Review Article

QUALITY OF LIFE CHANGES IN PATIENTS WITH OSTEORADIONECROSIS AND THEIR MEASUREMENT

Abstract

One of the most serious and debilitating complications of radiation therapy (RT) for patients with head and neck cancer (HNC) is osteoradionecrosis of the jaws (ORNJ). ORNJ is defined as radiation-induced ischemic bone necrosis with soft tissue necrosis in the absence of primary tumor, recurrence, or metastatic disease. Even though the incidence of ORNJ has dropped from about 20% to 2–8% as a result of recent advancements in RT techniques, this serious complication is still very challenging to predict, prevent, and treat. It is beyond dispute that ORNJ has detrimental effects on patients' quality of life (QoL). Pain, halitosis, taste disturbance, dysesthesia or anesthesia, trismus, difficulty chewing, swallowing, feeding, and speaking, fistula formation, pathological fracture , and localized, disseminated, or systemic infections are the most frequent symptoms of ORNJ that have an impact on the victim's QoL measures. However, ORNJ-specific QoL studies are scarce in this patient group despite ORNJ's significant harmful effects on the sufferers' physical appearance and functions, mood, and social relationships. By providing readily available information about the physical, social, and emotional effects of ORNJ as measured by general or HNC-specific QoL surveys, this review article aims to serve as a foundation for future studies addressing novel ORNJ-specific questionnaires.

Keywords: Osteoradionecrosis of jaw, radiotherapy, head and neck cancer, quality of life, questionnaires.

Introduction

Radiation therapy (RT) for head and neck cancers (HNC) can have serious side effects, including osteoradionecrosis of the jaw (ORNJ) (1). ORNJ is defined as "a potentially serious, delayed radiation-induced injury characterized by bone tissue necrosis, failure to heal, and irradiated bone for 3 to 6 months" (2, 3). The incidence of ORNJ in the head and neck ranges from 2% to 22% (4). ORNJ, as the term implies, is a late complication of RT or concurrent chemo-RT (CCRT), characterized by bone necrosis (1). The manifestation and disease course of ORNJ can range from mild asymptomatic bone exposure that heals with conservative treatment or remains stable to severe necrosis with pathologic fracture that demands surgical intervention and reconstruction (3). According to published data, the average interval between the end of RT and the emergence of ORNJ is 22–47 months (5-7). ORNJ is thought to manifest with a higher incidence rate and a shorter interval from the completion of RT or CCRT to its emergence, though these may vary widely between studies using different methodologies and assessment tools (8).

The recent introduction of more sophisticated RT techniques, such as intensity-modulated RT (IMRT), reduced the incidence of ORNJ from about 20% to 2-8%. (4,9,10). Patient-related variables (age, gender, history of smoking, history of alcohol use, diabetes mellitus, performance status, pre-RT dental interventions, pre-RT tooth extraction, post-RT tooth extraction), tumor-related variables (primary tumor site, T-stage, nodal status), and treatment-related variables (pre-RT surgery, pre-RT mandible surgery, induction chemotherapy (ICT), and CCRT, RT technique) are among the potential risk factors for ORNJ development (10). ORNJ can also develop spontaneously, though this is uncommon (11,12). ORNJ affects the mandible far more frequently than other bones in the head and neck region, though osteoradionecrosis of the maxilla, hyoid, and temporal bone has also been reported (13). Mandibular ORNJ is more common after RT for head and neck malignancies than other

bones, due to its relatively poor vascularization, greater susceptibility to trauma, and superficial location resulting in high radiation exposure (14,15).

Pain, bad breath (halitosis), dysgeusia, dysesthesia or anesthesia, trismus, difficulty with mastication, deglutition, difficulty feeding and speech, fistula formation, pathologic fracture, and localized, spreading, or systemic infections are all common ORNJ symptoms (16) ((Figure 2A-2B). ORNJ significantly reduces patients' quality of life (QoL) during and after oncologic treatment due to these serious symptoms and/or consequences such as in chewing, speaking, swallowing functions and facial deformities (17). Despite the fact that almost all studies show that ORNJ harms health-related quality of life (HRQoL) measures, research on this hot topic is scarce (18-21). The HRQoL evaluation collects information on patients' psychosocial well-being and the significance of the particular disease condition and its management. Accordingly, HRQoL-based analyses are becoming more and more popular as viable tools for assessing functional and psychosocial outcomes in concert with relapse and survival rates in a multitude of diseases (22). Hence, the purpose of this chapter is to review the detrimental effects of ORNJ on the affected patients' physical and daily functions, as well as their psychosocial status, and to contribute to the oncologic and dental literature in terms of raising awareness and determining the best-fit assessment tools that may be useful in the everyday practice of physicians in related medical fields.

