
4. Heath B, Michmerhuizen N, Donnelly C, et al. Head and neck cancer immunotherapy beyond the checkpoint blockade. *J Dent Res*. 2019;98(10):1073–1080.
5. Mestiri S, El-Ella DMA, Fernandes Q, et al. The dynamic role of immune checkpoint molecules in diagnosis, prognosis, and treatment of head and neck cancers. *Biomed Pharmacother*. 2024;171:116095.
6. Wei J, Zhong F, Wang W, et al. Effect of exonic microsatellite instability of B2M on the predictability of MSI/dMMR for immunotherapy. *J Clin Oncol*. 2019;37(15_suppl):2576.
7. Wise-Draper TM, Gulati S, Palackdharry S, et al. Phase II clinical trial of neoadjuvant and adjuvant Pembrolizumab in resectable local-regionally advanced head and neck squamous cell carcinoma. *Clin Cancer Res*. 2022;28(7):1345–1352.
8. Wu D, Li Y, Xu P, et al. A pilot phase II trial of neoadjuvant camrelizumab plus nab-paclitaxel and cisplatin (NeoCPC) for locoregionally advanced, resectable squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2023;41(16_suppl):6069.
9. Yu Y, Chen H, Huang Z, et al. Anti-PD-(L)1-based neoadjuvant therapy in head and neck carcinoma: a meta-analysis of prospective clinical trials. *Otolaryngol Head Neck Surg*. 2024;171(5):1321–1340.
10. Rosenberg A, Juloori A, Agrawal N, et al. Neoadjuvant nivolumab, paclitaxel, and carboplatin followed by response-stratified chemoradiation in locoregionally advanced HPV negative head and neck squamous cell carcinoma (HNSCC): the DEPEND trial. *J Clin Oncol*. 2023;41(16_suppl):6007.
11. Tang AL, O'Neil T, McDermott S, et al. Association of neoadjuvant Pembrolizumab for oral cavity squamous cell carcinoma with adverse events after surgery in treatment-naive patients. *JAMA Otolaryngol Head Neck Surg*. 2022;148(10):935–939.
12. Klochikhin A, Haddad R, Meirovitz A, et al. Abstract PO-002: pembrolizumab as neoadjuvant and adjuvant therapy in combination with standard of care in resectable, locally advanced head and neck squamous cell carcinoma: phase 3 KEYNOTE-689. *Clin Cancer Res*. 2023;29(18_suppl ment). PO-002.
13. Zotta A, Marciano ML, Sabbatino F, et al. Neoadjuvant immunotherapy in head and neck cancers: a paradigm shift in treatment approach. *Biomedicines*. 2024;12(10):2337.
14. Wu D, Li Y, Xu P, et al. Neoadjuvant chemo-immunotherapy with camrelizumab plus nab-paclitaxel and cisplatin in resectable locally advanced squamous cell carcinoma of the head and neck: a pilot phase II trial. *Nat Commun*. 2024;15(1):2177.
15. Gong HL, Tian S, Ding H, et al. [Clinical efficacy of induction chemo-immunotherapy for locally advanced hypopharyngeal carcinoma: a prospective phase II study]. *Zhonghua er bi yan hou tou jing wai ke za zhi*. 2024;59(4):350–356.
16. Bell R, Leidner R, Couey M, et al. Abstract B01: surgical outcomes following neoadjuvant hypofractionated radiation in combination with nivolumab: high rate of pathologic complete response in patients with p16+ head and neck squamous cell carcinoma. *Clin Cancer Res*. 2020;26(12_suppl ment_2):B01.
17. Wang K, Gui L, Lu H-Z, et al. Efficacy and safety of pembrolizumab with preoperative neoadjuvant chemotherapy in patients with resectable locally advanced head and neck squamous cell carcinomas. *Front Immunol*. 2023;14:1189752.
18. Lauber K, Dunn L. Immunotherapy mythbusters in head and neck cancer: the abscopal effect and pseudoprogression. *American Society of Clinical Oncology Educational Book*. 2019;39:352–363.
19. Groenewold MD, Olthof CG, Bosch DJ. Anaesthesia after neoadjuvant chemotherapy, immunotherapy or radiotherapy. *BJA Education*. 2022;22(1):12–19.
