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## An analysis of the symptoms of head and neck malignancies

### Analiza objawów występujących w przebiegu nowotworów złośliwych regionu głowy i szyi

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#### Abstract

**Aim:** The aim of this paper was to summarise the most common symptoms of head and neck malignancies, including their pathophysiology, based on current knowledge. **Materials and methods:** We analysed public databases (PubMed, Google Scholar) for the latest papers, mostly published between 2003 and 2023. These included reviews, systematic reviews, randomised controlled trials, and meta-analyses. Lack of access to full article and languages other than English or Polish were exclusion criteria. We did not use artificial intelligence. **Results:** The main symptoms of head and neck malignancies included difficult-to-heal wounds or ulcerations, lip pain, oral and pharyngeal pain, dysphagia, odynophagia, hoarseness, head or neck mass, otological problems, weight loss, asymmetrical obstruction of the nasal cavity, unilateral nasal bleeding, and paralysis or paresis of the facial nerve. While these symptoms are often attributed to non-malignant diseases, healthcare professionals should prioritise oncological considerations and interpret patient cases from a holistic perspective. **Conclusions:** Head and neck malignancies are often diagnosed already at advanced clinical stages. Patients presenting with the above-mentioned symptoms typically seek general practice or outpatient otorhinolaryngological consultation. It is crucial to acknowledge that these symptoms could be early signs of malignant diseases.

**Keywords:** oncology, symptoms, head and neck neoplasia, head and neck cancers

#### Streszczenie

**Cel:** Sumaryczne zestawienie objawów nowotworów głowy i szyi, z uwzględnieniem ich patofizjologii, a także dokonanie przeglądu piśmiennictwa. **Materiał i metody:** Analiza piśmiennictwa dostępnego w bazach danych (PubMed, Google Scholar). Dobierano możliwie najnowsze prace (w większości pochodzące z lat 2003–2023) o charakterze przeglądów, przeglądów systematycznych, badań randomizowanych z grupą kontrolną i metaanaliz. Kryteriami wykluczającymi były brak dostępu do pełnego artykułu i język artykułu inny niż angielski lub polski. Nie posłużono się sztuczną inteligencją. **Wyniki:** Do głównych objawów nowotworów głowy i szyi należą: trudno gojąca się rana lub owrzodzenie, ból warg, jamy ustnej lub gardła, dys- i odynofagia, chrypka, guz w okolicy głowy i szyi, otalgia, utrata masy ciała, asymetryczna niedrożność jamy nosowej i jednostronne krwawienia z nosa oraz niedowład/porażenie nerwu twarzewego. Chociaż w większości przypadków wymienione objawy będą wynikać z chorób o potencjalnie niezłośliwym charakterze, należy respektować zasady wzmożonej czujności onkologicznej, a także interpretować przypadki w sposób holistyczny. **Wnioski:** Nowotwory głowy i szyi wciąż są rozpoznawane na zbyt wysokim stopniu zaawansowania klinicznego. Pacjenci z wymienionymi objawami zazwyczaj w pierwszej kolejności zgłaszają się do lekarzy podstawowej opieki zdrowotnej lub rejonowych poradni otorhinolaryngologicznych. Należy zawsze brać pod uwagę chorobę nowotworową jako przyczynę dolegliwości u pacjentów.

**Słowa kluczowe:** onkologia, symptomy, nowotwory głowy i szyi, raki głowy i szyi

## INTRODUCTION

Despite their heterogeneous nature, head and neck cancers (HNCs) are classified as one group of oncological diseases due to multiple similarities in risk factors, clinical course and treatment options. They are mainly of epithelial origin. Epidemiologically, HNCs are one of the most common (7<sup>th</sup> most common) malignant tumours in humans, significantly (about 5×) more prevalent in men, around 60 years of age. There is also a noticeable increasing trend in the incidence among younger people (i.e. about 45 years of age), which is probably associated with human papillomavirus infections and endemicity (e.g. particularly high incidence in Southeast Asian countries)<sup>(1–4)</sup>. Despite the widespread implementation of educational and preventive programmes (targeting both patients and healthcare workers), approximately 60–70% of patients are still diagnosed at advanced clinical stages (III, IV), which a priori limits therapeutic options and worsens the initial 5-year survival prognosis.