The influence of ORNJ-related factors on daily life and QoL measures

ORNJ is a severe complication of RT or CCRT that has a substantial and detrimental impact on the QoL of HNC patients (23). These impacts on QoL are multifaceted, affecting patients' subjective well-being in physical, emotional, functional, and social dimensions. A detailed overview of QoL is required to appropriately measure therapy outcomes in ORNJ patients.

The most common clinical manifestations of ORNJ are a pain in the exposed jawbone and fistula formation in the affected mucosa (24). Other symptoms may include limited mouth opening, dysesthesia or anesthesia, dysgeusia, halitosis, tooth, and periodontal abnormalities, swallowing/chewing trouble, physical deformity, and pathological fractures (1, 24, 25). Without a doubt, all of these symptoms and ORNJ ramifications result in substantial deficiencies in practically all aspects of the afflicted patients' QoL scores.

Excruciating pain is one of the most distressing symptoms influencing QoL in ORNJ patients (26, 27). Most patients experience intense pain in the early and middle phases of ORNJ before the bone loses its viability. In stark contrast, when the clinical picture worsens, patients may not perceive pain owing to excessive loss of sensory pain nerve fibers in the late stages of the ORNJ course. While pain is a negative symptom that interferes with patients' tasks such as eating, drinking, swallowing, chewing, and social life (28), it is also a sign that the condition has not advanced too far and that the bone still retains vital features (29,30). Additionally, pain makes ORNJ patients uncomfortable or wakes them up frequently, disrupting their sleeping patterns (31).

Another common symptom of ORNJ is intra-oral or extra-oral fistulation of the commensurate tissues on the exposed bone (24). Furthermore, ORNJ progression may result in pathological fractures, as well as difficult-to-treat local or systemic infections (32). Restricting oral nutrition, ONJ-related fistulas, necrotic bone sequestration, and pathological jaw fractures can make swallowing and chewing difficult or even impossible (26). ORNJ-related pathological fractures are a difficult to manage group of fractures that almost always require surgical intervention (33). As a result, lengthier hospitalization periods may be required, raising treatment costs and putting patients in financial jeopardy (34).

According to a cross-sectional study of cancer patients, one of the most severe symptoms that reduced QoL for ORNJ patients was restricted mouth opening (21). Similarly,

Yang et al. reported that restricted mouth opening was the most severe ORNJ symptom, with a staggering incidence rate of 84.2%, of which 48.4% were scored as severe trismus (21). The mouth opening of ORNJ patients also showed a trend toward lessening with passing time after RT, as per the authors. Some studies contend that ORNJ may be listed among the well-known causes of restricted mouth opening, even though the mechanism is not fully understood (35, 36). With the progression of dental and periodontal infections, the favorable microenvironment may lead to ORNJ because dental treatments and oral care practices are challenging to perform in such patients (36). Numerous studies have ascertained that limited mouth opening harms QoL related to oral function, such as pain, eating, chewing, taste, saliva production, and dry mouth, as well as an increased incidence of jaw-related problems and dietary restrictions (38, 39). Moreover, severely limited mouth opening can lead to malnutrition or cachexia, which can have a negative impact on patients' health and QoL and even jeopardize their survival as a poor prognosticator in almost all cancer types (40). Indeed, limited mouth opening will cause patients to avoid social eating and be included in the social environment, resulting in loneliness, social isolation, and psychological disorders (41). Also, ORNJ or trismus-induced halitosis has significant unpleasant impacts on patients' QoL in terms of social isolation, relationships with social partners, and sexual performance (42).

