PREDICTORS AND ASSESSMENT OF HEAD AND NECK MALIGNANCY-RELATED PAIN

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ABSTRACT

Introduction: Head and neck malignancy is reported to be increasing in countries and have a much higher pain perception. The pain prevalence in head and neck malignancy patients is approximately 70% and is often reported to be inadequately treated. Objective: identify predictor factors to determine patients most at risk of pain. Method: This article uses a qualitative approach with a narrative review type. Results: Pain predictor factors can be divided into two broad groups: factors related to malignancy and factors not. Factors that are not related to malignancy include age, gender, demographic factors, and other factors related to comorbidities. While the predictors of pain related to malignancy are the location of the malignancy, stage, tumour size, and management. While the assessment of malignant pain must be adequate and use valid and reliable instruments for proper management of malignant pain. In clinical practice, a number of unidimensional, accurate, and reliable pain intensity measurements that are highly associated are used. Conclusion: Understanding the complex relations between cancer treatment, health behaviours, and pain might help doctors prevent, anticipate, counsel, and treat problematic symptoms in a community of head and neck malignancy patients.

Keywords: Auditory Brainstem Response (ABR), absolute latency, children.

Introduction

Head and neck cancer is one of the most common types of cancer worldwide, and its incidence is reported increasing in countries with limited resources. Globally, these malignancies account for 5–50% of all malignancies and 5-8% of whole-body malignancies in Europe and America, while in India they account for 30% of all malignancies. According to Indonesia's National Malignancy Register, head and neck malignancy ranks 4th out of the top ten malignancies.

Malignancy of the head and neck can occur in the sinuses, nasopharynx, larynx, oesophagus, thyroid, trachea, neck, and salivary glands. Malignancies of the nasopharynx, nose, paranasal sinuses, and larynx are the most common malignancies found in malignancies of the head and neck, followed by malignancies in the oropharynx, ears, and mouth. Head and neck malignancies are associated with high morbidity due to the complex and rich innervation of the head and neck region, erosive and aggressive disease processes, and a greater prevalence of psychosocial disorders than other malignancies.

Pain is also one of the causes of high morbidity in head and neck malignancies. Most of the patients experience pain due to the spread of the primary tumor and due to side effect of radiotherapy, chemotherapy or both. In general malignancy patients, pain is felt in more than 50% and 80-90% of malignant metastasized patients. Compared to other tumors, head and neck malignancies have a much higher pain perception. The pain prevalence is approximately 70% and is often reported to be inadequately treated. The pain can occur due to various sources related to the malignancy itself and the interventions used to treat it.

Pain management in head neck malignancy patients requires a comprehensive, interprofessional, and multimodality approach. Acute pain is extremely common in cancer patients during the diagnosis and therapy phases. Pain in cancer patients can progress from short-term to chronic difficulties that might last for months or years. Pain in cancer patients is becoming more acknowledged and recognised as a concern for 20% of those suffering from several major cancers.

Cancer pain discovered to be complex. These include postoperative pain syndrome (loss of sensation and function), nerve injury caused by radiation and osteoradionecrosis, and chemotherapy-induced peripheral neuropathy. Pain was found to affect quality of life after treatment significantly. Preventing and treating pain for people with head neck malignancy can improve patients' quality of life. Identifying predictors can facilitate specific targeted assessments and interventions.

Study Methods

The method in this article uses a qualitative approach with a narrative review type.

Study Results

Pain Definition

As per the International Association for the Study of Pain (IASP), pain can be defined as a distressing sensory and emotional encounter that arises from either real or potential harm to the body's tissues. It encompasses a personal journey, which is shaped by a complex interplay of various factors, including biological, psychological, and social elements. This multifaceted phenomenon involves not only the physical sensations associated with discomfort but also the intricate web of emotions that accompany it. It is crucial to recognize that pain is not merely a standalone physical sensation but rather an intricate fusion of bodily experiences and mental states, making it a deeply individualized and subjective encounter.

