Levels of scientific evidence of the quality of life in patients treated for oral cancer

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Received: 10/01/2013
Accepted: 03/02/2013

Abstract
Treatments used in cancer of the oral cavity have great impact on the physical, psychological and functional state of patients. There has been increasingly interest in evaluating the health-related quality of life using questionnaires among patients treated FOR oral cancer. Up to our knowledge no review on this theme has incorporated the level of evidence of the single identified studies. The objective of the present study is to determinate results and conclusions about the health-related quality of life of these patients, in view of scientific evidence. In general, the diversity of designs, level of evidence and questionnaires used for their assessment does not affect results, which indicate a decline in the health-related quality of life after treatment. This decline is greater when the tumor is large in size, and when radiotherapy is used, though the situation is seen to improve over the span of a year. Questionnaires on health-related quality of life provide concrete information regarding the impact of cancer treatment on patients.

Key words: Quality of life, oral cancer, questionnaire.
ment, changes associated with chewing, swallowing, salivating and speech are seen (2,3). Thus, the patient’s health-related quality of life (HRQoL) may be altered considerably. For these reasons, there is growing interest in evaluating the HRQoL using questionnaires among patients treated for oral cancer (4,5). The patient completed questionnaires are the most common method used to assess the HRQoL (2). They are composed for questions or items whose answers can be analyzed independently and be combined to obtain different domains (6).

The development of a hierarchy in the scientific evidence has allowed health professionals to do an evidence-based clinical practice (7). Up to our knowledge no review on HRQoL in patients treated for oral cancer has incorporated the level of evidence of the single identified studies. The aim of our study was to determinate results/conclusions about HRQoL drawn by studies of patients treated for oral cancer, and to identify possible differences according to the study design or level of scientific evidence.

Material and Methods
A bibliographic search was done using MEDLINE and Scopus databases, with the strategy (“oral cancer” OR “mouth neoplasms”) AND “quality of life” AND “questionnaire” in the period 1966-Dic 2012. Quality of life was used as the main search term, as it is a more common keyword than HRQoL (8). Furthermore, studies included in the bibliographic references of these papers were identified. After this initial search, the abstracts were read and the full paper if necessary, in light of the inclusion criteria in this study. The articles were included if they assessed the HRQoL, psychological aspects and/or functional aspects of patients treated for cancer of the oral cavity, oral and lip cancer, and/or oropharyngeal cancer, using a HRQoL questionnaire. The studies that incorporated other head neck cancers (nasal cavity, nasopharynx, larynx…) were excluded. This process resulted in 79 articles, referring to 62 independent studies. After that, the documents were classified according to their design as:

- Randomized clinical trials: randomized intervention studies where, after applying different treatments in cancer patients, the results are compared using HRQoL questionnaires.

- Studies of controlled cohorts: those evaluating the quality of life of the patients on one occasion (without repeated measurements) or on numerous occasions (longitudinal study), the results being compared with those of a control cohort or with populational data existing in the literature.

- Studies of non-controlled cohorts: longitudinal studies whose results were not contrasted with any other cohort.

- Transversal studies: those taking one measurement of the quality of life of patients without comparing results with any other cohort.

- Reviews: articles that offer an updated overview of the findings of previous studies.

Furthermore, the designs were coded according to the following levels of scientific evidence (9): 1 ++) Systematic review or meta-analysis of randomized clinical studies of a high quality or randomized clinical studies with a very low risk of bias. 1 +) Systematic review or meta-analysis of randomized clinical trials that were well conducted or randomized clinical trials with a low risk of bias. 1 –) Systematic review or meta-analysis of randomized clinical trials, or randomized clinical trials with a high risk of bias. 2 ++) Systematic review of cohort studies or case controls of high quality, or systematic review of cohort studies or case controls of high quality and entailing a low risk of confounding factors, bias or chance, and a high probability of causal association. 2 +) Studies of cohorts or case controls that were well conducted, with a low level of confounding factors, bias, chance and a moderate probability of causal association. 2 –) Studies of cohorts or case controls with a high level of confounding factors, bias, chance and a significant risk that the association was not causal. 3) Non-analytical studies, such as cross-sectional surveys or case series. 4) Expert opinions or non-systematic reviews.

No article selected for our study was excluded for methodological reasons (10,11). The authors summed up the main results and conclusions from the articles included under the different types of study designs. To achieve final consensus, a focal group was organized consisting of the authors of this article and following the Europe-Aid Evaluation Guidelines (12). Briefly, a focal group is a qualitative research technique that involves moderated meetings in the form of a structured, open group interview. After exposition and discussion of the different opinions, a final report was written up with the results and conclusions agreed upon.