Teeth and periodontal problems, difficulty chewing/swallowing, and limited mouth opening can all alter patients' food consumption, affecting their daily lives (34). Radiation caries are caused by a decrease in the patients' daily oral care and brushing frequency, as well as a reduction in the saliva buffer capacity and flow rate. As a result, deep caries in the teeth and infection in the periodontal tissues begin, preparing the environment for the formation of ORNJ (43,44). Surgical resection can be used to control the infection in the ORNJ area and clear the necrotic tissue (45), but, daily functions such as nutrition, chewing, and speaking may be compromised due to bone deformation in the jaw, multiple tooth loss, and aesthetic

and functional problems in the facial area, Because of facial deformities, the person may lose confidence and become socially isolated. According to Chieng and colleagues' research results in 109 patients with ORNJ, there were reductions in mood, anxiety, and overall QoL parameters in 28%, 30%, and 50% of these patients, respectively (46).

Anesthesia of the inferior alveolar nerve was one of the ORNJ presentation features observed in 7.4% of cases (47). In addition to anesthesia, ORNJ-related dysesthesia may also be present in some other patients (17,25). Dysfunctional eating, drinking, and speaking are among the expected effects of anesthesia or dysesthesia because these conditions impair the patient's motor and sensory functions. As a result of the deterioration of motor functions and loss of pain sensation, injury to the relevant regions during eating may occur, resulting in chronic ulceration and non-healing wounds if this injury persists.

ORNJ, as well as related symptoms and functional losses, may affect the patient's QoL in a variety of ways, as evidenced by the features listed above. Furthermore, ORNJ may shorten such patients' survival times by inducing weight loss on the way to fatal cachexia, uncontrolled resistant infections, or aspiration and intubation issues (48). Hence, it is critical to detect and treat ORNJ as soon as possible in order to improve the affected patient's QoL measures and, in some cases, life spans. Likewise, the use of QoL evaluations may be beneficial in alleviating the psychosocial problems of these patient groups (Figure 1).

Measurement Tools for Evaluation of QoL in ORNJ Patients

Despite advancements in RT techniques used to treat HNC, ORNJ continues to occur in a notable proportion of such patients. The adverse effects of ORNJ on the patient's physical, functional, psychological, and social aspects make it hard to manage RT--related conditions because they are typically unpredictable and severe (45). Outcome data on ORNJ patients, such as patient-reported health-related quality of life (HRQoL), can help inform discussions

with patients and their caregivers about treatment outcomes. The patient is the most recommended data source for QoL evaluations. To the best of our knowledge, few studies with relatively small cohort sizes have made an effort to ascertain how various treatments for ORNJ affect HRQoL domains thus far (49). Although ORNJ management is primarily based on actual signs and symptoms such as pain level, disfigurement, trismus, and diet type, it may be beneficial to document pre-treatment QoL scores in various domains. In this regard, outcome data on ORNJ patients, including HRQoL, are critical for use in discussions between clinicians and patients about management strategies and their expected success.

Despite the importance of QoL measures in expediting symptom interventions and comprehension of patients' perspectives on RT toxicities, we are aware of no prospective studies specifically evaluating the effect of ORNJ on QoL. However, several questionnaires are employed to assess QoL in HNC patients before and after treatment. Since 2000, version 4 of the University of Washington QoL scale (UWQoL) has been used for yearly postal surveys. It has been thoroughly validated using other QoL assessment tools and is well established for use in patients with HNC. The UW-QoL is the preferred method for scoring HNC patients' QoL because it is brief and straightforward to administer (25). This questionnaire has 12 single-question sections: pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood, and anxiety, with answers ranging from 0 (the worst possible response) to 100 (the best possible response). First used in the United States of America, this questionnaire has been translated and validated in many languages, including simplified Chinese, Hindi, Marathi, Brazilian Portuguese, Italian, German, Norwegian, Malay, Greek, Japanese, and Dutch (25). Using the UW-QoL, Rogers et al. (49) discovered significant differences in HRQoL in 71 patients with mandibular ORNJ. It was noted that all patients with stage III ORNJ had more difficulty chewing and swallowing than those with stage I or II ORNJ at 1-year assessments, probably owing to the adverse

effects of RT and bone necrosis. The authors concluded that patients with ORNJ had significantly higher rates of pain, appearance, activity, recreation, swallowing, and chewing issues than patients without ORNJ.

