Review Article



# Adjuvant therapies in head and neck cancer treatment and sedative techniques: a narrative review

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**Background and Objective:** Non-surgical therapies are widely employed in head and neck cancers. There is a need to review the abovesaid topic because these interventions may raise specific concerns in patients who need to undergo anaesthesia. In particular, airway complications pose a unique set of challenges. Procedural sedation may also be required in these treatment modalities. However, their implications in anaesthetic practices are infrequently mentioned in the literature. In this review, we provide an overview of the adjuvant therapies currently used in head and neck cancers, adverse effects of these treatments that will affect anaesthetic management, and relevant options for procedural sedation.

**Methods:** PubMed and Google Scholar databases were searched with related keywords. All publication types in English that were related to humans between 1995 and 2022 were included.

**Key Content and Findings:** Topics discussed include basic knowledge of radiotherapy, chemotherapy, immunotherapy and palliative aspects of head and neck cancer management. Specific radiotherapy-related complications present challenges to the anaesthetist, including ischemic stroke and carotid blowout syndrome, osteoradionecrosis, dental diseases, radiation-induced fibrosis, and temporomandibular joint diseases. We further explore non-pharmacological sedation techniques, such as hypnotherapy and virtual reality, and pharmacological agents, including midazolam, remimazolam, propofol, dexmedetomidine, ketamine, chloral hydrate and opioids. Each has unique properties and their use needs to be tailored to patient and procedural characteristics.

**Conclusions:** Adjuvant therapies in head and neck cancers are diverse, and many of their effects need to be considered by anaesthetists. Different sedative techniques, including non-pharmacological and pharmacological options, help to facilitate diagnostic and therapeutic procedures.

**Keywords:** Head and neck cancers; adjuvant therapy; radiotherapy-related complications; anaesthesia; procedural sedation

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## Introduction

### *Background*

Non-surgical adjuvant therapies are pivotal in the treatment of head and neck cancers. Not only do they complement surgical clearance of cancer and provide palliative symptom relief, radiotherapy with or without concurrent chemotherapy alone can be used as an alternative to surgical resection to

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**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of search | 1/8/2022 |
| Databases and other sources searched | PubMed, Google Scholar |
| Search terms used | See *Table 2* |
| Timeframe | 1995–2022 |
| Inclusion criteria | Inclusion: English article relating to humans |
| Selection process | Relevant information was extracted and interpreted by two reviewers |

**Table 2** Detailed search strategy

| Database | Search strategy |
|---|---|
| PubMed, Google Scholar | The following keywords were used in the search: "Head and neck cancer" AND "adjuvant therapies", "radiotherapy", "chemotherapy", "immunotherapy", "palliative care", "Photodynamic therapy", "Laser interstitial thermal therapy"; "radiotherapy-related complications" AND "head and neck cancers"; "adjuvant therapy" AND "anaesthesia"; "carotid blowout syndrome"; "osteoradionecrosis"; "radiotherapy" AND "trismus"; "sedation" AND "head and neck surgery"; "sedation" AND "hypnotherapy", "virtual reality", "midazolam", "remimazolam", "propofol", "ketamine", "dexmedetomidine", "chloral hydrate" |

achieve loco-regional control with comparable disease-free survival (1). Newer treatment modalities such as immuno-, photodynamic and laser thermal therapies have emerged to supplement traditional treatment options or palliate disease progression. These may need procedural anaesthetic input in out-of-theatre environments. Treatment-related side effects also raise significant anaesthetic concerns.

### *Rationale and knowledge gap*

While there have been major advancements in adjuvant oncological therapies, there is a paucity of mentions in the literature specifically highlighting the anaesthetic concerns that arise from non-surgical treatment options for head and neck cancers. Existing reviews mostly come from an oncological point of view focusing on disease outcomes. Few answer the question of how these treatments affect anaesthesia (2). A comprehensive summary of the major treatment modalities to date and their implications will be conducive to expanding anaesthetists' knowledge pertinent to their modern day-to-day clinical practices.

### *Objectives*

This article serves as an overview of the common and novel adjuvant therapies used in oral maxillofacial cancers, and their adverse effects that are pertinent to clinical anaesthesia. Techniques for sedation services in oral and maxillofacial procedures will also be explored. We present this article in accordance with the Narrative Review reporting checklist (available at https://joma.amegroups.org/article/view/10.21037/joma-23-2/rc).