## AIM OF THE STUDY

The aim of this paper was to summarise the symptoms of head and neck cancers, including their pathophysiology, as well as to perform a literature review. Additionally, the article is intended to serve as a type of compendium and guide for healthcare workers who encounter oncological problems in the population aspect.

## MATERIALS AND METHODS

We analysed textbooks and medical databases (PubMed and Google Scholar). The most recent papers (mostly from 2003–2023) in the form of reviews, systematic reviews, randomised controlled trials, and meta-analyses were selected. Lack of access to the full article and languages other than English and Polish were the exclusion criteria. No artificial intelligence was used.

## RESULTS AND DISCUSSION

The review was based on data from 6 textbooks and 29 articles.

It should be emphasised that the symptoms described will result from potentially non-malignant conditions in the vast majority of cases. This paper was intended to serve as an aid and a guide to facilitate the diagnosis. Interpreting symptoms without a holistic analysis of the clinical case is a dead end.

### A difficult-to-heal wound or ulcer

A difficult-to-heal wound or ulcer may be a symptom of broadly understood precancerous lesions/conditions or a manifestation of malignancy per se. This paper focuses on of head and neck pathologies.

## Ulceration

Ulceration is a loss of skin or mucous membrane, which leads to tissue disintegration and necrosis. Traumatic ulcers are usually caused by a mechanical factor and (despite severe pain) heal within 10–14 days after the causative factor has been removed. The healing time may be prolonged by additional factors, e.g. superinfections (which disrupts the clinical picture and limits oncological vigilance). Persistent ulceration may suggest neoplastic aetiology and requires histopathological verification. Oral ulcers may also be a symptom of primary diseases of the hematopoietic system, in which case a haematological consultation is needed<sup>(5)</sup>.

## Leukoplakia

Leukoplakia (“white spot”) is a white patch that cannot be rubbed off using non-invasive methods. It is the body’s response to factors irritating the mucous membrane. The floor of the mouth, the lower and lateral surfaces of the tongue, lips, as well as the buccal and gingival mucosa are most likely to get involved. Smoking is the main predisposing factor. The risk of local recurrent leukoplakia (after treatment) is 20–30%<sup>(5,6)</sup>. Among the many clinical variants, two forms of leukoplakia are particularly noteworthy: a) verrucous variant/non-homogeneous leukoplakia with about 70% risk of progression to invasive cancer; b) idiopathic leukoplakia, occurring in previously non-smoking women, characterised by a worse prognosis compared to smokers<sup>(5,7,8)</sup>.

The risk of malignant transformation increases with time (reaching 30% at 10 years of follow-up). The overall malignant progression of oral leukoplakia is 12%<sup>(1)</sup>.

## Erythroplakia

Erythroplakia, sometimes referred to as erythroplasia, is a red patch (erosion) that cannot be clinically or pathologically diagnosed as any other definable disease. The colour of the lesion results from the loss of physiological oral or pharyngeal epithelium, dilated blood vessels, and an oedematous/inflammatory submucosal reaction. Erythroplastic lesions are usually well-defined.

Like leukoplakia, erythroplakia has clinical significance (no histopathological significance); however, >90% of cells forming the eruption contain dysplasia or cancer cells. It is usually located on the lateral part of the tongue, in the vestibule or floor of the oral cavity and in the oropharynx. The lesion most often develops after the age of 60 years, more commonly in men<sup>(8)</sup>. Predisposing factors include, among others, poor oral hygiene, use of tobacco products and alcohol abuse<sup>(5,8,9)</sup>. In summary, each difficult-to-heal wound in the skin or mucous membrane requires otorhinolaryngological verification.

### Dysphagia, a sensation of pharyngeal obstruction. Lip, oral and pharyngeal pain

### Odynophagia (painful swallowing)

Swallowing is a complex sequence of integrated events involving the cooperation of various muscle groups, and

coordinated by the central nervous system. In addition to the efficient functioning of the anatomical structures involved, the correct sequence of events and cooperation of these anatomical elements are equally important. About 50 pairs of muscles, 5 pairs of cranial nerves and cervical plexus nerves participate in this act<sup>(10,11)</sup>.