There are few prospective studies, and retrospective research on health-related QoL (HRQoL) in patients with ORN has produced conflicting findings (49-52). Previous studies have frequently used questionnaires, such as a survey created by the European Organization for Research and Treatment of Cancer (EORTC), to describe the impact of HNC treatment on patients' HRQoL (31,53-55). It is common practice to use the popular QoL questionnaires QLQ-C30 and QLQ-HN35 for this purpose (56,57). Danielson et al. (58) used the QLQ-C30 and QLQ-HN35 modules to prospectively evaluate patient outcomes following reconstructive surgery for mandibular ORN in a study with 17 patients. The most robust finding of this study was a consistent decline in pain-related domains following microvascular reconstruction operations, as measured by the EORTC, QLQC30, and QLQ HN35 modules. As a result of these findings, one of the primary indications for this type of surgery in patients with severe ORNJ may be pain alleviation.

Despite the dissimilarities in underlying developmental mechanisms, the consequences of medication-related osteonecrosis of the jaw (MRONJ) and ORNJ on patients are comparable. As a result, while ORNJ-specific QoL questionnaires are scarce in the literature, the same questionnaires used to assess MRONJ-related effects can also be wisely employed for ORNJ assessments. Miksad et al., for example, collaborated with oncology, oral medicine, oral surgery, psychiatry, and QoL experts to develop a telephone call-based questionnaire to identify MRONJ-related QoL effects (59). A chart review was used to determine the suitability of the newly created questionnaire. The Oral Health Impact Profile (OHIP), a validated psychometric tool, was used to determine oral health-specific QoL before and after MORNJ. For cancer and MRONJ, four standard health conditions were created, and

preference values (utilities) were obtained for each condition using the Visual Analog Scale (VAS), EQ-5D, and time trade-off (TTO) questions. The emotional distress of 34 cancer patients with MRONJ was measured during and after the survey. OHIP scores were significantly lower regarding pain, eating disorders, self-consciousness, malnutrition, interrupted meals, irritability, and decreased life satisfaction. When VAS, TTO, and EQ-5D measures were added to the OHIP assessment, EQ-5D scores increased significantly with worsening MRONJ: pain/discomfort and anxiety/depression being the most significant contributors to diminished QoL measures. Analogously, Tenore et al. (60) used the recently created 12-item Short Form Survey (SF-12) to examine the relationship between MRONJ and QoL in 20 cancer patients. The primary investigator administered the SF-12 questionnaire, which is a shortened version of SF-36, in a face-to-face interview during their regular outpatient visit. The eight scales that this survey measures with its 12 items are: physical functioning (2 items), role physical (2 items), body pain (1 item), general health (1 item), vitality (1 item), social functioning (1 item), role emotional (2 items), and mental health (2 items). Scale responses vary both between and within the same scale. The Physical and Mental Component Summary (PCS and MCS, respectively) scores of the SF-12 questionnaire were generated using the standard scoring algorithms. The two most useful aggregate summary measures are the PCS and MCS scores, where low PCS and MCS scores represent a poor level of health (61). According to this study's findings and the study by Miksad et al. (59), QoL will be negatively impacted more severely as the MRONJ stage advances. The findings of this study were also highlighted the potential essentiality of including physical and psychosocial evaluations in the management of MRONJ patients (61). Capocci et al. (62) discovered that physical and mental health scores were significantly lower in stage III MRONJ patients than in those with stage I and II disease in another study. One of the most significant advantages of the SF-12 is that it does not require any special training to operate.

Furthermore, the SF-12 can be administered in a variety of modes, including static (paper), online mode, and interactive voice response.

As evident from the aforementioned studies, no ORNJ-specific questionnaire has been developed yet to measure QoL issues in HNC cancer patients with mutilating ORNJ. This unpleasant reality highlights the urgent requirement for the development of simple, short, but comprehensive ORNJ-specific surveys to reveal the true impact of this regrettably severe RT complication in HNC patients. However, it seems logical to advise the use of MRONJ-based QoL questionnaires for the assessments of ORNJ patients in a similar manner until the availability of such specific surveys.