20. Uppaluri R, Campbell K, Egloff A, et al. Neoadjuvant and adjuvant pembrolizumab in resectable locally advanced, human papillomavirus–unrelated head and neck cancer: a multicenter, phase II trial. *Clin Cancer Res*. 2020;26(19):5140–5152.
21. Mascarella MA, Olonisakin TF, Rumde P, et al. Response to neoadjuvant targeted therapy in operable head and neck cancer confers survival benefit. *Clin Cancer Res*. 2023;29(4):723–730.
22. Hanna G, O'Neill A, Shin K, et al. Neoadjuvant and adjuvant Nivolumab and Lirilumab in patients with recurrent, resectable squamous cell carcinoma of the head and neck. *Clin Cancer Res*. 2021;28(3):468–478.
23. AstraZeneca. *A Study of Adjuvant Durvalumab after Curative Intent Chemoradiation Therapy in Patients with Head and Neck Cancer (IMvoke010)*. 2019. ClinicalTrialsgov Identifier: NCT04276941.
24. Runnels J, Bloom JR, Hsieh K, et al. Combining radiotherapy and immunotherapy in head and neck cancer. *Biomedicines*. 2023;11(8):2097.
25. Mell LK, Torres-Saavedra PA, Wong SJ, et al. Radiotherapy with cetuximab or durvalumab for locoregionally advanced head and neck cancer in patients with a contraindication to cisplatin (NRG-HN004): an open-label, multicentre, parallel-group, randomised, phase 2/3 trial. *Lancet Oncol*. 2024;25(12):1576–1588.
26. Fletcher K, Johnson D. Chronic immune-related adverse events arising from immune checkpoint inhibitors: an update. *Journal for Immunotherapy of Cancer*. 2024;12(7):e008591.
27. Ramos-Casals M, Sisó-Almirall A. Immune-related adverse events of immune checkpoint inhibitors. *Ann Intern Med*. 2024;177(2):ITC17–ITC32.
28. Yin Q, Wu L, Han L, et al. Immune-related adverse events of immune checkpoint inhibitors: a review. *Front Immunol*. 2023;14:1167975.
29. Yoon J, Hong A, Kim H, Kang H-C. Characteristics of immune-related thyroid adverse events in patients treated with PD-1/PD-L1 inhibitors. *Endocrinology and Metabolism*. 2021;36(2):413–423.
30. Wei X-C, Guo Y, Zhang Y, Bu Y-S, Zhang F. Factors associated with immune-related thyroid dysfunction induced by PD-1/PD-L1 inhibitors in cancer patients: an observational study. *J Chemother*. 2024;36(8):654–661.
31. Khoja L, Khoja L, Day D, et al. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol*. 2017;28(10):2377.
32. Yang Y, Li L, Tian J, et al. Delayed immune-related adverse events profile associated with immune checkpoint inhibitors: a real-world analysis. *Front Pharmacol*. 2024;15:1453429.
33. Lee KK, Bain T, Flapan A. Cardiogenic shock secondary to immune checkpoint inhibitor associated myocarditis. *J Roy Coll Phys Edinb*. 2024;54(3):225–230.
34. Spallarossa P, Tini G, Sarocchi M, et al. Identification and management of immune checkpoint inhibitor-related myocarditis: use troponin wisely. *J Clin Oncol*. 2019;37(25):2201–2205.
35. Pradhan R, Nautiyal A, Singh S. Diagnosis of immune checkpoint inhibitor-associated myocarditis: a systematic review. *Int J Cardiol*. 2019;296:113–121.
36. Feng Y, Chang P, Liu J, Zhang W-S. Effects and mechanisms of perioperative medications on the hypothalamic pituitary adrenal response to surgical injury: a narrative review. *J Clin Anesth*. 2024;94:111367.
37. Abu-Sbeih H, Tang T, Faleck D, et al. Outcomes of immune checkpoint inhibitor-mediated colitis: multicenter cohort study. *J Clin Oncol*. 2021;39(15_suppl):2643.
38. Burla J, Bluemel S, Biedermann L, et al. Retrospective analysis of treatment and complications of immune checkpoint inhibitor-associated colitis: histological ulcerations as potential predictor for a steroid-refractory disease course. *Inflammatory Intestinal Diseases*. 2020;5(3):109–116.
