Chapter 9
Considerations in Advanced and Recurrent Head and Neck Cancer

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Advanced and recurrent head and neck malignancies contribute to significant mortality and morbidity for patients. Due to difficulty in physical examination, cancers in the oral cavity, oropharynx, and larynx often go undetected in their earlier stages. For this reason, head and neck cancer patients may present with more advanced disease than other cancer patients. As a result, the disease process and its aggressive treatment modalities can impact several aspects of a patient's quality of life.

According to the World Health Organization, health-related quality of life (HR-QOL) encompasses an "individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychosocial state, level of independence, social relationships, and their relationship to salient features of environment" [1]. In simplified terms, HR-QOL can be defined as the multidimensional impact an illness and its treatment have on a patient's perception of his or her physical, psychosocial, and functional capabilities. This chapter will delve into how advanced and recurrent head and neck cancer (HNC) can influence these domains of a patient's life.

Tools to Measure Quality of Life in Head and Neck Cancer

Assessment of quality of life is challenging in that there are several dimensions influencing a patient's life. Quality of life is largely dependent on a patient's perception of their functional, physical, and psychosocial status before diagnosis and treat-

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ment. Several validated instruments exist to help standardize our understanding of the impact that HNC and its treatment options have on HR-QOL (Table 9.1). These tools can be categorized into five distinct groups [2]:

1. Generalized: identifying the effects that any disease, both chronic and acute, can have on quality of life
2. Disease-specific: describing the impacts of cancer and the perception of cancer on quality of life

Table 9.1 Quality of life instruments in HNC

Instrument category	QOL instrument	Brief description
Generalized	EuroQOL Five Dimensions Questionnaire (EQ-5D) [3]	Questionnaire incorporating five domains – physical, social, mental, symptoms, and health state thermometer
	Medical Outcomes Study (MOS) Short Form – 36 (SF 36) [4]	General health questionnaire assessing QOL over the past 4 weeks; eight domains
	Sickness Impact Profile (SIP) [5]	Focused on chronic illness; questionnaire addresses psychosocial and physical domain
Disease-specific	EORTC Quality of Life Questionnaire (QLQ-C30) [6]	Focused on cancer patients, with domains including overall health, functional status, and symptom impacts
	Functional Assessment of Cancer Therapy-General (FACT-G) [7]	Designated for cancer patients; includes four domains – family, physical, emotional, and functional well-being in the past week
Site-specific	University of Washington QOL Questionnaire (UWQOL) [8]	Questionnaire specific to head and neck cancer patients with focus on functional status, symptom impact, and overall health. Psychologic domains are also included
	EORTC-Head and Neck Quality of Life Questionnaire [9]	Subset of EORTC for head and neck cancer patients, exploring seven domains of QOL, time frame is 1 week
	FACT-Head and Neck [10]	Questionnaire assessing how HNC impacts pt's family, physical, emotional, and functional well-being in the past week
	MD Anderson Symptom Inventory-Head and Neck (MDASI-HN) [11]	Questionnaire for HNC patients, addressing symptom severity, symptom interference, and treatment-related impacts on QOL
	Vanderbilt Head and Neck Symptom Survey (VHNSS) [12]	Detailed questionnaire focusing on how a variety of symptoms impact quality of life in the past week
Treatment-specific	UWQOL for surgical patients	UWQOL with additional questions specific to surgical treatment options
	Head and Neck Radiotherapy Questionnaire (HNRQ) [13]	Questionnaire focused on symptoms and disabling factors associated with radiation therapy
	Quality of Life Radiation Therapy Instrument Head and Neck Module (QOL-RTI/H&N) [14]	Quality of life questionnaire about radiation therapy and its impact on specific assessments like mucous, saliva, taste, cough, and local pain

Table 9.1 (continued)