IASP's comprehensive definition of pain emphasizes the wide-ranging impact it can have on individuals, acknowledging the significant role played by both physiological and psychological aspects. From a biological perspective, pain serves as a warning mechanism, alerting the body to potential harm or injury. It is the body's way of signaling that something is amiss and necessitates attention or action. Simultaneously, the psychological dimensions of pain are equally important, as they contribute to how an individual perceives, interprets, and copes with the experience. Factors such as prior experiences, beliefs,
expectations, and personality traits can significantly influence the way pain is perceived and managed. Moreover, the social context in which pain occurs plays a crucial role in shaping an individual's experience. Cultural, societal, and environmental factors all intertwine to influence how pain is expressed, understood, and treated within a particular community or society. The cultural beliefs, norms, and values surrounding pain can impact an individual's willingness to seek help, their expectations of treatment outcomes, and the support they receive from their social networks. Additionally, social determinants such as access to healthcare, socioeconomic status, and support systems can further influence an individual's experience of pain.

By acknowledging the multidimensionality of pain, the IASP's definition highlights the need for a holistic approach in understanding and addressing pain. It underscores the importance of considering the intricate interplay between biological, psychological, and social factors in providing comprehensive pain management and support. Embracing this comprehensive perspective enables healthcare professionals, researchers, and policymakers to develop more effective strategies to alleviate pain, enhance patients' quality of life, and promote a deeper understanding of this complex phenomenon.

When experiencing pain, the intensity of sensation is the first clinical assessment, but emotional, psychological, cognitive, and behavioral aspects are also involved in a person's subjective perception of pain. The etiology of pain is reported to be multifactorial. Not all types of pain in malignant patients are related to tumors and, consequently, not all types of pain considered and defined automatically as pain due to malignancy. A prospective study conducted on many oncology patients has shown that up to 17% of the pain felt in this group of patients is due to antineoplastic treatment and about 10% due to other etiologies not associated with malignancy. Pain could result from tissue damage due to various mechanisms such as mucosal injury, ischemia, edema, inflammation, ulceration, infection can cause pain. Local invasion caused by tumor enlargement may cause visceral pain, while tumor compression or direct infiltration of nerve fibers may be the cause of neuropathic pain. Head and neck malignancies are associated with neuropathic pain compared to other oncological diseases.

Pain can also be related to psychological factors related to changes in vital functions obtained from these areas (chewing, swallowing, phonation, and breathing) and also due to changes in facial aesthetics in some cases. The therapeutic management of head and neck malignancies involves a range of approaches that vary based on the stage of the disease. These approaches, which may be used individually or in combination, typically include surgery, chemotherapy, and radiotherapy. However, it is essential to note that regardless of the treatment modality employed, postoperative pain is a significant concern in cases of head and neck malignancies, with prevalence rates reported to reach as high as 80%.

Postoperative pain in these cases can be particularly challenging due to various factors associated with surgical procedures. The trauma inflicted on nerve fibers during surgery, along with potential disruptions and subsequent derangement of these fibers, can contribute to an exacerbation of pain perception. This process has the potential to induce various distressing sensations, such as hypersensitivity, dysesthesia, or paresthesia, further complicating the experience for patients.

The underlying causes of postoperative pain in head and neck malignancies can be attributed to both tissue and nerve injuries. Tissue injury during surgery can result in muscle spasm and inflammation, leading to pain. Additionally, nerve injury can contribute to the development of both inflammatory and neuropathic pain. These forms of pain often manifest as persistent, severe, and challenging to manage, posing significant hurdles for patients on their path to recovery.

Given the complexity and diversity of pain experienced by individuals following surgical intervention for head and neck malignancies, it is crucial for healthcare professionals to employ a comprehensive and multimodal approach to pain management. This approach may include a combination of pharmacological interventions, such as analgesics and anti-inflammatory medications, along with non-pharmacological techniques like physical therapy, acupuncture, and psychological support. By addressing pain from multiple angles, healthcare providers can strive to mitigate the physical discomfort and emotional distress associated with postoperative pain, thereby enhancing the overall well-being and quality of life of patients undergoing treatment for head and neck malignancies.

Pathogenesis and Pathophysiology of Pain

Pain is generally considered an unpleasant sensation. The physiology of pain can be broadly divided based on the origin of the sensory experience felt. Both types referred to as nociceptive and neuropathic pain. Nociceptive pain, which occurs in response to a stimulus that activates specific receptors called nociceptors, involves a series of intricate processes that culminate in the transmission of information from the site of stimulation to the brain. These processes, known as transduction and transmission, are essential for the perception of pain. The nerve endings housing nociceptors are classified as primary afferents, terminating in a region of the spinal cord called the dorsal horn. When stimulated, these nociceptors generate action potentials that travel along the primary afferent fibers, releasing excitatory amino acids like glutamate and aspartate, as well as neurotrophins from the nerve endings located in the dorsal horn of the spinal cord.