## Methods

A literature search was performed using the PubMed and Google Scholar databases between 1995 and 2022. The following keywords were used in the search: "Head and neck cancer" AND "adjuvant therapies", "radiotherapy", "chemotherapy", "immunotherapy", "palliative care", "Photodynamic therapy", "Laser interstitial thermal therapy"; "radiotherapy-related complications" AND "head and neck cancers"; "adjuvant therapy" AND "anaesthesia"; "carotid blowout syndrome"; "osteoradionecrosis"; "radiotherapy" AND "trismus"; "sedation" AND "head and neck surgery"; "sedation" AND "hypnotherapy", "virtual reality", "midazolam", "remimazolam", "propofol", "ketamine", "dexmedetomidine", "chloral hydrate". All publication types in English that were related to humans were included. The titles and abstracts of all literatures were screened for relevance. Relevant information was extracted and interpreted by two reviewers (*Tables 1*,*2*).

## Overview of adjuvant treatment modalities

### *Radiotherapy*

Radiotherapy and surgery are the two most commonly used modalities in the treatment of head and neck cancers. For early-stage cancer, surgical excision and radiotherapy offer similar cure rates. Considerations in the selection of therapy include side effect profiles, need for organ and functional preservation, patient condition and preference. Radiotherapy offers a higher rate of organ function preservation, such as swallowing, phonation and speech (1).

For locaregionally advanced lesions, single modality treatment is associated with poorer outcomes. Radiotherapy in combination with chemotherapy offers superior disease control. It has been shown that concomitant chemotherapy is associated with a survival benefit of 6.5% at 5 years and an improved rate of organ conservation compared to radiotherapy alone (3). Alternatively, radiotherapy can also be administered as an adjuvant treatment after primary surgical excision. Risk factors like positive margins, extracapsular extension and extranodal disease increase the possibility of locoregional recurrence postoperatively. Adjuvant radiotherapy is used to achieve a higher rate of cure.

In radiotherapy, ionising radiation energy is directed at tumour tissues, generating free radicals in the process to cause DNA breaks that stop tumour cell reproduction. Definitive radiotherapy approaches include external beam radiotherapy (EBRT) and brachytherapy. Recent advances in radiotherapy technology have improved patient outcomes tremendously. Three-dimensional highly conformal techniques such as intensity modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) are now the standard of care. They demonstrate reduced morbidity after treatment by minimising damage to the surrounding tissue structures. For example, in IMRT, non-uniform beam intensities are used to direct maximal doses at the planned target while minimising irradiation of normal tissue. It has been shown to reduce xerostomia in a multicentre randomised controlled trial (4). Now, image-guided adaptive radiation therapy can even allow adjustment of radiation plan according to changes in tumour size and organ shifts during each session to avoid excessive doses to normal healthy tissues (5).

Usual doses of radiotherapy are measured in Greys (Gy). A traditional standard definitive treatment will give a total dose of 60 to 70 Gy fractionated over seven weeks with a dose of around 2 Gy given each session (6). Other treatment regimens with hypo- or hyper-fractionation schedules exist to cater for patients' individual needs.

Brachytherapy is not commonly used in radiotherapy for head and neck cancers. The radioactive source in the form of an intralesional implant device is placed surgically within or right next to the targeted tumour. Its advantage over EBRT is that it can deliver high doses of radiation to targeted tumour cells while sparing surrounding tissue (7,8). In selected cases, some institutions offer intraoperative radiotherapy delivered directly onto the surgical bed so that large doses of radiation do not need to go through normal tissues. This is especially beneficial in recurrent cancers with prior radiotherapy, in whom further salvage EBRT treatment is restricted (9).

### *Chemotherapy*

In the treatment of head and neck cancer, chemotherapy is usually used in conjunction with other treatment modalities, most commonly with radiotherapy in locally advanced diseases. It is believed that chemotherapeutic agents can confer radiosensitising effects, improving local control and increase survival (10). Less frequently, neoadjuvant chemotherapy is given before radiotherapy, but almost never before surgery. It also has a role in recurrent or metastatic diseases, failed local control and palliative treatment (10).