Additionally, the abundantly distributed sensory nerve endings and pain receptors make the upper airway area susceptible to nociceptive stimuli. The oral cavity, lips and pharyngeal area are supplied by branches of nerves V, IX and X, which form submucosal plexuses<sup>(10,12)</sup>. Dysphagia is a subjective or objective impairment of swallowing of both liquids and solids. Patients sometimes describe dysphagia as a sensation of pharyngeal obstruction, which may be accompanied by painful pharynx, oral cavity and the swallowing process itself (odynophagia).

Dysphagia arising from HNCs is usually mechanical. A growing tumour narrows the gastrointestinal tract, impairing normal reflexes, and tumour invasion to muscle or nerve structures causes disintegration of the complex swallowing process. Progression from solids to liquids is a characteristic feature of neoplastic dysphagia. Pain (also during swallowing) arises from the involvement of nervous structures. Due to the multiple neural connections, pain can radiate to other structures (primarily to the ear, see below: otalgia). Dysphagia, odynophagia and pain occur primarily in the case of pharyngeal (all three levels), laryngeal and oral malignancies<sup>(13)</sup>.

In summary, patients presenting with dysphagia, odynophagia and oral or pharyngeal pain require clinical evaluation and a thorough examination of the oral cavity and pharynx. If no evident causes of these disorders are identified, an otorhinolaryngological consultation or endoscopy of the upper gastrointestinal tract is necessary.

### Hoarseness

Anatomical classification distinguishes three levels of the larynx: upper (supraglottic), middle (glottis with a centimetre area below the lower surface) and lower (subglottis). Vocal folds, which are made of squamous epithelium, lamina propria (superficial, middle and deep layer – vocal ligament) and vocal muscle, are the most important structure from the point of view of voice production<sup>(14)</sup>.

The process of voice production (normative features) involves the external and internal laryngeal muscles. These are innervated by branches of the X (vagus) nerve: the superior laryngeal nerve (supplying the cricothyroid muscle) and the inferior laryngeal nerve (terminal branch of the recurrent laryngeal nerve, supplying the internal laryngeal muscles)<sup>(15)</sup>.

Hoarseness is defined as an abnormal change in voice quality that occurs as a result of structural or functional disorders of the vocal folds (or the larynx in a broader sense). This symptom occurs in many diseases, including infectious, occupational, iatrogenic, but also neoplastic (benign and malignant) conditions. Hoarseness develops when the

vocal folds or, at a more advanced stage, the supraglottic, subglottic and laryngeal pharynx, are involved. In some cases, it can also be a symptom of proliferative diseases of the mediastinum, thyroid gland or parathyroid glands, which by compressing the recurrent laryngeal nerve consequently cause vocal fold dysfunction<sup>(16,17)</sup>.

Hoarseness may generally develop in laryngeal neoplasms as a result of two phenomena. Firstly, a tumour growing in the mucous membrane affects the vibration process and disrupts the spread of the mechanical wave, thereby altering the voice. Secondly, an advanced tumour that infiltrates muscle layer or cartilage of the larynx, causes mechanical immobilisation of the vocal fold.

Hoarseness persisting for more than 3 weeks requires an ENT consultation. A change in the nature of already existing hoarseness is another alarming symptom<sup>(15,18)</sup>. To summarise, hoarseness (or its change) persisting for more than 3 weeks requires an ENT consultation.

### Head or neck tumour

A tumour is a pathological mass in the body. The extremely abundant lymphatic vascularisation of the head and neck area (about 150–400 lymph nodes) makes this region particularly susceptible to all types of reactions, manifesting as a “lump”<sup>(19)</sup>.

Most head and neck masses are inflammatory in nature and are accompanied by symptoms of primary infection. These may be purulent lesions (e.g. abscess, phlegmon) or nodal reactions<sup>(20)</sup>. Other causes include congenital, vascular and glandular tumours (salivary, thyroid). These lesions are not malignant<sup>(19)</sup>.