In addition to the ascending pathway involved in transmitting pain signals to the brain, there are descending pathways that play a crucial role in modulating the perception of pain. These pathways involve the activity of various neurotransmitters, with noradrenaline and 5-HT (serotonin) being particularly important in inhibiting pain. Within the descending pathway, two significant areas in the brainstem, namely the periaqueductal grey (PAG) and the nucleus raphe magnus (NRM), exert their influence in reducing pain. The periaqueductal grey and nucleus raphe magnus act as key modulators of pain by exerting inhibitory control over the transmission of pain signals. These brainstem regions are involved in the descending modulation of pain, effectively suppressing pain perception and providing relief. The PAG and NRM achieve this by releasing neurotransmitters like noradrenaline and 5-HT, which interact with receptors in the spinal cord to dampen the transmission of nociceptive information.

Understanding the complex interplay between ascending and descending pain pathways is crucial for comprehending the mechanisms underlying nociceptive pain and its modulation. By exploring the intricate processes of transduction and transmission, as well as the involvement of neurotransmitters and specific brain regions like the PAG and NRM, researchers and healthcare professionals can gain insights into the development of effective pain management strategies. Furthermore, this knowledge opens avenues for potential
therapeutic interventions that target the modulation of pain perception, ultimately improving the quality of life for individuals experiencing nociceptive pain.

**Pain Classification**

Pain is a multifaceted and subjective phenomenon, and its classification can be approached from various perspectives, taking into consideration factors such as the underlying pathophysiology, type of stimulus, location, duration, and severity. In the context of malignancy-related pain, it is common to categorize it into two broad categories: nociceptive pain and neuropathic pain.

Nociceptive pain refers to the type of pain that arises from the activation of specialized nerve endings called nociceptors in response to actual or potential tissue damage. This category encompasses pain that is typically associated with malignancies, as the presence of tumors can exert pressure on surrounding tissues, cause inflammation, or result in injury to nerves or other structures. Nociceptive pain is often described as a throbbing, aching, or sharp sensation and is generally localized to the area of the body where the damage or stimulation occurs.

On the other hand, neuropathic pain involves abnormal pain processing resulting from a dysfunction or injury to the nervous system itself. In the context of malignancies, neuropathic pain can arise from direct compression or invasion of nerves by tumors, damage caused by cancer treatments such as surgery or radiation therapy, or as a result of chemotherapeutics-induced peripheral neuropathy. Neuropathic pain is characterized by sensations such as shooting or burning pain, tingling, numbness, or hypersensitivity. It is often described as a more constant and persistent type of pain compared to nociceptive pain.

By recognizing and distinguishing between nociceptive and neuropathic pain in the context of malignancies, healthcare professionals can tailor their approach to pain management accordingly. Treatment strategies for nociceptive pain may involve the use of nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, or local anesthetics to alleviate pain and reduce inflammation. In contrast, neuropathic pain often requires the use of medications such as anticonvulsants or antidepressants that target abnormal nerve signaling and provide relief from the specific symptoms associated with neuropathic pain.

Furthermore, this classification of malignancy-related pain based on nociceptive and neuropathic components serves as a foundation for a more comprehensive and individualized approach to pain management. By understanding the underlying mechanisms and characteristics of each pain type, healthcare providers can combine different treatment modalities, including pharmacological interventions, physical therapies, and psychological support, to address the diverse aspects of pain experienced by individuals with malignancies. This holistic approach aims to alleviate suffering, improve overall wellbeing, and enhance the quality of life for patients dealing with the complexities of pain associated with cancer.

**A. Nociceptive Pain**

Nociception, also referred to as nociperception, is the intricate response of the body's sensory nervous system to actual or potentially harmful stimuli. This complex process involves the activation of specialized sensory endings known as nociceptors, which play a crucial role in detecting and transmitting signals related to the perception of first-stage pain. Within our bodies, two primary types of afferent nociceptors, namely Aδ fibers and C fibers, are responsible for responding to various harmful stimuli.