Most known in the treatment of head and neck cancers are cisplatin, 5-fluorouracil, taxanes (a type of drug that blocks cell growth by stopping mitosis) and epidermal growth factor receptor (EGFR) inhibitors. Most notably, EGFR inhibitors target a unique cellular mechanism and present a different toxicity profile to conventional chemotherapeutic agents. Overexpression of EGFR was found in the majority of squamous cell carcinoma in head and neck cancers. For example, cetuximab, an EGFR inhibitor, is a mouse-human chimeric monoclonal antibody that binds to the extracellular EGFR, "switching off" downstream intracellular signalling, thus halting tumour cell replication (11).

### *Immunotherapy*

Cancer cells naturally express antigens that can be targets for native immune cells. However, molecular mechanisms such as those involving the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis and cytotoxic T-lymphocyte antigen 4 (CLTA-4) promote self-tolerance that prevents immune cells from recognizing and attacking cancer cells. Immunotherapy targets these

molecular pathways to enable immune cells like T-cells, monocytes, natural killer cells and macrophages to respond to tumour cell growth. Currently, immunotherapy is used in conjunction with chemoradiotherapy in locally advanced, recurrent and metastatic diseases. Common immune checkpoint inhibitors are pembrolizumab and nivolumab. It is foreseeable that immunotherapy will be used extensively in the treatment of head and neck cancers (12,13).

### *Other treatment modalities*

#### Photodynamic therapy (PDT)

Photoactive substances (photosensitizers) are introduced via the parenteral route. These are selectively retained by cancer cells and, when activated by light of a specific wavelength that matches the absorption characteristics of the agent, the resultant short-lived highly unstable excited state generates hydrogen peroxide and other reactive oxygen species that cause damage to the tumour cells. It is a non-thermal reaction and the resulting necrosis is only localised so there is limited scarring with good preservation of function and cosmesis (14). The administration of light can be done in a minor procedure setting. Anaesthesia may be needed, especially for deeper structures that are accessible only by endoscopic means. Also, of particular relevance is "interstitial PDT", where laser fibres are introduced via needle and catheter insertion under image guidance to deep tissues (15). Post-operative swelling is a well-documented consequence. Anaesthetists have to be aware of the potential challenges with airway management in the treatment of airway structures, such as the floor of mouth and the base of tongue. Careful planning is required. Tracheostomy and use of airway exchange catheters have been reported (16).

#### Laser interstitial thermal therapy (LITT)

Laser catheters are implanted into the tumour to inflict thermal damage by protein denaturation and coagulative necrosis at temperatures above 43 ℃. It is a relatively safe option for recurrent head and neck cancers in which the chance of surgical clearance is low, for instance due to the proximity of vital structures and aggressive nature of tumours (17). Although strong evidence of improved survival awaits, it can be an option for palliative control of clinical symptoms such as pain and functional disabilities (18).

### *Palliative therapy*

As with palliative care of many other malignancies, palliation for head and neck cancers is a multidisciplinary effort requiring holistic consideration of the patient's medical, psychological, and social needs. Symptoms such as dysphagia, tumour bleeding and pain might benefit from palliative interventions such as debulking surgery, radiological endovascular interventions, radiotherapy and chemotherapy, PDT and LITT (19). Unique to head and neck cancers, airway control is a major concern in deciding the extent of intervention in end-of-life care. Tracheostomy and stenting can relieve airway obstruction, while palliative sedation and opioids for relief of dyspnoea should be considered in the terminal stages. Adequate pain control of primary or metastatic tumour sites improves quality of life. Apart from pharmacological treatment according to the WHO analgesic ladder, palliative radiotherapy or pain interventions can be considered. Early referral to an oncologist and a pain specialist is recommended. Treatment of symptoms such as nausea and vomiting, constipation and aerodigestive tract secretions can improve patient comfort tremendously. The decision on drug treatment should take into consideration the patient's tolerance to oral medication. Involvement of the speech therapist and the nutritionist is essential.

Psychological and spiritual well-being with a strong social network of support systems is equally, if not more, important. Psycho-cognitive symptoms such as anxiety, depression, delirium and confusion should be recognized and managed. Allied health professionals such as physiotherapists, occupational therapists, clinical psychologists, and medical social workers can offer valuable input.

## Adjuvant therapy related side effects relevant to anaesthetists

### *Radiotherapy-related complications*

#### Carotid complications

Radiotherapy causes carotid artery disease in two distinct ways: ischemic strokes and the carotid blowout syndrome (CBS).