Instrument category	QOL instrument	Brief description
Symptom-specific	Liverpool Oral Rehabilitation Questionnaire [15]	QOL questionnaire focusing on oral function and denture satisfaction
	Voice-related QOL (V-RQOL) [16]	Questionnaire describing communication-related difficulties associated with compromised voice and/or laryngeal structures
	MD Anderson Dysphagia Inventory (MDADI) [17]	Questionnaire includes global, emotional, functional, and physical subscales to describe QOL impacts of dysphagia in HNC patients
	Xerostomia Questionnaire (XQ and XQOL) [18]	Questionnaire assessing the physical functioning, psychologic functioning, social functioning, and pain/discomfort in patients with dry mouth
	Shoulder Pain and Disability Index (SPADI) [19]	Questionnaire focuses on two domains: pain and disability related to shoulder pathology

3. Site-specific: evaluating how head and neck cancer influences quality of life
4. Treatment-specific: examining how interventions for HNC affect quality of life
5. Symptom-specific: assessing how specific sequelae of HNC impact quality of life

Together, these instruments seek to measure the various elements of HR-QOL. Given the wide variety of validated questionnaires, a major pitfall of quality of life-driven research is the lack of a "gold standard" tool. Additionally, depending on primary tumor site and stage, patients with HNC can experience a range of different symptoms impacting quality of life. No QOL instrument effectively accounts for such variation. Even treatment-specific or symptom-specific tools will reflect variation in response based on intervention itself. For example, patients who undergo free flap reconstruction may perceive questions on a UWQOL Surgery survey differently than those who undergo local reconstruction. Finally, when studying HR-QOL among patients, it is challenging to account for differences in baseline quality of life. Patients with HNC may have several comorbidities that are largely unrelated to their tumor. Therefore, when choosing a QOL instrument, it is critical that clinicians define their research question and understand the degree of detailed information required to answer that question. Ultimately, tool selection should consider study objective, patient population of interest, and the strengths and weaknesses of the QOL tool itself [3].

The Psychosocial Impact of Advanced and Recurrent HNC

Evidence suggests that there are specific patient and treatment factors associated with improved psychosocial quality of life scores. For example, males with advanced HNC report higher social and emotional quality of life. Additionally, time since

therapy completion is positively correlated with the psychosocial quality of life score. This correlation is stronger when patients report participation in rehabilitative therapy following their cancer treatment. As functional status improves, emotional and social well-being also improves. This section will delve into the various psychosocial factors that should be considered when evaluating quality of life in advanced HNC patients.

Self-Esteem and Impacts of Disfigurement

Oftentimes, high levels of anxiety and increased social isolation are documented in patients with advanced and recurrent HNC. Several studies indicate that these sentiments are linked to a patient's body image [4]. Advanced head and neck tumors are usually quite visible, and depending on location, degree of ulceration, and extent of facial involvement, they significantly influence an individual's self-esteem. In a retrospective study of patients with oral or maxillofacial cancer, most patients admitted to preoperative distress related to fear of disfigurement [5]. About 60% of those patients also reported feeling stigmatized from cancer-related appearance. Local and free flap reconstructions after tumor resection further contribute to perceptions of disfigurement. Interestingly, gender did not impact quality of life scores related to body image and self-esteem. Age was inversely related to body image scores – older individuals plagued with advanced HNC are significantly less impacted by their appearance or disfigurement [4]. In other studies, worsened quality of life scores related to self-esteem and body image were noted in patients with inaccurate preoperative expectations – demonstrating the importance of patient counseling and understanding prior to surgical resection of HNC.

Depression and Emotional Coping

Compared to patients who solely undergo surgery, advanced HNC patients with multimodal treatment or nonsurgical treatment report significantly higher rates of depressive symptoms [6]. Length of posttreatment time is linked to a significant decrease in depressive symptoms; QOL scores associated with depression are about 40% lower for survivors 15 years out from treatment, than for patients only 120 days out from treatment [6]. Emotional coping style also influences overall quality of life among patients with advanced and recurrent HNC. Patients who rely on avoidance strategy endorse poorer overall HR-QOL. Similarly, passive coping styles (associated with closing off to spouses, inexpression of emotion, and more pessimism) contribue to more psychosocial distress for patients and their loved ones [7].

