

HRQOL in Oral Cancer Patients

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The scope of the present entry was to highlight possible sources of bias that could be encountered when evaluating HRQOL (Health-Related Quality of Life) in patients treated for oral cancer. The second aim was to lay the foundation of a standardized protocol for cohort selection, data collection, and stratification that could enhance knowledge in the field.

Keywords: quality of life ; HRQOL ; head ; neck ; oral cancer ; oncology

1. Introduction

Patient-reported outcomes (PROs) provide precious information about troubles in everyday life and the perception of psychological and physical wellness from the patient's perspective. Over recent decades, PROs have gained more relevance in treatment decision making, so much so that the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) consider them — including the quality of life — as a relevant end point to approve new therapies ^{[1][2][3]}. To approach such a complex topic as the quality of life in oncological patients, they commonly refer to health-related quality of life (HRQOL). A distinction between these concepts has been made to exclude influences from domains that are not related to the patient's health status ^[4], at least theoretically.

The concept of “quality of life” was firstly introduced by Heckscher ^[5], and in 1977 was adopted as a “keyword” by the United States National Library of Medicine ^[6]. Since then, several definitions have been proposed ^{[7][8]}. The WHO defined quality of life as “individuals perceptions of their position in context of the culture and value systems in which they live and in relation to their goal, expectations, standards, and concerns” ^[9].

Head and neck tumors and their treatment may negatively affect patients' HRQOL, which is considered an essential secondary outcome of treatment nowadays ^{[10][11]}. For this reason, having reliable evaluation tests is mandatory to better understand how and why specific medical interventions should be chosen and adapted according to individual needs. The quest towards the perfect quality of life evaluation test led researchers to understand some key points to be focused on: a test should be reproducible, sensitive, and easy to understand ^[12]. Questionnaires developed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group are widely used in current literature to address these needs. A core questionnaire (EORTC QLQ-C30) is associated with site-specific validated modules (EORTC QLQ-H&N35/43), consisting of single- and multi-item scales that measure several head and neck symptoms ^{[13][14]}.

HRQOL is a complex topic and needs to be analyzed taking into account every potential influencing factor. Various sociodemographic, disease-specific, and treatment-specific aspects have been recognized as affecting HRQOL ^{[12][15][16][17][18][19][20]}. Several researchers have investigated its intrinsic multidimensionality, concluding that HRQOL plays a role in treatment decision making, but none have verified what the relevant items are and how this feature is assessed. The scope of the present review was to highlight possible sources of bias that could be encountered when evaluating HRQOL in patients treated for oral cancer. The second aim was to lay the foundation of a standardized protocol for cohort selection, data collection, and stratification that could enhance knowledge in the field.

2. Disease- and Treatment-Specific Variables

2.1. Cancer Site

Although HRQOL in HNC patients has gained great relevance during recent decades, most published studies still have not considered that cancer site might have a significant impact ^{[21][22][23][24][25][26]}. Indeed, the most common reason for exclusion in the screened articles was directly related to this aspect (**Figure 1**). This potential source of bias is scantily contemplated concerning the HNC regions (e.g., oral cavity, oropharynx, larynx, etc.), and much less considering oral subsites.