If the tumour persists for more than 3 weeks (possibly with growing size), diagnosis should be extended to include malignancies of the head and neck organs or primary or secondary (metastatic) hematopoietic neoplasms. An ultrasound scan may be helpful as it helps guide further diagnosis (assessment of the primary lesion, assessment of the regional lymph nodes and adjacent organs, e.g. salivary glands, palatine tonsils, base of the tongue). Alarming lymph node ultrasound findings include:

- round shape (except for the submandibular region) or longitudinal-transverse diameter ratio (the so-called Solbiati index) <2;
- no hyperechoic hilum;
- heterogeneous hypoechogenicity;
- non-hilar Doppler flow type;
- irregular capsule outline;
- formation of bundles;
- calcifications;
- focal necrosis.

It is worth emphasising that the size of the lymph node itself (without interpreting other factors) is not a reliable differentiating factor<sup>(21)</sup>.

Additional investigations, such as computed tomography (CT), magnetic resonance imaging (MRI), or even positron

emission tomography (PET), are needed in some cases. Cytopathology and histopathology are performed to specify the type of tumour<sup>(19,22)</sup>.

In order to understand the aetiology of one of the most commonly studied head and neck masses, i.e. enlarged lymph nodes, it is necessary to briefly recall their anatomical groups.

Based on anatomical and clinical features, the American Head and Neck Society in cooperation with the American Academy of Otolaryngology – Head and Neck Surgery proposed a classification of the head and neck lymphatic system (levels): I – submental (Ia) and submandibular (Ib) lymph nodes, II – upper jugular, III – middle jugular, IV – lower jugular, V – posterior triangle, VI – anterior cervical, VII – anterior superior mediastinal nodes. This division does not include lymph nodes in other areas, e.g. retropharyngeal, retrostyloid, where traditional anatomical nomenclature is used<sup>(22–25)</sup>.

Suspicion of metastasis should prompt search for the primary tumour. Statistically, malignancies are most often found in level II nodes. Some types of tumours metastasize to characteristic nodal groups, which results from the anatomy of lymph drainage to regional lymph nodes, e.g. tumours of the lower lip and floor of the mouth metastasize to level I nodes; oral cavity and salivary gland cancer metastasizes to level I and II nodes; middle and lower pharyngeal cancer invades level II and III nodes; laryngeal cancer metastasizes to level II, III and IV nodes; nasopharyngeal cancer invades retropharyngeal and retrostyloid nodes, but also level II, III, IV, and V nodes (this is the first symptom in 75–80% of cases<sup>(27)</sup>); nasal and paranasal sinus cancers metastasize to level I, II and V nodes<sup>(22,23)</sup>.

It is worth emphasising that lymph node metastases are a poor prognostic factor<sup>(19,22,28)</sup>.

In conclusion, a non-inflammatory head and neck mass persisting for more than 3 weeks requires a thorough diagnosis to determine its aetiology and nature.

## Otalgia

The literature generally distinguishes two types of otalgia: primary and secondary. In the first case (sometimes referred to as “otodynia”), pain originates within the ear and may be due to, among other things, an inflammatory condition.

The term “otalgia” usually refers to secondary otalgia, which means pain that originates from outside the ear, with the simultaneous absence of pathological factors in the (external or middle ear) ear<sup>(29,30)</sup>.

This is due to the exceptionally abundant sensory innervation of the ear structures. Stimuli (afferent) transferred from other structures can sometimes be perceived as ear pain per se.

Each episode of secondary otalgia requires meticulous diagnosis to rule out cancer (including diagnostic imaging of temporal bone pyramid, neck CT, sometimes also MRI)<sup>(31)</sup>.

## Innervation of the ear structures contributing to the development of otalgia<sup>(30–32)</sup>

### **Branches of the C2 and C3 cervical nerves – the great auricular nerve**

They mainly provide sensory sensation to the skin of the retroauricular area and the auricular lobe. Secondary otalgia occurs in the course of inflammatory and neoplastic diseases of the neck region, including the skin (angle of the mandible and the lateral part of the neck), the muscular structures of the neck, the atlantoaxial joint (injuries), lymph nodes and cysts (lateral, medial).

### **The third branch of the trigeminal nerve (V3, mandibular nerve) – the auriculotemporal nerve**

It supplies the auricle (anterior-superior part, also the tragus), the pre-auricular region, the external auditory canal (skin, anterior-superior surface) and the tympanic membrane (anterior-lateral quadrant).