Ischemic strokes usually happen as a late complication of neck irradiation. The 15-year cumulative stroke risk after neck radiotherapy is 12%. Pre-existing risk factors like smoking, diabetes and underlying carotid artery stenosis increase the risk further (20). Preventive measures to manage these risk factors are recommended. While currently there are no standard post-radiation screening protocols in place, ultrasound screening at appropriate intervals according to

risk factor profiles can be considered (21-23).

The risk of CBS increases with the cumulative dose of irradiation (24). It occurs at an incidence of up to 17% after re-irradiation. The time of presentation varies, with a median time of 7.5 months from start of irradiation (25). The aetiology of CBS can be a combination of radiotherapy and tumour invasion with associated inflammation. Predisposing factors include recurrent radiotherapy, high cumulative radiation dose of more than 130 Gy, recurrent tumour, prior neck dissection, development of mucocutaneous fistula and wound infection (24,25). CBS can be classified by urgency and severity into three categories:

(I) Threatened: exposed carotid artery, no evidence of bleeding;
(II) Impending blowout: sentinel or self-limited bleeding;
(III) Active blowout: massive haemorrhage.

Treatment options include endovascular occlusion or stenting of the carotid defect, and surgical ligation with vascular bypass if the site of bleeding is unfavourable (25). Mortality is high, because, unlike post-surgical CBS, radiotherapy-related CBS can happen in regions where urgent control of bleeding cannot be easily achieved (26). One notable example is nasopharyngeal carcinoma (NPC)-associated CBS with skull base osteonecrosis (27). It poses a unique set of challenges. Firstly, maintenance of hemodynamic stability is difficult when there is massive bleeding from the carotid artery. Secondly, the emergent situation might require rapid establishment of a definitive airway. Thirdly, bag-mask ventilation, laryngoscopy, intubation, and front of neck access may all be difficult in a patient with a fibrotic oedematous face and neck after irradiation, osteoradionecrosis, and poor dentition. Fourthly, profuse airway bleeding intensifies the difficulty in airway control and increases the risk of aspiration. Airway management should include the expertise of the attending anaesthetists, as well as the availability of a multidisciplinary input (general surgeons, ENT surgeons, neurosurgeons, radiologists, intensivists etc.).

Baroreceptor damage from irradiation may also complicate hemodynamic management, with poorly predictable changes in the cardiovascular parameters.

**Airway changes after radiotherapy**

Airway management in a patient with a history of head and neck irradiation can turn the night of an on-call anaesthetist into a nightmare. The incidence of difficult airways in this population can be as high as 55% (28). Appreciation of the possible anatomical and physiological changes after radiotherapy will help to anticipate potential difficulties and enable appropriate planning and preparation of the essential equipment, personnel and location for airway manipulation. Several airway related conditions will be described below.

**Osteoradionecrosis (ORN)**

This is a process of ischemic necrosis resulting in exposed, irradiated bone structures in the absence of recurrent or residual tumour. It is usually a consequence of vascular obliteration resulting from radiotherapy. The overall incidence ranges from 3–7% regardless of radiotherapeutic technique employed (29). Risk factors include male gender, older age, tobacco and alcohol use, high radiation dose, extensive tumour, poor oral hygiene and dentition (30). It can happen any time after radiotherapy but most are reported in the first 3 years (31). It happens most commonly in the mandible, due to high radiation exposure and relatively poor vascular supply. It can cause pain, trismus, infection and pathological fractures, and can even result in an absent mandible, causing significant mandibular space reduction, leading to mask-ventilation difficulties (32).

**Dental disease**

There is a higher incidence of dental caries, periodontal disease and dental loss, due to a mixture of hyposalivation, oral microbiome changes, and loss of supporting soft tissues (31). This can be a risk factor for osteoradionecrosis. Loose teeth can pose risks during airway manipulation, with possible dislodgement and airway obstruction that may require further surgical extrication. Mask ventilation may also be difficult in edentulous patients.