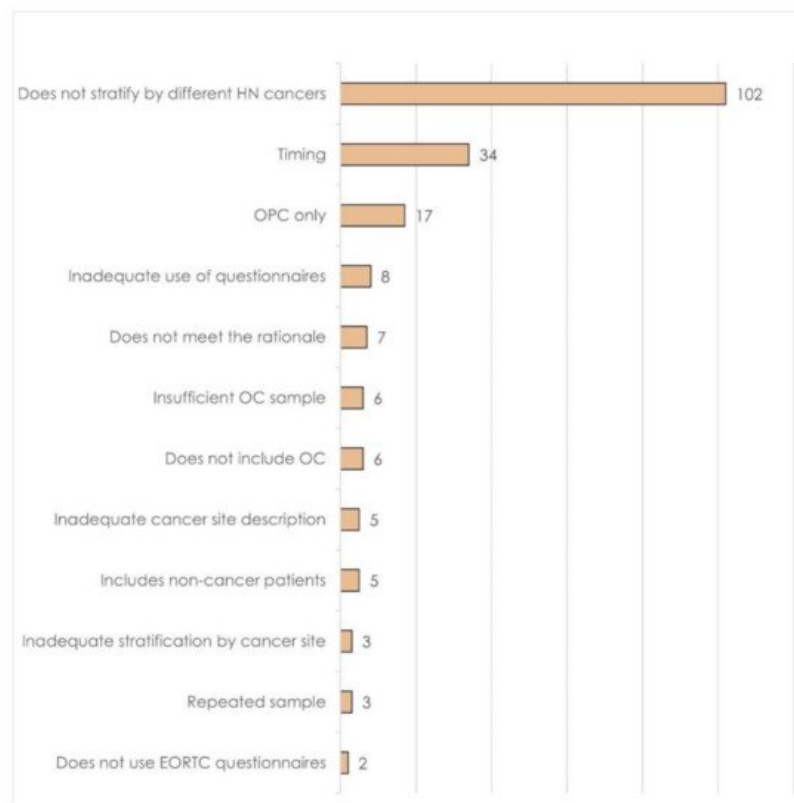


Figure 1. Reasons for the exclusion of the screened articles.

Interestingly, findings reported by Kovacs et al. [22] demonstrated that cancers arising from different oral subsites differently affect HRQOL, while Pierre et al. [24] and van Gemert et al. [27] found no significant variations. Such controversies should be addressed by analyzing larger samples that allow performing a more reliable data stratification. At the same time, it must be highlighted that the cohort selection would overcome this issue by including more homogeneous cases, as performed by some included articles [28][29][30][31][32].

2.2. Cancer Stage

Most likely, the cancer stage represents one of the most challenging variables to correlate with HRQOL, since the multitude of baseline confounding must be considered. For example, compared to early-stage cancers, advanced stages require more frequently adjuvant therapies and they need more extensive surgeries, which may include a mandibular resection, implying more demanding reconstruction strategies. The appraisal of findings reported by Beck-Broichsitter et al. [33] and Becker et al. [34] provided a clear demonstration of possible controversies that could be encountered due to some omitted variable biases. The authors compared the same T-stage subgroups (Tis-2 vs. T3/4) and one found no significant differences, while the other reported worse results for almost all questionnaire items in advanced-stage cancers. Controversies like this are repeatedly presented in the screened papers, some reporting no differences [35][36][37][38], others reporting substantial ones [9][39][21][24].

In our opinion, the cancer stage could be considered in a wider context, including almost all baseline confounding. The only exception is represented by those middle-stage cancers that could or could not be eligible for adjuvant therapies based on clinical and histological features. Future studies will provide adequate piece of evidence to reliably correlate these variables.

2.3. Mandibular Resection

Although it has been previously stressed that mandibular resection strongly impairs patients' HRQOL [16][40], the generic findings of included studies are inconsistent. Becker et al. [34] were the sole researchers reporting worse results in patients undergoing mandibular resection compared to those who did not. A mandibular resection group was also studied distinguishing marginal from segmental resections. Unsurprisingly, the former demonstrated better questionnaire results.

Like most of the selected variables, the controversies observed among included articles suggest the existence of baseline confounding. We suppose that the need for adjuvant therapies (particularly the RT), the reconstruction, the cancer stage, and the extent of surgical resection could be the most probable sources of bias, since the mandible involvement is commonly associated with advanced cancer stages.

2.4. Extent of Resection

Van Gemert et al. [27] were the sole researchers who stratified the studied sample according to the extent of resection (specifically in the horizontal size). Conversely to what was documented elsewhere [16][41], they reported minimal differences. Since the current knowledge in reconstructive techniques allows surgeons to adequately restore even complex and extended defects, the authors suggest that accurate and successful reconstructions could justify these findings. We agree with this hypothesis, despite the fact that surgical complications and secondary surgery must be excluded or carefully examined during data analysis to ensure the absence of possible omitted variable biases. Thus, influences from the aforementioned baseline confounding (see cancer stage paragraph) should be considered.

