Head and Neck Cancer Radiation Therapy With and Without Chemotherapy May Result in Decreased Health-related Quality of Life Followed by a Return to Baseline Over a 1-year Period

**SUMMARY**

**Selection Criteria**

The paper presents a systematic review of the health-related quality of life (HRQoL) literature for HNSSC patients treated by radiation therapy with or without chemotherapy and without surgery. A hybrid quality assessment tool was applied to develop the final inclusion criteria of eligible manuscripts. The electronic databases EMBASE and MEDLINE were searched for articles from those databases’ beginnings through 2012. MeSH categories for the search were “quality of life,” and “head and neck neoplasms” and “carcinoma” and either “radiotherapy” or “radiation,” excluding the terms “esophagus,” “thyroid,” “sarcoma,” “lymphoma,” and “melanoma.” Eligibility criteria included studies on adults, written in English, using non-surgical treatment only that included radiotherapy with and without chemotherapy, having over 50% of subjects with HNSCC diagnoses, and use of a validated HRQoL instrument. After a title review to determine initial eligibility, references not previously identified in the electronic search were hand searched. Abstract review and, when necessary, the reading of the full texts of the papers remaining after the title review plus the identified hand-searched articles were conducted to determine eligibility. One reviewer performed the eligibility assessment and discussed unclear cases with a second reviewer; a third reviewer arbitrated unresolved disagreements.

Two hundred seventy-six reports were identified in the databases; title review eliminated 151, while an additional 24 papers were added by hand searching, for a total of 149 reports for detailed eligibility assessment. Of these 149, 53 met all inclusion criteria. Study designs of eligible papers included cross-sectional, prospective, and pre-post methodologies; no clinical trials were identified.

Final inclusion of articles for review included the quality evaluation. Two investigators independently reviewed the eligible articles performing a quality assessment using a 13-item tool derived by the authors from two relevant papers. Eighteen papers met the 9-of-13-item inclusion threshold, of which meeting the validity criterion for HRQoL instruments was a requirement. A third reviewer acting as final arbiter resolved any disagreements.

**Key Study Factors**

The key study factor for this review was radiation treatment with or without chemotherapy in HNSCC patients. A secondary study factor included different radiotherapies: intensity-modulated RT (IMRT), and 3D conformal RT (3D-CRT) or conventional RT.

**Main Outcome Measurements**

The primary outcome was self-reported HRQoL both overall and for specific HRQoL domains. Outcomes were derived from cross-sectional and
prospective studies and had to be measured from one of three validated and reliable HRQoL instruments: (1) UWHNC-Qol, (2) EORTC QLQ-C30, and (3) FACT-H&N.

Main Results
Of the papers meeting eligibility criteria, 34% (18) also met the authors designed quality criteria threshold (9/13 quality definitions) of study/reporting for final inclusion in the review.

A decline in overall HRQoL and some domains (social, and head and neck) over the first 6 months from treatment initiation was followed by an approximate return to self-reported baseline HRQoL. However, the only paper that used study control subjects suggests that this baseline may not be representative of patients’ predisease norm. This apparent HRQoL improvement may reflect adaptation and patients’ perceptions relative to the acute toxicity they experienced during active treatment. The evidence for the observed U-shaped pattern of scores across the first year of treatment demonstrated some inconsistency in the reports regarding specific HRQoL domain responses to treatment. Notably, xerostomia was a HRQoL item that was a persistent patient issue past the first year of therapy. IMRT may have delivered better HRQoL than conventional radiotherapy.

Only one study compared radiation-only (n = 11) with radiation and chemotherapy (n = 5), a small sample size noted by the authors. This and other reports regarding radio/chemotherapy, however, suggest that patients receiving this combined treatment did show the same HRQoL patterns with possibly worse effects than with radiation-only treatment.

Conclusion
The authors conclude that for non-surgical HNSSC patients some HRQoL domains and overall HRQoL scores decline after the initiation of radiotherapy with and without chemotherapy. This is followed by the HRQoL approximately returning to baseline levels over the subsequent year. The observation of HRQoL return to baseline levels is accompanied by an authors’ caution that this observation may in fact represent patient adaptation or a response shift. IRMT may have less of an effect on HRQoL than conventional or 3D-CRT. The effect of chemotherapy may further worsen radiotherapy sequelae in some domains of HRQoL. Treatment-induced xerostomia is generally a long-term HRQoL issue, extending well beyond the first year of therapy.