Results
Table 1 shows the results of the bibliographic search conducted. There was an increase in the number of publications over time. We found that the general questionnaires were used in most often (European Organization for Research and Treatment of Cancer Quality of Life Questionnaires, EORTC-QLQ, closely followed by University of Washington Quality of Life Questionnaire, UW-QOL). Only four studies used the oral health impact profile (OHIP), a specific questionnaire for assessing changes in the oral health-related quality of life. The main results and conclusions from the articles are presented according to their design in the table 2. Only 2 experimental studies were found: one study classified as 1 ++ (maximum level of evidence), and another with
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The existence of a gold standard with unified criteria would allow the studies to be compared in a more rigorous manner. Overall, however, they do manage to cover the most common problems in a structured way, proving to be a useful tool for enhancing communication between health professionals and patients, which is essential in the area of cancer (6,13). Despite the heterogeneity of the designs, the results/conclusions are on the same line: a decrease in the HRQoL after treatment (14-22), which appears to parallel the magnitude of the tumor (2,4,23-31), and the use of radiotherapy (2,4,5,29,32-40). After a year, this declining trend turns around (15,16,18,20,22,41-47). The improvement in HRQoL over time is a result to be taken with some caution. Coping mechanisms, or adaptation to a new situation, may be one reason, but we must not forget that the data are based on surviving patients without relapse.

The existence of two randomized clinical trials evidences the practicality of incorporating the measure of HRQoL in these types of studies. Accordingly, HRQoL would have sufficient scientific backing to become a key consideration in the treatment planning process, as in situations where there are virtually no differences in associated survival rates (48). Moreover, we should underline the lack of studies with controlled cohorts. The most of them compare the results of the patients with populational data or with the results of their partners/spouses whose life quality is likewise affected by the illness (3,49). It would be interesting to carry out new research studies designed in such a fashion that each patient would have a control paired up by age and sex that would allow for comparison of results in a less biased way.

Despite therapeutic advances and enhanced survival, oral cancer patients inevitably face some decrease in HRQoL (28,50). They are not always satisfied with the information received, especially in relation to the changes they experience in their lifestyle after treatment(51,52). Health professionals have a variety of validated questionnaires, allowing them to familiarize themselves with the after-effects of oral cancer and therapy to the improvement of this communication. Online questionnaires can be used to overcome the lack of time and resources of health professionals dealing with these patients (53).

In conclusion, the diversity of study designs (level of evidence) does not appear to affect the results of studies. Construction of a standard questionnaire and its use in studies with a high scientific level of evidence would help make the differences found in the HRQoL become an important element in planning treatment for patients with oral cancer.

Discussion

Quality of life has been considered to be an important outcome parameter in oral cancer (8), which explains the increasing number of studies on HRQoL found over the time period analyzed here. There is great diversity in the questionnaires used, or even combined, perhaps due to the fact that the concept of HRQoL is associated with multiple functional and psychosocial factors. The existence of a gold standard with unified criteria would allow the studies to be compared in a more rigorous manner. Overall, however, they do manage to cover the most common problems in a structured way, proving to be a useful tool for enhancing communication between health professionals and patients, which is essential in the area of cancer (6,13).

Table 1. Summary of the bibliographic search.

| Number of articles |
|-------------------|
| **Period**        |
| 1984-1987         | 2 |
| 1988-1991         | 2 |
| 1992-1995         | 4 |
| 1996-1999         | 11 |
| 2000-2003         | 9 |
| 2004-2007         | 13 |
| 2008-2012         | 38 |
| **Total**         | 79 |

| **Location of tumor** |
|-----------------------|
| Oral cavity           | 33 |
| Oral and oro-pharyngeal cavity | 22 |
| Oral cavity and lip   | 6 |
| Base of the tongue    | 5 |
| Oral cavity, oro-pharyngeal cavity and lip | 5 |
| Bottom of the mouth   | 4 |

| **Questionnaire used for HRQoL** |
|----------------------------------|
| EORTC-QLQ<sup>a</sup>           | 26 |
| UW-QOL<sup>b</sup>              | 22 |
| PSS-HN<sup>c</sup>              | 8 |
| SF-36<sup>d</sup>               | 6 |
| OHIP<sup>f</sup>                | 4 |
| Others<sup>g</sup>              | 15 |

| **Design**                      |
|---------------------------------|
| Randomized clinical trial       | 2 |
| Controlled cohort study         | 10 |
| Non-controlled cohort study     | 29 |
| Cross-sectional study           | 34 |
| Review                          | 4 |

<sup>a</sup> Review articles not included. The sum of the articles of this section is not equal the total of articles found because some of them combine questionnaires listed in the table.
<sup>b</sup> EORTC-QLQ: European Organization for Research and Treatment of Cancer Quality of Life Questionnaires.
<sup>c</sup> UW-QOL: the University of Washington Quality of Life.
<sup>d</sup> PSS-HN: the Head and Neck Performance Status Scale.
<sup>e</sup> SF-36: Medical Outcomes Study Short Form 36-item Health Survey.
<sup>f</sup> OHIP: Oral health impact profile.
<sup>g</sup> Studies not using EORTC, UW-QOL, PSS-HN, SF-36, or OHIP.

There were 10 controlled cohort studies, with a 2 + level of evidence, whose results were not conclusive. The 29 studies of non-controlled cohorts together with the 34 cross-sectional studies (level of scientific evidence 3) plus the 4 reviews found (level of evidence 4) make manifest that the patients treated with radiotherapy have a poorer HRQoL.
Table 2. Summary of main findings/conclusions from studies, according to study design and level of evidence.