2.5. Surgical Approach

Within the included studies, the impact of the surgical approach on HRQOL was supposed to explain some of the findings. Ferri et al. [29] were the only ones who considered this variable for data analysis. They compared two different treatment protocols: transoral partial pelviglossectomy followed by a buccinator artery myomucosal flap versus a pull-through partial pelviglossectomy followed by various free flaps. Significantly better results were reported in the former group.

The comparison of different surgical protocols implies taking into account some baseline confounding. For example, the pull-through resection involves various deep structures of the mouth floor that can more likely be restored by using free flaps [42], as clearly recognized by the authors. The cancer stage, adjuvant therapies, and the extent of resection also represent possible baseline confounding variables, since the cancer extent might force the surgeon to choose more invasive surgical approaches.

As reported elsewhere in the literature, the surgical approach seems to impact HRQOL in treated patients. Although disease-free survival still represents the primary outcome, minimally invasive approaches should be considered whenever it is possible, in order to reduce post-operative morbidity [43][44][45][46][47].

2.6. Neck Dissection

Some contradictory results were retrieved from the included studies concerning the ND as an HRQOL determinant. Kovacs et al. [22] described progressively worse results comparing patients who did not receive ND to those treated by selective ND (lev. I–II) and those by type III modified radical ND. We agree with the authors' opinion about the possibility of baseline confounding since patients undergoing ND most frequently even underwent adjuvant RT. Future studies comparing patients receiving RT/CRT only and those treated by surgery with neck dissection and adjuvant RT/CRT will probably clarify these doubts.

2.7. Reconstruction

Unsurprisingly, reconstruction was the most investigated among surgery-related variables. It is commonly believed that the quality of reconstruction is strictly associated with patients' functional and aesthetic outcomes and post-treatment HRQOL [48][49]. Knowledge in reconstructive surgery has been taking great strides forward since free flaps were introduced for the restoration of head and neck defects [48][49][50]. Performing a systematic review of the literature on reconstructive strategies in patients not eligible for free flaps, we surprisingly highlighted a growing interest toward more conservative solutions over the last few years [51][52][53].

Despite the huge literature, reconstruction still raises disputes about which surgical reconstructive protocol is the best to restore oral defects [54][55][56][57][58][59]. Similarly, the findings reported by included studies showed widely controversial results. In this regard, it should be noticed that huge differences within the studied populations do not permit a reliable comparison of the observed outcomes. In our opinion, the evaluation of the impact of reconstructive procedures on HRQOL implies several risks of bias that must be considered. For instance, careful attention should be paid to patients who developed surgical complications, by excluding them or by performing an accurate sample stratification. Furthermore, the related complications may heavily impair the functional outcome, requiring a much longer recovery time, long-term rehabilitation programs, or even secondary surgery. Moreover, according to the chosen procedure, free flaps may lead to various donor site morbidity [60][61]. All these aspects should be considered for their potential effects on HRQOL.

Reconstruction strategies are mainly chosen according to the defect size and composition: small to moderate simple defects may benefit from reduced donor site morbidity by performing local flaps, while large and/or composite defects need free or regional flaps to be restored [51][62]. Therefore, the evaluation of the reconstruction as an HRQOL determinant should consider some baseline confounding variables, such as the cancer stage, the extent of resection, the mandibular involvement, and the adjuvant therapies. None of the included studies considered simultaneously all these independent

variables during the data analysis. Conversely, many of them investigated various reconstructive procedures grouping different flaps together. In our opinion, a reliable comparison should firstly consider the studied flaps separately to minimize evitable biases.

2.8. Radiotherapy and Chemotherapy

Almost all the included studies agreed about the deteriorating effects of radiotherapy on HRQOL. Kovacs et al. [22] performed an accurate study comparing patients who received adjuvant RT, adjuvant CT, or adjuvant CRT. Interestingly, there were no significant differences between adjuvant RT and adjuvant CRT groups, which both demonstrated significant worse results compared to patients who did not undergo post-surgical therapies.