Caretakers

Quality of life scores of caretakers of advanced HNC patients need to be considered as well. As expected, emotional support from spouses and family members bolster HNC patient's perception of personal well-being. Thus, baseline fatigue and health status of caregivers impact the QOL scores of HNC patients. Several studies reveal that caregivers of head and neck cancer patients report poorer mental health than the general population [8, 9]. Distress was most often associated with disruption of daily life schedule because of caretaking, poor coping and communication styles of patients, and presence of feeding tubes [10]. Further, caretakers of advanced cancer patients were at an increased risk of morbidity and mortality, related to an inability to address their own medical needs [11]. Risk factors for caretakers with poorer psychosocial health include providing more hours of care, disrupted social interaction, and disrupted attention of self-care [12].

The Physical Impact of Advanced and Recurrent HNC

Depending on extent of tumor invasion and treatment option, advanced and recurrent HNC also affects patients' physical capacities. Physical impairment can greatly diminish quality of life. Furthermore, patients with better physical self-efficacy before diagnosis and throughout treatment have been shown to have better survival outcomes [13]. This section will delve into the various physical factors to consider when evaluating quality of life in advanced HNC patients.

Disability in Activities of Daily Living

Pain contributes significantly to disability in activities of daily living (ADLs). Debilitating pain associated with treatment negatively impacts general activity, walking, normal work, sleep quality, and life enjoyment. In a multicenter study, patients with advanced-stage HNC had significantly higher pain scores than those with other types of malignancy, with a greater percentage requiring analgesics during cancer treatment course [14]. The higher prevalence and severity of pain was hypothesized to be due to location of tumors, as most anatomical structures of the head and neck are pain-sensitive and concentrated in a small space [15]. Treatment-related pain may often be neuropathic in nature, attributed to surgical nerve sacrifice, adjacent tissue edema, or local neurotoxicity.

Furthermore, feeding tube dependence and postoperative recovery impair patients' independence in ADLs. Comorbidities and age prior to cancer treatment also affect ability to perform ADLs. Furthermore, treatment modality impacts patients' activity status. Systemic weakness from chemoradiation was found to be

very debilitating during treatment course and in the immediate months posttreatment. Interestingly in a study evaluating patient-related outcomes for free flap reconstruction in elderly patients, 75% of subjects denied major limitations to activities of daily living once 32 months out from surgery [16].

Deconditioning and Malnutrition

Oftentimes, advanced and recurrent head and neck cancer causes unintentional weight loss. Chemotherapy and radiation have both been noted to decrease muscle mass among head and neck patients, leading to deficits in mobility and decrease in physical activity [17]. Among advanced HNC patients, more than 50% report sedentary lifestyle with very few participating in light to moderate physical activity. Elderly HNC patients are least likely to partake in physical activities, contributing to worse quality of life and prognosis [18]. Early and consistent physical activity during treatment course has been shown to improve perception of personal well-being and global quality of life among HNC patients [19]. It also contributes to decrease in fatigue, one of the primary distressing QOL-related outcomes reported by patients with HNC [20]. Additionally, malnutrition is common in advanced HNC patients. Malnutrition is attributed to factors like dysphagia, decreased appetite, and malabsorption from disease and treatment; it negatively impacts both HR-QOL and prognosis. Prophylactic feeding tubes and pretreatment nutritional counseling have both been shown to mitigate the severity of malabsorption in cancer patients.

The Functional Impact of Advanced and Recurrent HNC

When discussing health-related quality of life in HNC patients, functional status contributes significantly to a patient's overall well-being. Head and neck anatomy is integral to functions like chewing, swallowing, and speech production. Shoulder and neck mobility are also crucial for several activities of daily living. Thus, advanced HNC and its treatment modalities can negatively impact patients' functional quality of life in several ways. This section will discuss the various impacts that advanced and recurrent HNC has on a patient's functional quality of life.