COMMENTARY AND ANALYSIS
The term head and neck cancer (HNC) refers to cancers of the lip, oral cavity, pharynx, nasal cavity and paranasal sinuses, inner ear, and larynx. Worldwide in 2008, over 600,000 new cases of HNC were reported. In the United States HNC comprises 3% to 5% of all cancers. “The cosmetic, functional, and psychosocial results of oral cancer treatment (a major category of HNC) may combine to produce devastating effects on patients. A variety of functions can be affected, including speech, deglutition, management of oral secretions, and mastication. HNSSC and its associated treatment can affect HRQoL, which is a multidimensional construct that includes physical and psychological functioning, social interactions, and treatment satisfaction.

The systematic review assessed here generally followed the Institute of Medicine’s (IOM) Standards for Systematic Reviews. Two areas of the methodology that are ambiguous in the report are the IOM recommendation for (1) working with a librarian trained in systematic reviews and (2) that two reviewers independently screen and select studies, i.e., the authors state that “one reviewer performed the eligibility assessment and discussed equivocal cases with a second reviewer.” However, the final conclusions would likely not have been materially different. Several issues that may weaken the findings are related to the significant number of cross-sectional and site-aggregated studies included. A major strength is that a quality assessment tool based on published recommendations was conducted to define the final review inclusion.

The evidence presented supports the primary conclusion that overall HRQoL and some specific QoL domains are adversely affected after radiotherapy, with an eventual return to approximately the pre-treatment baseline. The review also states that this “return to baseline” may in fact represent patient adaptation or a response shift related to lower expectations relative to their treatment nadir and perceptions of their pre-treatment HRQoL from that experience. It is striking that only one study included controls and that study supports the idea that an acceptable or perceptible baseline HRQoL for HNSSC patients has moved to an inferior level compared to that of their pre-HNSSC life. The issue of what baseline means in terms of optimum HRQoL for these patients deserves further investigation to truly establish the goalposts that clinicians and researchers should be striving to achieve for HRQoL outcomes with cancer treatment. It appears that IMRT has less of an effect on HRQoL than conventional radiotherapy or 3D-CRT, so achieving the goal of minimizing sequelae by using IMRT may also be supported.

Regarding the added effect of chemotherapy on HRQoL, the literature is too sparse for any meaningful conclusions, although the limited number of available reports suggests that trends were for worse HRQoL. Additional well-designed HRQoL outcome studies in HNSSC patients for evidence assessment are needed comparing radio/radio-chemotherapy, as well as site-specific HRQoL outcomes. One reviewed paper identified baseline HRQoL as predictive of survival. Although this single report cannot be taken as definitive evidence, the finding
suggests a relevant HRQoL/disease process interrelationship that may have treatment implications and is a hypothesis that should be a priority research topic.

An additional purpose of the systematic review was to assess the quality of the peer-reviewed literature of HNSSC HRQoL outcomes. The application of the quality criteria limited the final review to 18 of the 53 eligible papers meeting inclusion criteria and resulted in the report that “…several potentially high-impact reports did not pass quality assessment.”\(^1\) Given that only one-third (18/53) of the eligible papers met quality criteria for final review inclusion and that the quality criteria are generally basic expectations in a methodology description, there is a potential loss of excellent data from studies that may well have been expertly conducted.

This systematic review highlights two issues of importance regarding HRQoL research: (1) there remain many areas of research to understand HRQoL as it applies to HNSSC treatments, site differences, and prognostic value and (2) reporting on study methodologies merit the comprehensive inclusion of operations in order to be a part of the evidence base.

The review primarily speaks to the head and neck cancer oncological community, including dentists involved in the treatment, support, and rehabilitation of HNSSC patients. More generally, the strong evidence that xerostomia is commonly a persistent adverse effect and may affect other domains such as eating and swallowing should be noted by all dental practitioners, as these patients often return to their community dentists with persistent therapy-induced problems related to oral health. This systematic review provides the current evidence on HRQoL by radiotherapy.

REFERENCES


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