**Lymphedema and fibrosis**

Radiation-induced oedema are common and can be internal or external. Internal oedema involves mucosa and underlying soft tissues e.g., base of tongue, floor of mouth, pharynx and larynx, presenting possibly with hoarseness of voice, dysphagia and increased snoring and airway obstruction. External oedema can be in the face and neck, causing swelling and tightness with decreased range of motion. Subsequent fibrosis can ensue, causing significant challenges to airway management. Swallowing can be impaired, increasing aspiration risks. Tongue and floor-of-mouth fibroses, together with restricted neck movement, all contribute to a significant degradation of the laryngoscopic view during intubation. In the presence of trismus due

to fibrotic muscles of mastication, oral intubation by laryngoscopy may even be impossible (28,32).

**Trismus and temporomandibular joint (TMJ) disease**

Trismus refers to limited jaw opening, which is generally caused by a combination of spasm, fibrosis and contraction of muscles of mastication (33). Mucositis, xerostomia, radiation induced cellulitis also contribute to pain on mouth opening and the development of trismus. The incidence ranges from 5–45%, depending on radiotherapy techniques employed. Interincisor distances of 20–40 mm have been suggested as an indicator of trismus (34). It can give rise to debilitating functional predicaments including malnutrition, infection and speech impairment. Early jaw mobilisation exercises (35) and IMRT (36) are beneficial in preventing trismus. It should be noted that radiotherapy-induced trismus may not improve with anaesthetic induction or muscle paralysis, unlike trismus due to pain or inflammation (28). Limited mouth opening may preclude laryngoscopy, and alternative airway management strategies such as fibreoptic intubation and surgical front of neck access may have to be considered.

**Other RT-related complications**

Xerostomia, mucositis, oesophageal toxicity with dysphagia may not only cause significant decline in quality of life, but may also adversely impact physiological well-being (31). Nutritional deficiencies, aspiration, airway mucosal changes are all relevant anaesthetic concerns. Radiation-related endocrine disorders such as thyroiditis and hypopituitarism (28), if suspected, also warrant investigation before surgery.

### *Chemotherapy/immunotherapy-related toxicity*

Chemotherapeutic agents are associated with significant organ toxicity that might complicate perioperative care. It is imperative to understand the potential adverse effects and fine-tune anaesthetic management accordingly (2). *Table 3* summarises the potential side effects of commonly used chemotherapeutic and immunotherapeutic agents. In general, anaesthetists have to be conscious of the myelosuppressive effect that affects haemoglobin levels and platelet counts. Nephrotoxicity and hepatotoxicity will alter pharmacokinetics, and agents that further jeopardise renal and liver function should be avoided (e.g., NSAIDs, Cox-2 inhibitors, and acetaminophen). Cardiopulmonary toxicities herald the need for optimization and close intra- and post-operative monitoring. Immunotherapy may produce hormonal disorders that require hormonal replacement therapy (12,13). Consultation with an endocrinologist can be beneficial. It is also not uncommon for patients who are on corticosteroids to be in a state of relative adrenal insufficiency, and thus perioperative steroid cover needs to be considered.

## Sedation techniques

Not infrequently, anaesthetists encounter requests for the provision of anaesthesia to facilitate minor procedures or adjuvant therapeutic modalities in the course of head-and-neck cancer treatment. The anaesthetist's role can range from producing relative immobility and tolerance during painful procedures, to facilitating painless procedures on patients exhibiting low levels of compliance. Providing conscious sedation is one option. Here we depict an overview of some selected pharmacological and non-pharmacological options in contemporary practice.

### *Pharmacological techniques*

**Midazolam**

Midazolam is popular, especially amongst non-anaesthetic practitioners, due to the ease of administration, reversibility (flumazenil) and regulatory issues. It is a short-acting γ-aminobutyric acid A (GABA-A) receptor agonist with an onset time of 3 to 5 minutes after IV administration (37). It can be given intramuscularly, orally and buccally in patients without IV access, but with an inevitably longer onset time and a less reliable sedative effect. It has a potent anterograde amnesic effect that can be desirable in some patients but disturbing to the others (38). It has a relatively longer half-life of 1.8–6.4 hours with active metabolites, such as 1-α-hydroxymidazolam, resulting in a longer duration of action and less predictable recovery (37). It is also well known to sometimes cause paradoxical excitation in children and delirium in the elderly. Despite being cardiovascularly stable, it carries the risk of respiratory depression particularly when used in combination with opioids, a practice that is commonly adopted since midazolam does not have analgesic properties. It is suitable for short, non-painful procedures when used as a sole agent.