Dysphagia

Advanced-stage HNC (stages III–IV) is associated with severe swallowing dysfunction, especially with oral cavity and oropharyngeal tumors [6]. This is not only due to extent of tumor spread into anatomic structures critical in chewing and initiating

swallow but also because of the indicated treatment modality. Advanced and recurrent HNC often requires multimodal therapy, and both nonoperative treatment and surgery + adjunctive therapy are linked with worse dysphagia. However, increasing use of transoral robotic surgical resection has demonstrated improvement in dysphagia scores, when compared to standard chemoradiation for advanced oropharyngeal tumors [21]. As with several other symptoms impacting quality of life, dysphagia has also been shown to improve with time since treatment (Fig. 9.1). However, after about 6 years posttreatment, patients do report recurrence and worsening of dysphagia [6]. One option to mitigate these symptoms is swallow rehabilitation therapy. For example, patients with tongue resections who participate in swallow therapy report significantly improved dysphagia scores than patients who did not participate [22].

Speech Impairment

Difficulty with voice and speech is reported most often with oral cavity, oropharyngeal, and laryngeal tumors. Tongue and laryngeal involvement particularly impact a patient's ability to effectively communicate. Patients undergoing partial glossectomy maintain better articulation than those undergoing hemi-glossectomy [23].

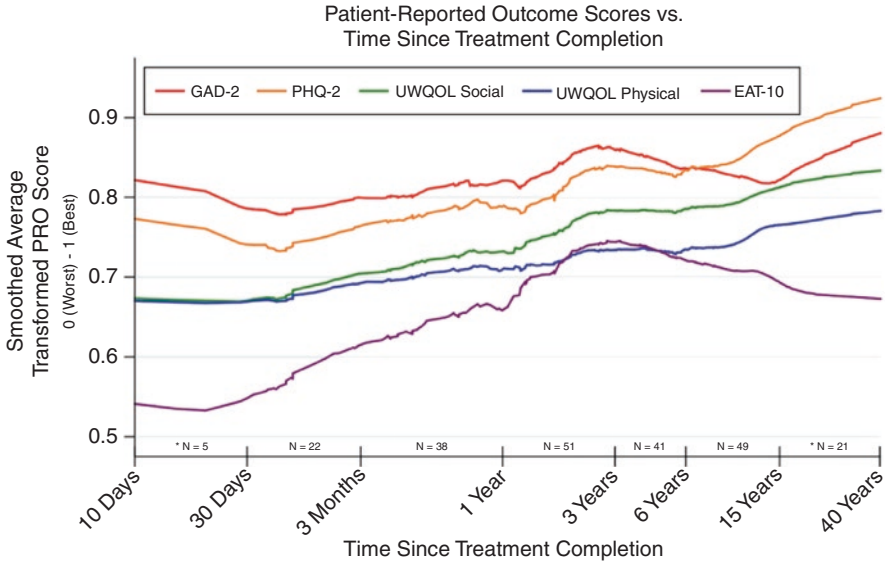

Fig. 9.1 Patient-related QOL outcomes vs time since treatment completion [22]; EAT-10 = Eating Assessment Tool-10; GAD-2 = Generalized Anxiety Disorder-2; PHQ-2 = Patient Health Questionnaire-2; PRO = patient-reported outcomes; UWQOL physical = University of Washington Quality of Life Physical Subscale; UWQOL social = University of Washington Quality of Life Social-Emotional Subscale. (From Nilsen et al. [6], with permission)

Further, local flap reconstruction of tongue defects is associated with quicker improvement in speech quality than free flap reconstruction. In advanced oropharyngeal cancer, voice changes are often peak within 1 month of therapy; patients report recovery in speech quality by 12–18 months following treatment [24]. However, in a study evaluating speech impairment in stage IV disease treated with concurrent chemotherapy and radiation, over 65% of patients reported late presentation in difficulty with voice, articulation, and speech 10 years following treatment [25].