These nociceptors are equipped with specialized free nerve endings that are widely distributed throughout the body, particularly in the skin, muscles, joint capsules, bones, and several major internal organs. Their strategic locations allow them to effectively detect and respond to a range of potentially damaging and harmful stimuli. Nociceptors are specifically designed to be highly sensitive to different types of stimuli, including chemical, mechanical, and thermal stimuli that can potentially cause harm to the body.

When these specialized nerve endings encounter stimuli that exceed a certain threshold, they become activated and initiate a series of processes that culminate in the transmission of pain signals to the central nervous system. For instance, Aδ fibers are responsible for transmitting sharp, well-localized pain signals, while C fibers transmit dull, poorly localized pain signals. The activation of these nociceptors triggers the generation of action potentials, which then propagate along the nerve fibers, eventually reaching the spinal cord and transmitting nociceptive information to higher brain centers for further processing and perception of pain.

By understanding the intricate mechanisms of nociception and the diverse distribution of nociceptors throughout the body, researchers and healthcare professionals can gain insights into the fundamental processes underlying the perception of pain. This knowledge serves as a foundation for developing targeted interventions and strategies to manage and alleviate pain effectively. By comprehending the specific characteristics and sensitivities of nociceptors to different types of stimuli, healthcare providers can employ tailored approaches that aim to address the underlying causes of pain, promote healing, and enhance the overall well-being of individuals experiencing nociceptive pain.

**B. Neuropathic Pain**

Lesions or dysfunctions of the nervous system cause neuropathic pain. Pain is described as a sensation such as burning, stabbing, being shot, or electrocuted, and is related to changes in color and local temperature. This pain can occur due to nerve compression or tumor invasion, especially in malignancies of the head of the neck.

**C. Inflammatory Pain**

Inflammatory pain is a complex biological response orchestrated by the body's tissues in response to a harmful stimulus. Its primary purpose is to initiate a cascade of events aimed at eliminating necrotic cells and triggering the activation of tissue repair processes. When tissues are damaged, a series of intricate mechanisms come into play to initiate the inflammatory response.

One of the key components of the inflammatory response is the recruitment of neutrophils, which are the first inflammatory responders to arrive at the site of damage. These neutrophils migrate to the affected area through the bloodstream, guided by chemical signals released by the damaged tissues. Once they reach the site of injury, neutrophils engage in various activities to combat the harmful stimulus and promote tissue healing.

Another important player in the inflammatory response is mast cells. Inflammation triggers the degranulation of mast cells, leading to the release of a multitude of chemical mediators. These mediators include substances like histamine, prostaglandins, and cytokines, which contribute to the characteristic signs and symptoms of inflammation, such as redness, swelling, and pain.

Additionally, inflammation can induce the release of platelet activating factor (PAF), which is a potent lipid mediator involved in the inflammatory cascade. PAF promotes the activation and recruitment of other immune cells to the site of injury, amplifying the inflammatory response. Moreover, inflammation stimulates the release of serotonin (5-HT) from
circulating platelets, further enhancing the inflammatory process.

The orchestration of these inflammatory mediators and cellular responses serves as a defense mechanism to eliminate harmful stimuli and initiate the repair of damaged tissues. By understanding the intricacies of the inflammatory response, healthcare professionals can develop targeted strategies to manage and alleviate inflammatory pain. These strategies may include the use of anti-inflammatory medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, to mitigate the inflammatory process and provide relief from pain and discomfort.9

Pain predictors
Patients with head and neck cancer frequently endure pain, even after therapy is ended. The prevalence of bodily pain in patients with head and neck cancer has been calculated to be 70%, which is vastly greater than the prevalence reported in other cancer patients. Pain felt up to a year after diagnosis can predict lengthy quality of life and is linked to a lower chance of survival. Pain is also a powerful predictor of impairment in people with head and neck cancer. Pain has been identified as a negative prognostic factor.11

Pain predictors can be divided into two broad groups: factors related to malignancy and factors not related to malignancy.18

Predictors of Pain Unrelated to Malignancy
A. Age
Pain is more common in younger age groups than in the elderly. Derks et al. compared patients with oral cavity, pharyngeal, and laryngeal cancer between the ages of 45 and 60, while Infante-Cossio et al. compared patients with squamous cell carcinoma of the head and neck between the ages of 65 and 65,10