**Remimazolam**

This is a novel, ultrashort-acting benzodiazepine approved by the FDA on July 3, 2020, for procedural sedation in adults. It is structurally similar to midazolam but has a rapid offset owing to its organ-independent elimination by tissue

**Table 3** Summary of chemo-immunotherapeutic agent toxicities

| Examples | Class | Mechanism of action | Toxicities |
|---|---|---|---|
| Cisplatin carboplatin | Platinum-based alkylating agent | Alkylation of DNA causing interstrand crosslinking and damage | Severe nausea and vomiting |
| | | | Heart failure, fluid overload, atrial fibrillation, torsade de pointes |
| | | | Nephrotoxicity |
| | | | Hepatotoxicity |
| | | | Hearing impairment, tinnitus |
| | | | Peripheral neuropathy |
| | | | Myelosuppression |
| | | | Pneumonitis |
| | | | (Carboplatin has less oto- and nephro-toxicities but more myelosuppression compared to cisplatin) |
| 5-FU | Anti-metabolite | Structural analogue of pyrimidine to interfere with nucleotide synthesis | Myocardial ischemia (10% incidence, caused by coronary spasm and endothelial injury) |
| | | | Severe mucositis |
| | | | Myelosuppression |
| | | | Pneumonitis |
| | | | Thrombotic microangiopathy |
| Docetaxel paclitaxel | Taxanes | Mitotic inhibition by stabilising microtubules in the polymerised state | Ventricular arrhythmias, bradycardia, Atrioventricular blocks |
| | | | Interstitial pneumonitis |
| | | | Peripheral neuropathies |
| Cetuximab | EGFR-inhibitor | Monoclonal antibody that binds to EGFR to stop the intracellular signalling cascade that leads to cell division | Primarily skin toxicity e.g., acne like rash, dermatitis |
| | | | Corneal erosions, keratitis |
| | | | Pneumonitis |
| Pembrolizumab nivolumab | Immunotherapy | Inhibition of PD-1/PD-L1 axis, which normally promotes self-tolerance of the immune system, to restore anti-tumor immune response | irAEs |
| | | | Endocrinopathies |
| | | | ❖ Autoimmune thyroid disease, hypothyroidism, hyperthyroidism |
| | | | ❖ Hypophysitis |
| | | | ◆ Low ACTH, TSH, FSH, LH, GH, prolactin |
| | | | ◆ Radiographic swelling of pituitary gland |
| | | | ❖ Adrenal insufficiency |
| | | | ❖ Diabetes mellitus |
| | | | Skin reactions |
| | | | Gastrointestinal: diarrhoea/colitis |
| | | | Hepatotoxicity |
| | | | Pneumonitis |
| | | | Opportunistic infection |

5-FU, 5-fluorouracil; EGFR, epidermal growth factor receptor; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1; irAEs, immune-related adverse events; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; GH, growth hormone.

esterase hydrolysis to inactive metabolites (37,39,40). When used for procedural sedation, the recommended dose is 5 mg IV over 1 minute, with supplemental IV doses of 2.5 mg given at 2 minute intervals (41). Adjustment has been suggested for patients of older ages, with concomitant opioid use and higher ASA classes. Phase 3 trials have all supported the sedative efficacy of remimazolam in a range of endoscopic procedures. Peak sedation was achieved 3–5 minutes after administration, and the ready-to-discharge time was 49.8–64 minutes after the last dose, which was significantly shorter than midazolam (42-44). While it is uncertain whether these data can be translated to oral maxillofacial procedures with greater stimulation and longer procedural times, it may be a safe and attractive option. When compared to propofol, there are advantages in terms of less pain on injection, higher respiratory rates and oxygen saturations, and lower incidence of hypotension, despite comparable onset and recovery times (40). Flumazenil is also effective in reversing remimazolam (41).

**Propofol**

Also targeting the GABA-A receptors of the central nervous system, propofol has excellent titratability, is fast in onset and clearance, and enables a highly predictable recovery. It is also an effective antiemetic (45). It is preferred when rapid recovery is desired and when considerable stimulations are expected, as a deeper plane of anaesthesia can be achieved without significantly compromising the recovery time, especially when used with short-acting opioids or ketamine. The administration regime is variable, ranging from boluses, body weight-based constant rate infusion or pharmacokinetic target-controlled infusion (TCI). It has several drawbacks, however. Safe use of propofol is best administered by anaesthetists who are experienced in predicting its behaviour, skilled in resuscitation and are able to apply sufficient monitoring (46,47), as the dosage requirement is highly variable depending on the patient's age and comorbidities. Also, propofol is a potent cardiorespiratory depressant. When used inappropriately, hypotension and respiratory depression can result. Pain on injection is not generally a problem with the MCT/LCT formulation (48).