Work-Related Disability

Advanced head and neck cancer, treated with multimodal treatment or nonsurgical treatment, is also associated with an overall increase in work-related disability. In a multi-site study, 384 patients who worked prior to their diagnosis with HNC were surveyed. Of this sample, more than half of the patients in this study were disabled by their head and neck cancer or treatment [26]. Patients with head and neck cancer who have undergone chemotherapy or neck dissection or have high pain scores are at increased risk for disability from their cancer or their treatment.

Factors contributing to these trends include:

- The need for frequent hospital visits
- Systemic impact of treatment and associated health complications (i.e., immunocompromise, debilitating pain, etc.)
- Impaired neck and shoulder mobility, especially in professions requiring manual labor
- Financial burden of ongoing multimodal treatment

Tumor-Related Factors and Their Impact on Quality of Life

Inherent variation in quality of life exists depending on tumor site and tumor stage. As one would expect, late-stage tumors (III and IV) are associated with poorer quality of life than early-stage disease. Metastatic disease and recurrent disease often require systemic therapy, which contribute to poorer functional and physical status for patients.

Nasopharyngeal and sinonasal cancers are associated with the least impact on quality of life, with the exception of tumors with orbital involvement. Patients with oropharyngeal cancer reported better HR-QOL scores than those with hypopharyngeal cancer [27]. These differences were often associated with the varying treatment modalities indicated for each tumor site. For example, oropharyngeal and oral cavities significantly impact malnutrition, dysphagia, and generalized weakness [28]; advanced-stage disease in these regions requires chemotherapy and/or radiation. In

contrast, late-stage hypopharyngeal and laryngeal tumors more likely impact speech or physical disfigurement, as would be expected with total laryngectomies.

In addition to tumor site and stage, HPV status can impact quality of life for HNC patients. In a large retrospective study comparing QOL, symptom, and functional outcomes of HPV-positive HNC and HPV-negative HNC, patients with HPV-negative cancers reported worse overall quality of life [29]. This is likely because HPV-negative patients are typically older and have more comorbidities at baseline. In the HPV-associated OPC, patients report returning to baseline quality of life or improved quality of life, 1 year after treatment. This was true no matter which treatment modality was utilized.

Treatment Modalities of HNC and Their Impact on Quality of Life

Treatment modalities of advanced and recurrent disease impact every domain of quality of life among HNC patients. Unfortunately, given the severity of malignancy, multimodal management is often indicated. Most studies indicate that multimodal treatment, while effective in treating HNC cancer, negatively impacts health-related quality of life [6]. There are a variety of QOL domains affected by HNC and its treatment options.

Overall, numbness, difficulty with phonation, and pain were commonly reported adverse effects of surgery. Weight loss, fatigue, and loss of appetite were primarily associated with chemotherapy or radiotherapy. This section will delve deeper into the QOL considerations of each treatment modality.

Operative Intervention and Its Impact on QOL

Early-stage head and neck cancer can often be addressed with curative surgery without long-term costs in quality of life. However, locally advanced disease requires more extensive procedures with significant functional and physical deficits. Common symptoms adversely impacting quality of life in surgical candidates include [6, 30]:

- Disfigurement
- Speech and swallow difficulty
- Lymphedema and fibrosis
- Impaired jaw and/or shoulder mobility
- Postoperative pain

Traditionally, operative intervention has been associated with poorer quality of life outcomes than nonsurgical intervention (chemotherapy and radiation). In the short term, surgery in head and neck subsites like the oropharynx and larynx

required invasive approaches for appropriate access. Surgery for locally advanced oropharyngeal cancer previously required open craniofacial defects, associated with poor swallowing function, speech difficulty, and longer hospital stays. Conservative therapy was found to be just as effective in treatment, with fewer quality of life sequelae and less morbidity. However, with the advent of transoral approaches to oral cavity, oropharyngeal, and even thyroid malignancy, recent studies report improved quality of life outcomes with surgery. Compared to patients treated with radiation, patients undergoing surgical resection of oropharyngeal cancer report improved overall quality of life, social functioning, nausea, and financial stress [31]. Furthermore, advances in reconstructive options for head and neck cancer have improved functional status and cosmesis, contributing to better quality of life.