B. Gender
Study conducted by Hammerlid et al. found a significant relationship with sex. In the study, women had higher pain scores than men. This is consistent with the findings of a study by Infante-Cossio et al.,14

C. Demographic
Low levels of education are associated with more intense pain. Education level can also predict the quality of life of malignancy patients. Education is reported to affect pain treatment. Education aims to improve patients’ knowledge and attitudes about pain. 11

D. Depression
Pain is closely associated with depressive characteristics. Depression people are more sensitive to bodily discomfort, which leads to depressive symptoms, particularly in cancer patients. Depression is also linked to risky habits such as smoking and alcohol misuse. Depression treatment can aid in the cessation of substance usage.11

Prediktor Nyeri Berkaitan Keganasan
A. Site of malignancy
According to Chaplin et al., patients with laryngeal cancer have significantly less pain than those with oral cavity tumors. According to Infante-Cossio et al., pain in patients with oropharyngeal malignancies is greater than in patients with other malignancies.10

B. Stage and Size
Several studies report a significant association between pain and the stadium. Another study found that patients with advanced stages (stages T3 and T4) had more pain than T2 tumors.11

C. Management

Some studies indicate that the non-surgical group experienced more severe pain than those treated surgically or without postoperative radiotherapy. Patients occasionally felt more pain after treatment.10 Pain is sometimes exacerbated by surgery, neck dissection, and radiation10.

Pain Assessment

Proper assessment of malignant pain using appropriate and trustworthy measures is critical for effective pain management.22 In clinical practice, several simplistic, accurate, and trustworthy pain intensity measures that are highly associated are used. Some things that can be asked and provide information on the history include location, onset and pattern of pain, pain description, severity, aggravating and lightening factors, previous treatments, and psychological assessment.13

Questionnaires such as the Verbal Rating Scale, Numerical Rating Scale, Visual Analog Scale (VAS), Brief Pain Inventory (BPI) and Hospital Anxiety and Depression Scale (HADS) are valuable tools because they can provide objective analysis for pain patients, therefore they can be used as a basis for further management. In addition, the Leeds Assessment of Neuropathic Signs and Symptoms (LANSS) can also be used to identify neuropathic pain.12

A. Verbal Rating Scale
The Verbal Rating Scale (VRS) is a commonly employed categorical scale that enables patients to subjectively express and quantify their perception of pain intensity. While the VRS can take different forms, an illustrative example of this scale is a 4-point system where patients are presented with a set of descriptors to choose from, including none, light, medium, or severe, corresponding to different levels of pain intensity.

The use of a categorical scale like the VRS has several advantages. Firstly, it provides a standardized framework for pain assessment, allowing for consistency and comparability across different patients and healthcare settings. This uniformity aids in tracking pain intensity over time and assessing the effectiveness of interventions. Secondly, the simplicity of the VRS makes it accessible to individuals with varying levels of health literacy or language proficiency, ensuring that patients from diverse backgrounds can effectively communicate their pain experiences.

However, it is important to note that the VRS is just one of many pain assessment tools available, and its suitability may vary depending on the specific context and individual preferences. Healthcare providers should consider the unique needs of each patient and select an appropriate pain assessment tool accordingly. Furthermore, it is essential to engage in open and ongoing communication with patients, encouraging them to provide additional information and context about their pain experience beyond a simple categorical rating. This scale is more useful in the postsurgical period, since naturally verbal does not rely so much on visual and motor coordination. Verbal scales use words instead of lines or numbers to describe the pain level. The scale used can be no pain, moderate, or severe. Pain relief can be expressed as not going away, slightly reduced, moderately reduced, or good/pain disappears altogether. This scale limits the patient’s choice of words, it cannot distinguish between different types of pain.13

B. Visual Analog Scale

VAS assessment is the most widely used way to assess pain. This linear scale visually illustrates the gradation of pain levels that a patient may experience. The pain range is 10 cm long, with or without marks on each centimeter. The marks at both ends of this line can be numbers or descriptive statements. One end represents no pain, while the other represents the worst pain
possible. The scale can be made vertical or horizontal. VAS is used in pediatric patients over eight years of age and adults. The main benefit of VAS is that its use is effortless and simple.11