**Dexmedetomidine**

Dexmedetomidine is a selective centrally acting α2-adrenoreceptor agonist, which provides anxiolysis, sedation, and analgesia through central sympathetic tone suppression. The recommended IV loading dose is 0.5–1 mcg/kg over 10 min, followed by a maintenance infusion at 0.2–0.7 mcg/kg/h (49). It can also be given intranasally at a dose of 2–3 mcg/kg via a mucosal atomizer device, with an onset time of around 20–30 minutes (50). Dexmedetomidine produces sedation that resembles natural sleep, and is easily reversible when given external verbal or tactile stimuli (51). It produces moderate bradycardia and hypotension at steady state, without significant compromise in respiratory drive, provided that airway patency is maintained.

Several studies comparing dexmedetomidine to midazolam in procedural sedation established superiority in its reliability, analgesia and overall patient and clinician satisfaction. It has similar cardiorespiratory safety profiles when carefully titrated (38,51-53). Dexmedetomidine was also found to produce less cognitive impairment, amnesia and delirium which are desirable in minor oral surgery. In a study comparing dexmedetomidine plus midazolam versus propofol plus midazolam sedation in dental surgery, less unexpected patient movement was reported in the dexmedetomidine plus midazolam group (54). It has become a popular sedative, especially in painless, non-stimulating procedures. However, a longer onset time and a slower recovery to full alertness will be expected.

**Ketamine**

Ketamine is a phencyclidine derivative that primarily works as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist to achieve a state of dissociative anaesthesia. It has an ample safety margin, preserving normal airway reflexes and respiratory drive whilst achieving a reliable sedative-hypnotic and analgesic state. It is a sympathomimetic (55). The excellent analgesic property of ketamine also gives it additional benefits during painful procedures (56). Ketamine can be administered via almost any route, including intravenous, intramuscular, intranasal, sublingual and rectal routes (55,57). It is used extensively in minor head and neck surgeries and dental procedures (57), being the drug of choice in patients who present with a difficult airway, reactive airway disease or difficult IV access (55). Side effects include emesis, increased aerodigestive secretions, and emergence phenomena (56,58). With preserved laryngeal reflexes, increased secretions can potentially cause laryngospasm (59,60). Psychomimetic effects, such as confusion, hyperexcitation and hallucination, are more pronounced in adults than children (61), and premedication with benzodiazepines has been shown to reduce its incidence (62). It should be used with caution in patients with uncontrolled hypertension (59).

"Ketofol" is a combination of ketamine and propofol and

can be considered for short and painful procedures (63). The two IV medications, which produce hypnosis by two distinct mechanisms, are complementary to each other: the cardiovascular depressant effects of propofol can be mitigated to some extent by ketamine, while propofol reduces the nausea and agitation associated with ketamine (55).

### Chloral hydrate

Chloral hydrate has a long history of use in paediatrics. It is a GABA-minergic sedative, with an active metabolite trichloroethanol (64,65). The NICE 2010 guidelines recommend chloral hydrate for children under 15 kg undergoing painless procedures e.g., diagnostic imaging (66). In general, the recommended oral dosage is 30–50 mg/kg with a maximum dose of 2 g, although a wide dose range has been described (67). The ease of administration has made it widely popular. However, its success rate in achieving the desired level of sedation declines as the child grows. It has a bitter taste, which is especially problematic when a large volume needs to be given. It has no analgesic properties so it is not suitable for painful procedures. The onset time can be quite variable and the duration of action long. It has a half-life of up to 66 hours in neonates, 40 hours in infants and 12 hours in children. Furthermore, there is no reversal agent available. Safety concerns include prolonged or re-sedation, and subsequent respiratory depression, which can be fatal (68,69). Other serious adverse reactions reported include cardiotoxicity causing arrhythmias and hypotension, irritating gastrointestinal effects such as vomiting and diarrhoea, and paradoxical excitation (70). Adequate monitoring and proper management by trained personnel is recommended when chloral hydrate is used.