Neck Dissections

Oftentimes, neck dissection of cervical lymph nodes is indicated for curative treatment of more aggressive HNC. However, a study reported that 48% of their patients undergoing neck dissection were unable to return back to work, because of debilitating shoulder pain from the procedure [32]. The same study concluded that when controlled for other demographic and clinical variables, patients who underwent neck dissection were twice as likely to experience work-related disability than those patients who did not undergo the procedure. Neck dissections have been associated with worse pain scores and decrease in quality of life related to functional status. In radical or modified radical neck dissections, sacrifice of the accessory spinal nerve and/or internal jugular vein can lead to debilitating neck pain and reduced mobility. Lymphedema and scarring associated with the procedure also impacts body image and appearance [30]. With that being said, one study determined that functional status and appearance-associated distress improves for most patients undergoing nerve-sparing neck dissection, when reassessed 2 years postoperatively [33].

Reconstructive Surgery

Patients offered local reconstruction demonstrate better quality of life score than those who underwent free flap reconstructions, especially for oral cavity and oropharyngeal tumors [23]. QOL domains that are significantly better in local reconstructions included chewing, swallowing, speech, and postoperative pain. Radial forearm free flaps have been found more effective in mitigating these aspects of quality of life, when compared to anterolateral thigh free flaps (ALTFF); this is likely related to less muscle bulk [34]. For example, hemi-glossectomy patients undergoing radial forearm free flap reconstruction demonstrated more understandable speech, improving chewing, and better swallowing than ALTFF patients. Regardless of these initial postoperative differences, patients undergoing both local and free flap reconstructions reported improved general quality of life 1 year after

surgery [23]. Postoperative time is associated with improvement in most domains of HR-QOL in surgical HNC patients [6].

PEG Tube Dependence

Patients with advanced HNC often require a feeding tube to treat nutritional compromise from their disease process and treatment. Studies have demonstrated that prophylactic percutaneous endoscopic gastrostomy (PEG) tubes have reduced morbidity than those placed therapeutically for malnutrition in HNC patients [35]. However, presence of feeding tube is linked with significantly lower quality of life scores among HNC patients [28]. Physical quality of life is impacted by adverse symptoms associated with enteral feeding. Adverse symptoms include nausea, vomiting, diarrhea, reflux symptoms, PEG site infection, and adjacent skin irritation. Such effects also contribute to work-related disability. Furthermore, patients report lower psychosocial QOL, linked to frustration of one's condition, embarrassment of appearance, and inability to partake in social dining.

Tracheostomy Tube Dependence

Unlike with PEG tubes, tracheostomy tubes are not associated with lower psychosocial QOL scores. Studies report that although tracheostomy tubes interfere with functional quality of life related to activities of daily living, there is no significant distress or anxiety associated with its presence [28]. Further, patients with tracheostomy tubes do not report decreased physical QOL. With a safe airway, patients with advanced HNC are actually able to perform concrete task such as lifting, walking, and carrying better than at baseline.

Radiation Therapy and Its Impact on QOL

Typically, definitive radiation therapy is the treatment modality of choice for early-stage head and neck cancers. However, it is also indicated for locally advanced HNC; specifically, radiation is offered to patients with unresectable tumors or patients who desire nonsurgical organ preservation. The effects of standard radiation therapy in HNC patients are often related to damage to normal structures like salivary glands, oral mucosa, dentition, and musculature. Common symptoms impacting quality of life include xerostomia, painful mucositis, loss of taste, and trismus. Patients treated with radiation therapy report significant problems with oral and nutritional intake, with most common symptoms being xerostomia and decrease in taste [36]. Further, in a study evaluating the impact that radiation therapy had on dysphagia, more than 80% of patients complained of worsened swallow ability immediately after treatment [37]. One year following treatment, these symptoms

improved, with only 15% of patients complaining of persistent dysphagia. Concurrent chemotherapy was noted to have worsened dysphagia scores.