C. Numeral Rating Scale
The numeral rating scale (NRS) consists of numbers 0–10 to measure pain intensity. The patients assessed their discomfort on this scale. In this approach, patients can utilize all personality scales: speech issues do not interfere with thinking or comprehension. NRS is simple, easy to understand, and sensitive to dosage, gender, and ethnic differences. It is better than VAS especially for assessing acute pain.14

D. Brief Pain Inventory
A Brief Pain Inventory (BPI) assessment is a quantitative analysis that uses a scale from zero to ten and measures pain intensity during walking, daily activities, social activities, work, and sleep. The assessment of pain was presented in the questionnaire as the most severe, least intense, and average pain felt in the last twenty-four hours. BPI is considered a multidimensional instrument. The BPI includes seven items that assess how pain has interfered with general activities, mood, ability to walk, regular work (including work outside the home and household chores), relationships with others, sleep, and enjoyment of life. Respondents were asked to rate the degree of pain disturbance on each activity from 0 (not bothersome) to 10 (annoying at all) numerical scale. Responses to the seven items were then averaged to form a BPI score. This analysis yielded two dimensions of the underlying disorder: disturbances with activity (walking, working, general conditioning, sleep) and effectiveness-related disorders (relationships, mood, enjoyment of life).10

E. Hospital Anxiety and Depression Scale
The Hospital Anxiety and Depression Scale (HADS) assessment is a scale used to measure symptoms of anxiety and depression in non-psychiatric hospital patients. HADS is not intended to be used as a complete diagnostic tool but is helpful for identifying hospital patients requiring a further psychiatric evaluation. The HADS consists of 14 items that reflect the mood in the past week, divided equally into two subscales: anxiety and depression13.

F. Leeds Assessment of Neuropathic Signs and Symptoms
The Leeds Assessment of Neuropathic Signs and Symptoms (LANSS) assessment is the first questionnaire specifically designed to distinguish neuropathic pain from nociceptive pain. LANSS assessment has a pain questionnaire and a sensory testing component. The pain questionnaire asked respondents to answer yes or no to five questions. The sensory component is assessed by lightly touching the painless and painful locations with a cotton swab and comparing the patient’s response to gouging the skin with a syringe on the painless and painful areas. Each affirmative response is weighted, and the overall score is computed by adding the values of all positive remarks. The LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) demonstrated consistent high accuracy rates in classifying neuropathic pain versus nonneuropathic pain across multiple patient samples, including the original development sample, cross-validation sample, and additional samples with malignancy and mixed chronic pain conditions14.

Effective Pain Management
The World Health Organization (WHO) has developed a 3-step conceptual model for pain management, which serves as a practical and effective guide for administering and adjusting analgesic medications. This model simplifies the process of selecting and titrating pain medications.28

Depending on the pain scale, therapy is initiated according to the pain level. For mild pain starting at step 1, moderate pain at step 2, and severe pain at step 3. Patients with severe pain can immediately receive 3rd step opioid therapy as soon as possible12–13.

Adjuvant (or analgesia) analgesics are medications that will greatly improve pain control when added to primary analgesics. They can also serve as primary analgesics (e.g., tricyclic antidepressant medications for postherpetic neuralgia). These medications can be added to pain management at each step of the ladder of pain therapy, according to WHO.11

Several alternative therapies can be used to help reduce pain in patients. Behavioral management techniques aim to help patients regain control skills that may have previously been lost due to illness or weakness. These approaches include cognitive behavioral training (CBT), hypnosis, reiki biofeedback, and relaxation therapy. These techniques provide a calming diversion and break the cycle of pain-anxiety-tension. Physical modalities such as TENS and acupuncture can be used in conjunction with other approaches11.

Palliative care focuses on enhancing patients’ quality of life by identifying, assessing, and managing pain and other physical, psychosocial, and spiritual issues. Its primary goal is to provide comfort, preserve dignity, and promote overall well-being.14

Conclusion
Managing pain in head and neck malignancy is still a challenge. And multimodality management is required. Understanding the complex relationship between malignancy treatment, health behaviors, and pain is instructive for clinicians faced with prevention, anticipation, counseling, and treatment of troubling symptoms in a population of head and neck malignancy patients.

References