Referred pain primarily occurs in inflammatory and neoplastic diseases involving mucous membranes of the oral cavity and gingiva, the palate (soft, hard), the floor of the mouth, the temporomandibular joint, the mandible (including the teeth), nasal and paranasal sinuses, and the parotid gland.

### **Facial nerve**

The facial nerve carries a relatively small number of sensory fibres, providing sensory innervation to the auricle area (lower part), the mastoid process, the tympanic membrane (lower area, light reflexion), and the external auditory canal (skin, posterior surface).

Otalgia mainly occurs in nerve VII pathologies (e.g. Bell's palsy or tumours of the nerve), the mucous membrane of the nasal cavity and the sphenoid and ethmoid sinuses (parasympathetic fibres), as well as the tongue (anterior 2/3, taste fibres).

### **Glossopharyngeal nerve – Jacobson nerve**

The sensory innervation is provided to the mucous membrane of the tympanic cavity (including the inner surface of the tympanic membrane) and the mastoid process, the auditory tube, and the central part of the outer surface of the tympanic membrane<sup>(30)</sup>.

Secondary otalgia occurs in pathologies involving the nasal and oral parts of the pharynx (palatine tonsils), tongue (posterior 1/3, base of the tongue), muscles (stylohyoid, pharyngeal muscles), retropharyngeal and parapharyngeal spaces, and the stylohyoid ligament (Eagle's syndrome).

### **Vagus nerve – Arnold's nerve**

The sensory innervation of the ear region supplies the auricle, the external auditory canal (skin, posterior-inferior surface), the tympanic membrane (posterior part), and the skin of the retroauricular region.

Referred pain occurs in inflammatory and neoplastic diseases of the oral pharynx (uvula, pharyngeal sphincters), larynx (especially when the process involves cartilage structures), laryngeal pharynx (piriform recess), the trachea, the oesophagus, and the thyroid gland.

Interestingly, paralysis of the posterior wall of the auditory canal may cause coughing. This phenomenon is explained by stimulation of the auricular branch of the vagus nerve (Arnold's nerve reflex)<sup>(33)</sup>.

In summary, due to the abundant sensory innervation of the ear, ear pain (after excluding otogenic aetiology) obliges the doctor to conduct meticulous diagnosis, especially for neoplasms, with emphasis on the pharyngeal, laryngeal, oesophageal and oral regions.

### Weight loss and cancer cachexia

Weight loss, cachexia and wasting are very often the first reason for a patient to make a medical appointment and the first cancer symptom noted by the patient. It is estimated that 3/4 of patients with newly diagnosed head and neck cancer experience weight loss of >10% within 6 months or a body mass index (BMI) of <20 kg/m<sup>2</sup><sup>(34)</sup>.

Cancer cachexia is a multifactorial syndrome characterised by progressive loss of skeletal muscle (with or without loss of fat mass) that cannot be fully reversed by conventional nutrition and leads to functional impairment.

A negative protein-energy balance due to eating and metabolic disorders is the starting point for the pathophysiological process.

The literature on the subject distinguishes three stages of cancer cachexia: pre-cachexia (body weight loss ≤5% and metabolic disorders or lack of appetite), cachexia (body weight loss >5% within 6 months or >2% in patients with BMI <20 kg/m<sup>2</sup> or with sarcopenia) and refractory cachexia, i.e. cachexia characterised by active catabolism (cancer does not respond to treatment, or becomes procatabolic) or the presence of factors that prevent further treatment of weight loss<sup>(35)</sup>.

Cancer patients develop cachexia mainly as a result of reduced nutrient supply, increased protein turnover (including loss of muscle mass), insulin resistance, and increased lipolysis<sup>(35)</sup>.

Anorexia, or the loss of desire to eat (lack of appetite), which commonly occurs in cancer patients, is responsible for the loss of lean body mass. It is caused by both the tumour itself (e.g. digestive tract tumour), and the cytokines produced by the tumour (including IL-1α, IL-1β, IL-6, TNFα or leptin). Additionally, enhanced synthesis of acute phase proteins leads to their increased breakdown and consequently greater nitrogen loss (from urea). Protein breakdown is higher than protein synthesis, despite normal supply of non-protein energy<sup>(35)</sup>.