**Randomized clinical trial, with level of evidence 1++**
- Changes in the amplitude of the shoulder at six weeks and at six months are associated with changes in the HRQoL (54).

**Randomized clinical trial, with level of evidence 1+**
- The patients who are trained in swallowing obtain better scores on the HRQoL questionnaire than the patients who receive no such training (55).

**Controlled cohorts, with level of evidence 2+**
- The average impact on oral HRQoL (OHQoL) is between 29% and 71% higher (worst OHQoL) in the patients than in the general population (21).
- In terms of HRQoL, there is no consensus. Some studies report it to be worse than for the control cohort [two times as many subjects in the patient cohort affirms having problems in at least one domain (50), or the mean scores in their QoL are between 7% and 78% less (57)], whereas other studies find them to be similar (3,45,49,58-60).
- Patients who have not received radiotherapy have higher salivary flow rates and significant better results for physical function, dyspnea, swallowing, social eating, dry mouth and nutritional support (61).

**Non-controlled cohorts, with level of evidence 3**
- Better HRQoL before and six months after treatment are predicting factors of greater survival rates (22,36,62).
- Patients receiving combined treatment (surgery plus radiotherapy and/or chemotherapy) have between 10% and 28% lower mean scores in HRQoL one year after treatment as opposed to patients who have only surgical treatment (15,35,37-39,63), and as much as 54% less in domains such as chewing or dryness of the mouth (36,64).
- Compared with pre-treatment, the mean scores in HRQoL are between 8% and 31% lower after treatment (14,15,17-20,22,65,66). Accordingly, at one year’s time, they are 1% to 20% better (15,17,18,46,65), or scores similar to those of pre-treatment are obtained (22,42,43,45,50,67,68).
- Survivors present a significantly reduced overall rating of HRQoL at 1 year follow-up (69).
- Patients with larger tumours and neoplasms in the posterior part of the mouth present poorer quality of life (28).
- Hyperbaric oxygen therapy may positively influence the long-term radiotherapy sequelae (70).
- Older age, eating difficulty, speech difficulty, and depression are significant predictors of orofacial pain generated after surgical and radiation therapy (71).
- The functional results of soft palate reconstruction are superior to total anterior tongue resection (72).

**Cross-sectional studies, with level of evidence 3**
- Patients with a tumor over 4 centimeters in size have average scores in domains such as physical state, cognitive function, eating in public or dryness of the mouth that are 11% to 70% lower than patients with smaller tumors (4,23,27,31).
- Patients treated with radiotherapy have mean HRQoL scores 8% lower than patients who do not receive radiotherapy (34). In domains such as eating or chewing the mean scores may be as much as 29% lower (5,33,34,40).
- Chemotherapy, as the initial treatment, combined with radiotherapy or followed by surgery, leads to HRQoL scores similar to those obtained with other therapies (surgery followed by radiotherapy) (73,74).
- There are authors who find that the type of mandibular resection does not affect HRQoL (33). Others conclude that patients with continuity resections have significantly worse values in the HRQoL domains than patients with only partial resections (75). Restoration of mandibular continuity after hemimandibulectomy leads to improved function and a superior HRQoL in appropriately selected patients (76).
- The existence of functional problems is associated with higher levels of depression (4,77,78) and with impairment of postoperative HRQoL (79,80).
- After treatment of oral cancer and prosthetical rehabilitation, men show a significantly higher OHQoL than women (81).
- HRQoL is similar between patients treated with selective neck dissection and patients treated with sentinel node biopsy procedure (82).
- After ablative surgeries, patients reconstructed with free flap have better speech and shoulder functions as well as better mood status than patients reconstructed with pectoralis major myocutaneous flap (83). When the reconstruction with free flap involves the commissure, HRQoL is lower than other places in the oral cavity (84).
- Patients who have had resections and reconstruction with free anterolateral thigh perforator flaps describe problems with chewing, taste and saliva and low scores in the domains handicap, psychological disability and social disability (85).
- Older patients (65 years or over) report better physical and emotional function than younger patients (86,87).
- Prevalence of clinical anxiety and depression is with within the range 22%-32% in the patients that underwent major surgery (88).
- Primary radiation for advanced base of tongue cancer achieves excellent functional status and HRQoL (89-91).
- Total glossectomy produces important problems with eating, speaking and socializing (92,93).
- Local reconstructive methods are successful in the management of early oral cancers involving the tongue and floor of mouth and patients report satisfactory levels of quality of life (94).

**Reviews, with level of evidence 4**
- With regard to gender, there is no consensus about the existence of differences in HRQoL (2,6).
- Regarding age, young patients have a poorer emotional function and a greater risk of psychological stress. Older patients have poorer scores in physical function (2,6).
- Poorer HRQoL is seen with tumors located in the posterior region, larger tumors and patients who are treated with radiotherapy or cervical surgery (2,6,47).
- Prospective studies are needed over longer time periods to define the duration of symptoms (95).
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Acknowledgements
This study was financed by Programa de Formación del Profesorado Universitario del Ministerio de Educación, Cultura y Deporte and Research Group CTS-503 (Dental Public Health, University of Granada).