Hyper-Fractionated Radiation

In late-stage head and neck cancer, several studies report a role in hyper-fractionated radiation. This is sometimes utilized in patients who cannot tolerate concomitant chemotherapy due to adverse side effects or recurrent disease unresponsive to chemotherapy. Further, in a meta-analysis comparing survival outcomes in stage III and stage IV head and neck cancers treated with radiation, hyper-fractionated radiation (compared to standard radiation) demonstrated a statistically significant improvement in overall survival at 5 and 10 years posttreatment [38]. However, hyper-fractionated radiation is also associated with worse HR-QOL scores. Patients complained of worse mucositis, neck and throat pain, and nausea 3 months after initiation of radiotherapy [39].

Hypo-Fractionated Radiation

Advanced HNC may not always be eligible for definitive treatment. Palliative radiation was noted to have less of a cost on quality of life. Unlike fractioned radiotherapy (modality of choice for definitive treatment), hypo-fractionated radiation therapy has been demonstrated to allow for effective palliative control of locally far advanced HNC, with improved QOL scores. This treatment option often involves moderately high treatment doses, with a shorter treatment course and ideally fewer hospital visits [40]. When assessing hypo-fractionated radiation therapy in incurable head and neck cancer, over 60% of patients reported improvement in overall quality of life and pain scores at the end of treatment [41].

Chemotherapy and Its Impact on QOL

Patients with advanced HNC undergo systemic treatment. While chemotherapy is not necessarily curative for HNC on its own, it has been shown to improve survival and cure outcomes when administered in adjunct to radiation therapy. However, chemotherapy toxicity can significantly impact patients' HR-QOL. Adverse effects associated with some of the most common concomitant chemotherapy agents include [42]:

- Nausea/vomiting
- Myelosuppression
- Nephrotoxicity
- Paresthesia
- Tinnitus and hearing loss

Furthermore, patients undergoing chemoradiation report swallow dysfunction and pain; concurrent chemotherapy has been shown to worsen dysphagia scores among patients [37]; however, these symptoms have been shown to improve in 12–24 months following treatment [43]. In addition to impact on functional QOL, chemotherapy impacts physical QOL. Patients with head and neck cancer are more susceptible to opportunistic infection. One study reported that febrile neutropenia occurred in a third of chemotherapy cycles, with severe sepsis or serious infection noted in 46% of episodes [44]. Patients undergoing chemo regimen TPF (docetaxel, cisplatin, and fluorouracil) experienced a higher incidence of febrile neutropenia than those treated with DC (docetaxel, cisplatin).

Induction Chemotherapy

Sequential chemotherapy administration in the form of induction chemotherapy followed by concurrent chemoradiation is often administered in organ-preserving management [45]. Some studies have noted that induction chemotherapy does not significantly improve survival in advanced head and neck cancer. However, there is evidence supporting induction chemotherapy's role in organ-preserving treatment of laryngeal cancer. Immediately following induction chemotherapy, HNC patients have reported improvement in pain and swallowing-related quality of life for the emotional, functional, and physical domains [46].

Palliative Chemotherapy

For incurable advanced and recurrent HNC, metronomic chemotherapy is more frequently utilized for palliation. Metronomic chemotherapy involves frequent administrations of low-dose antineoplastic drugs, with an intent to decrease rapid growth of cancer (without tumoricidal intent). One study found oral metronomic therapy consisting of celecoxib daily and methotrexate weekly was associated with improved social and functional QOL scores [47]. Significant improvement was noted in 50% of patients at their 2-month follow-up; 40% of patients continued to report improvement in quality of life in these domains at 6-month follow-up.

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