### Opioids

Opioid supplementation is only necessary for stimulating and painful procedures. Commonly, agents with rapid onset and offset are given intravenously to reduce pain at critical steps e.g., local anaesthetic infiltration, surgical incision, and endoscope insertion. Fentanyl has an onset time of 2–3 minutes, and is given in 10–20 mcg aliquots with a total dose of 1–2 mcg/kg when used for sedation. Morphine can be given in 0.5–2 mg boluses to a total of 0.1 mg/kg if prolonged analgesia is desired. These opioids should be given with caution when combined with hypnotics like midazolam and propofol as they have synergistic effects on respiratory drive suppression. Naloxone should be available for emergency reversal (71-73).

## *Non-pharmacological techniques*

### Hypnotherapy

Hypnosis refers to a psychological state involving focused attention to utterly decrease perceived environmental awareness (74). Its use is increasingly described in dental procedures to decrease needle pain and discomfort (75-77). It has also been shown to be effective in cancer pain control (78,79), painful procedures in cancer patients such as chemotherapy, and wound management in burns victims (77). Breast cancer surgeries have been performed under local anaesthesia and hypnosis alone with total avoidance of general anaesthesia (80,81).

Quite similar to anaesthesia, the process of hypnotherapy starts with induction, followed by therapeutic suggestions to maintain and deepen the state of hypnosis, and concludes by emergence with or without posthypnotic suggestions for continued comfort (81). Its effect stems from immersing the patient in a perceptual or imaginative experience and dissociation from the environment (82).

It appeals to healthcare practitioners and patients as all the risks and adverse responses to anaesthesia can be eliminated. It has also been shown to improve pain control, reduce nausea and relieve anxiety (83,84). It has even been theorised to decrease cancer metastasis by suppressing catecholamine release (81). However, hypnosis requires expertise for its safe and effective performance. Success also depends much on patients' 'suggestibility", a concept in hypnosis that describes the responsiveness to social cues that leads to compliance with instructions or relative suspension of judgment (85). Requirement of an appropriate environment and time needed for induction may also negate its practicability in a busy, high-turnover centre. It is also potentially perilous if a therapist with malicious intent instils harmful ideas by suggestion during hypnosis. Further clinical data on safety and efficacy awaits.

### Virtual reality

Virtual reality is a technology that can be extended to healthcare. Typically, the patient wears a headset so that he or she receives visual and auditory stimuli, and is immersed in an alternate virtual dimension dissociated from reality. Schematically, it works similarly to hypnosis (86). Research has started to investigate its use in pain management, anxiolysis and procedural sedation. It works by directly altering the perception and signalling of pain stimuli through changes of attention, emotion, and memory formation.

Positive outcomes have been reported in paediatric day surgery (87) and dental procedures (88). Whether used as an adjunct or as a sole technique, virtual reality can be an excellent choice due to its non-invasive nature and ease of application. However, surgical access can be limited by the bulky headset. Hygienic maintenance of the device is also a concern. Whether exposure to different genres of virtual environment or repeated exposure to the same environment will affect its efficacy are also areas yet to be explored (82,86).

### *Strengths and limitations of the review*

This review explores the adjuvant therapies used specifically in head and neck cancers with basic knowledge that is relevant to anaesthetists. In particular, newer therapeutic modalities, such as immuno-, photodynamic and laser thermal therapies, which were seldom discussed in the anaesthetic literature are introduced in this review. However, the exact clinical impacts of various oncological treatment side effects on anaesthetic practices cannot be fully delineated due to the scarcity of data from the existing literature. Also, some of the non-pharmacological techniques introduced here are still in the exploratory stages.

## Conclusions

Adjuvant treatments in oral maxillofacial cancers are diverse. Apart from well-recognized hazards from traditional radiotherapy and chemotherapy, newer modalities such as immunotherapy, photodynamic and laser thermal therapies also entail unique concerns for both procedural sedation and anaesthesia. Sedation techniques should be chosen according to expertise, patient preferences and suitability, logistical constraints and the desired effects. A multi-disciplinary model enhances holistic patient care, and understanding the roles of the different participants will enable more empathetic and comprehensive considerations when providing healthcare, improving patient safety and outcome.

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