Discussion

The number of patients with ORNJ is anticipated to increase in the future despite improvements in RT and diagnostic methods because prolonged survival times have made it possible for many late complications to manifest. While managing this debilitating complication and enhancing patients' QoL requires meticulous evaluation of the unpleasant effects of ORNJ on HRQoL, research on this topic of utmost importance is still scarce. Available limited data has demonstrated that patients with ORNJ experience myriad issues, including dysphagia, dentition, activity limitations, trismus, teeth and gums, dry mouth, halitosis, tinnitus, ear obstruction, and difficulty hearing (20, 21). Questionnaires are frequently used to identify and evaluate these detrimental effects on patients' QoL, but the lack of ORNJ-specific tests makes it challenging to estimate the QoL measures with accuracy in such populations.

Although there are more retrospective studies on the signs and treatments of ORNJ, studies on MRONJ-related QoL are more prevalent in the literature, with no prospective studies examining the QoL of ORNJ victims currently available. It should not be forgotten that the patient is the primary consideration in ORNJ's QoL questionnaires. As a result, the

questions that will be asked should include all of the patient's complaints and be as objective as possible. Given these considerations, Chieng et al. (46)'s recently published study provided a unique opportunity to reflect on outcomes in routine care. Incorporation of patient-reported outcome measures (PROM) into standard follow-up in this study allowed for repeated measures with a 12-year longitudinal assessment with few patients missed, as well as the opportunity to report patients' HRQoL before ORNJ diagnosis. However, because the vast majority of ORNJ patients were indeed referred by ENT (ear-nose-throat) specialists, not every patient had a true longitudinal follow-up. This circumstance has highlighted the need for a questionnaire that can be used across all medical specialties to help with patient follow-up and standard ORNJ diagnosis and treatment.

Although they are not specific to ORNJ, FACT-HN and EORTC QLQ, EORTC QLQ -HN 35 are two comprehensive and well-known QoL measures that are currently available for HNC patients (63-65). The FACT and QLQ-C30 questionnaires and their original generic counterparts are lengthy and hard to administer in clinics with a higher workload. As a result, UWQOL questionnaire, a questionnaire that is self-administered that assesses HRQoL, was created with the need for a concise, user-friendly, and comprehensive tool that adequately addresses general and HNC-specific QoL issues over past seven days (66). This questionnaire is ideal for use in both routine clinical practice and longitudinal studies to assess and compare changes in QoL in HNC patients with communication problems and/or dysfunction. Even though it is practical and offers helpful details about the general health of the tested HNC patient, it still lacks questions specific to ORNJ and its consequences.

Given the available data, it appears essential to develop ORNJ-specific QoL surveys that address the physical, psychological, and social effects of ORNJ in affected patients. Because the median time from completion of RT or CCRT to the appearance of ORNJ is approximately 36 months, and the risk continues to rise over time, longitudinal prospective

QoL research is required to reflect the true impact of ORNJ on HRQoL measures. Such ORNJ-specific surveys may enable us to diagnose ORNJ-related issues and initiate the appropriate treatment measures promptly. However, only a multidisciplinary approach involving radiation oncologists, medical oncologists, oral and maxillofacial surgeons and radiologists, clinical nurses, dietitians, psychotherapists, physiotherapists, and speech and language therapists will be capable of accomplishing this difficult task.

Conclusion

The questionnaires used to measure how ORNJ affects patients' QoL differ from one another and almost invariably portray the condition in general rather than in the context of a specific patient, making data comparison challenging. Therefore, it is crucial to use validated questionnaires to assess the impact of ORNJ on QoL from the patient's point of view. Future prospective randomized clinical trials are undoubtedly required to provide comprehensive data on how ORNJ interacts with activities of daily living. To help clinicians determine the best time to manage a specific symptom and inform and patients educate, it would be helpful to identify the onset and course of the symptom using larger, well-validated questionnaires. Future studies with these goals and appropriate designs will hopefully provide useful data and best management practices in light of the adverse repercussions of ORNJ.