Healthy individuals adapt to starvation mainly by slowing down the metabolism and inhibiting protein breakdown. Production of catabolic hormones that stimulate

gluconeogenesis and cause increased insulin resistance increases in chronic diseases (including cancer). For example, hypercortisolaemia stimulates protein breakdown (e.g. in muscles), increases glucose production in the liver, and reduces glucose uptake in muscles<sup>(35)</sup>.

Furthermore, during fasting, free fatty acids are released into the plasma at levels exceeding the demand for fats, consequently leading to fatty liver and deterioration of its function (a result of conversion into triacylglycerols)<sup>(35)</sup>.

Functional disorders (including dys- and odynophagia) play an important role particularly in the group of patients with head and neck cancers, making it impossible to meet the nutritional demands<sup>(35)</sup>.

Summarising, limited food supply and switching to catabolic pathways lead to weight loss and malnutrition in patients with head and neck malignancies.

### Facial nerve paresis/paralysis

Due to its complicated course and functional complexity, the facial nerve is the most likely to be damaged of all cranial nerves.

Bell's palsy, which has an idiopathic aetiology and is responsible for 70% of all incidents, is the most common cause of peripheral paresis or paralysis of nerve VII. It should also be noted that facial nerve can be damaged in the course of infectious diseases (including reactivated varicella-zoster virus infection, i.e. Ramsay Hunt syndrome) or neurogenic disorders, or develop as a complication of otitis media (acute or chronic)<sup>(36–38)</sup>.

Paresis or paralysis (usually unilateral) is a relatively rare symptom of neoplastic diseases (2.2–5% of cases). These include, among others, neoplasms of the parotid gland, salivary duct carcinoma and adenocarcinoma in particular<sup>(39)</sup>, neoplasms of the facial nerve or vestibulocochlear nerve, e.g. schwannomas and neurofibromas, tumours of the posterior cranial fossa or nasopharynx, and metastatic lesions<sup>(36,38–40)</sup>.

To conclude, neoplastic diseases should be considered (especially of the parotid gland) when consulting patients with facial nerve paresis or paralysis, unilateral or partial in particular.

### Nasal obstruction with nosebleeds

Nasal obstruction and nosebleeds are common reasons for medical consultations. According to EPOS 2020, chronic sinusitis, the symptoms of which include nasal obstruction, affects 5–12% of the population<sup>(41)</sup>.

A constellation of symptoms in the form of simultaneous (asymmetric) nasal obstruction not responding to proper conservative treatment and accompanied by nosebleeds should raise oncological concern and a suspicion of possible maxillo-ethmoidal or nasopharyngeal cancer. It is estimated that broadly understood nasal symptoms occur in 73.4% of patients with nasopharyngeal cancer<sup>(27,42,43)</sup>.

Despite its benign nature, juvenile nasopharyngeal angiofibroma, a rare (approximately 0.05% of head and neck cancers) tumour of the nasal pharynx or the posterior part of the nasal cavity, which is most prevalent in male adolescents (7–21 years), deserves attention. Abundant vascularisation of the tumour tissues is a unique feature of this neoplasm. Invasive diagnosis (especially without appropriate protection) can have tragic consequences. Clinical suspicion of this clinical entity requires urgent vascular imaging and treatment in specialised centres<sup>(44,45)</sup>.

Summarising, persistent (especially asymmetric) nasal obstruction with accompanying bleeding requires further diagnosis with emphasis on maxillo-ethmoid and nasopharyngeal endoscopy.

## CONCLUSIONS

1. Head and neck cancers are still diagnosed at late stages. Comprehensive and non-mutilating (despite the use of modern reconstructive techniques) therapy is significantly limited or impossible.
2. The main symptoms of head and neck cancer include a poorly healing wound or ulcer; pain in the lips, mouth, throat; dys- and odynophagia; hoarseness; a mass in the head or neck region; otalgia and weight loss; asymmetric nasal obstruction and unilateral nosebleeds; and paresis or paralysis of the facial nerve.
3. Patients presenting with the above symptoms usually report to a primary care physician or to a regional otolaryngology clinic in the first place. Possible neoplasm should always be considered as the cause of symptoms presented by patients.

### Conflict of interest

*The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.*

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### Author contributions

*Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript: MJS. Critical review of manuscript: VH. Final Approval of manuscript: MJS, VH.*

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