39. Tian Y, Abu-Sbeih H, Wang Y. Immune checkpoint inhibitors-induced hepatitis. *Adv Exp Med Biol*. 2018;995:159–164.
40. Hountondji L, Faure S, Palassin P, et al. Time to use the right classification to predict the severity of checkpoint inhibitor-induced liver injury, as assessed for causality using the updated RUCAM. *Aliment Pharmacol Ther*. 2024;60(11-12):1561–1572.
41. Rai M, Go M. Nivolumab induced adrenal insufficiency: rare side-effect of a new anti-cancer therapy - immune-checkpoint inhibitors. *Cureus*. 2020;12(4):e7625.
42. Yeung S, Qdaisat A, Bischof J, Caterino J, Kyriacou D, Coyne C. A case series of adrenal insufficiency (likely due to hypophysitis) in cancer patients treated with immune checkpoint inhibitors. *Am J Emerg Med*. 2024;227:e1–227.e5.
43. Wu J-M, Chang K-H, Hsu FL-T. Immunonutrition of perioperative therapy for colorectal cancer. *Formosan Journal of Surgery*. 2023;56(1):9–11.
44. Tang YH, Bergmann J, Vaidya D, Faraday N. Association of preoperative immune checkpoint inhibitor therapy with cardiopulmonary instability and organ injury after high-risk surgery. *Critical Care Explorations*. 2024;6(4):e1068.
45. Rivet V, Sibaud V, Dion J, et al. Immune checkpoint inhibitor-related acquired

amegakaryocytosis thrombocytopenia: a case report and literature review. *Front Oncol*. 2024;14:1353896.
46. Mo D, Yang X, Xu G, et al. Signal detection of immune thrombocytopenia associated with immune checkpoint inhibitors. *Sci Rep*. 2024;14(1):23699.
47. Krenn M, Grisold A, Wohlfarth P, et al. Pathomechanisms and clinical implications of myasthenic syndromes exacerbated and induced by medical treatments. *Front Mol Neurosci*. 2020;13:156.
48. Huang Y-T, Chen Y-P, Lin W-C, Su W-C, Sun Y-T. Immune checkpoint inhibitor-induced myasthenia gravis. *Front Neurol*. 2020;11:634.
49. Lu M, D'Sylva C, Hramiak I, Joy T. Mon-370 Isolated secondary adrenal insufficiency in the absence of hypophysitis secondary to immune checkpoint inhibitors. *Journal of the Endocrine Society*. 2019;3(Suppl 1):MON–370.
50. Yu H, Chen J, Zhou Y, et al. Impact of prophylactic dexamethasone on the efficacy of immune checkpoint inhibitors plus platinum-based chemotherapy in patients with advanced Non-Squamous Non-Small-Cell lung cancer. *Int Immunopharmacol*. 2023;125(Pt B):111138.
51. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors. *Am J Clin Dermatol*. 2018;19(3):345–361.
52. Abdallah N, Patel S, Nagasaka M, Kim S, Kim H, Sukari A. Radiation therapy and immune-related side effects in patients treated with PD-1 inhibitors. *J Clin Oncol*. 2018;36(5_suppl):207.
53. Rocchetti J, Price J. Abscopal effect in a patient with metastatic melanoma receiving hypofractionated radiation therapy and dual immune checkpoint inhibition: a case report. *Cureus*. 2024;16(11):e74662.
54. Fiorica F, Belluomini L, Giuliani J, et al. Abscopal effect and resistance reversion in nivolumab-treated non-small-cell lung cancer undergoing palliative radiotherapy: a case report. *Immunotherapy*. 2021;13(12):971–976.
55. Bang A, Bang A, Wilhite T, et al. Multicenter evaluation of the tolerability of combined treatment with PD-1 and CTLA-4 immune checkpoint inhibitors and palliative radiation therapy. *Int J Radiat Oncol Biol Phys*. 2017;98(2):344–351.
56. Zhou H, Guo Z, Wang T, Cai L, You P. Abstract 922: comparison of adverse effects of different combination therapies of immune checkpoint inhibitors and radiotherapy: a systematic review and meta-analysis. *Cancer Res*. 2024;84(6_Supplement):922.
57. Buchwald Z, Wynne J, Nasti T, et al. Radiation, immune checkpoint blockade and the abscopal effect: a critical review on timing, dose and fractionation. *Front Oncol*. 2018;8:612.