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FIGURE LEGENDS

Figure 1. Impact of osteoradionecrosis on health-related quality of life parameters

Figure 2. A. Osteoradionecrosis (blue arrow) of Jaw in the left retromolar area of mandible, B. Panaromic radiograph of osteoradionecrosis (blue arrow) of in the left retromolar area of mandible

Figure 1

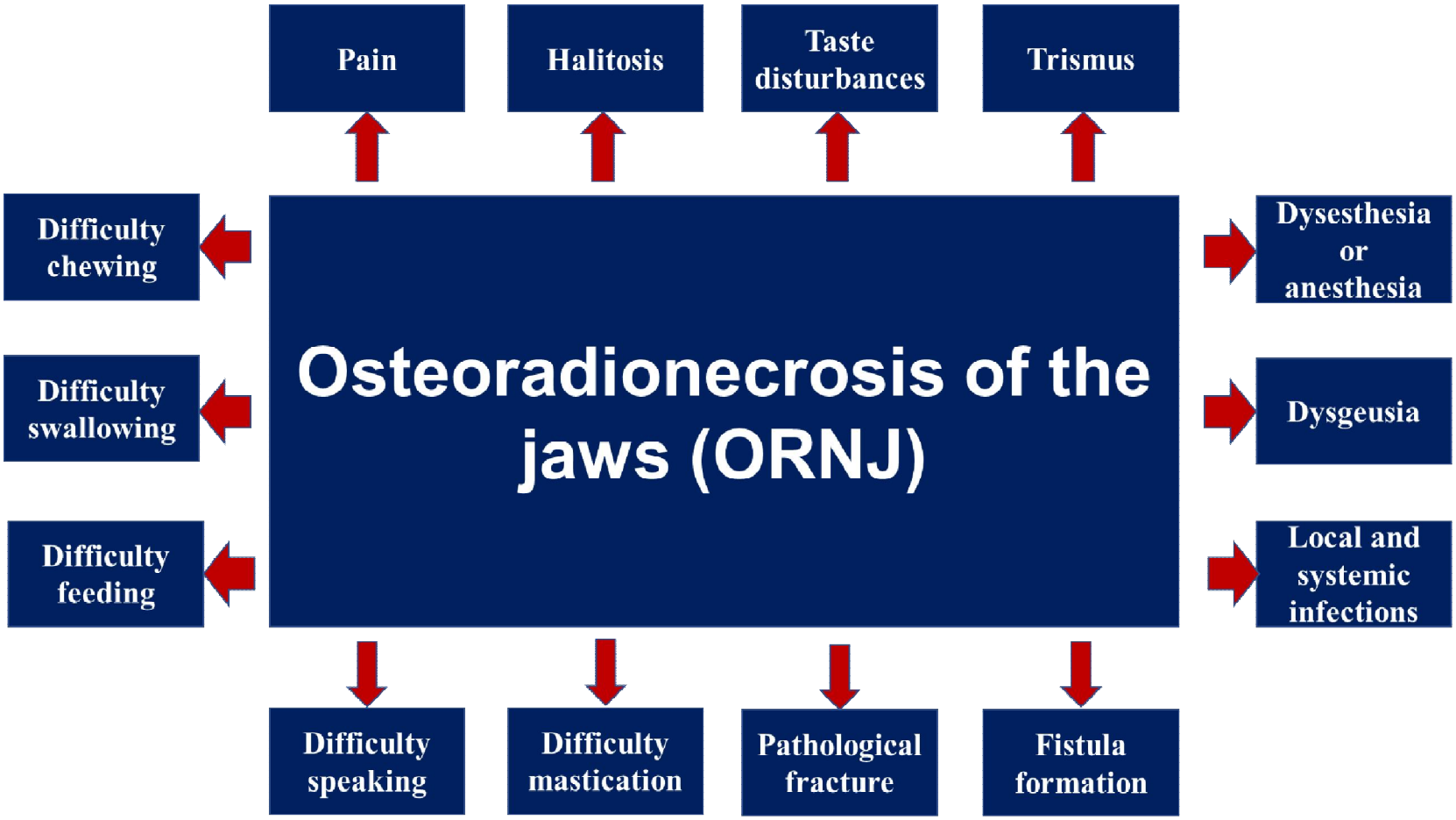
Pain
Halitosis
Taste disturbances
Trismus
Difficulty chewing
Difficulty swallowing
Difficulty feeding
Osteoradionecrosis of the jaws (ORNJ)
Dysesthesia or anesthesia
Dysgeusia
Local and systemic infections
Difficulty speaking
Difficulty mastication
Pathological fracture
Fistula formation

Figure 2.