Some symptom-related items were found to be particularly affected: dry mouth, sticky saliva, and mouth opening were almost always impaired. These findings were in line with those already widely reported in the published literature [63][64][65][66][67][68][69].

The evaluation of HRQOL demonstrated less interest in studying the effects of neoadjuvant therapies and adjuvant CT alone. This could be attributed to the uncommon use of these treatment protocols in HNC and it would be interesting to investigate the existence of different influences on HRQOL between neoadjuvant therapies and post-surgical ones.

Further compelling aspects derive from the adopted RT technique. The accurate analysis performed by Huang et al. [39] underlined that the most recent 3D radiotherapy (3DRT) and the intensity-modulated radiotherapy (IMRT) result in a better impact on patients' HRQOL, as largely accepted in the current literature [70][71]. Nevertheless, most included studies did not specify which techniques were used in the studied samples, producing a relevant source of bias.

As mentioned above, adjuvant therapies suffer from several baseline confounding factors that should be always considered during the data appraisal. Nonetheless, the trends in the reported findings overtly suggest that it can be considered as one of the main HRQOL influencing factors.

2.9. Synchronous Lesions, Recurrences, and Metachronous Lesions

Although rare, the presence of synchronous lesions in the oral cavity inevitably requires larger resective surgeries that negatively influence the HRQOL, but only three studies clearly excluded these patients [28][29][38].

On the other hand, it might appear obvious that a recurrence of previously treated tumors or the development of further cancers may strongly impair HRQOL, especially by affecting psychological status and symptoms [72][73][74]. Nevertheless, only 12 of the included papers considered this aspect during cohort selection [33][75][29][39][21][76][37][31][23][24][27][38]. Mair et al. [31] were the only ones who conducted an analysis to compare disease-free patients to those who developed a recurrence. Their results strongly support the initial hypothesis, but we should make a point to note the potential sources of bias that might be encountered. Indeed, progression-free survival strongly depends on the cancer stage, which also reflects the invasiveness of the adopted treatment.

2.10. Major Surgical Complications and Secondary Surgery

Only a minority of the included studies considered these variables. Girod et al. [77] investigated the differences between the reconstruction of OC defects by using split thickness skin graft and acellular dermal matrix. They stratified the results by surgical complications, distinguishing patients who experienced a graft failure from those with regular healing. No significant differences were found, but the small sample size and the missing stratification by other variables might have affected their results.

It is reasonable to believe that post-surgical complications and recurrences may impact the HRQOL. In our opinion, this might be related to the resulting functional and aesthetic impairments or to the need for secondary surgery, which may impair the psychological status and the symptoms [72][73][74]. The included studies did not investigate this relation and it could be an interesting food of thoughts for future studies.

3. Conclusions and Recommendations for Future Studies

The number of controversies found in the current literature demonstrates a substantial lack of evidence regarding HRQOL determinants in HNC patients. Therefore, none of the potential influencing variables should be excluded from data analysis based on the authors' opinion only.

Currently, many of the published articles considered a minority of potential determinants. The data analysis is commonly performed on the basis of each independent variable individually. By approaching such a complex and multidimensional aspect as the HRQOL in this way, the reliability of the reported findings might be strongly weakened due to several selection and omitted variable biases that could be encountered. Since the EORTC Quality of Life Group was founded in 1980, a standardized guideline for cohort selection is still lacking. Thus, the crucial task to avoid the described biases is charged to examiners' knowledge only.

We strongly believe that almost all the identified determinants should be investigated. This implies that much larger samples and much more data must be collected. At the same time, particular attention should be paid to cohort selection to achieve better comparability among the studies. This scope will probably be attained by creating a shared and standardized online data set.

Considering the complex net of baseline confounding highlighted in this manuscript, a suitable strategy could be the use of further evaluation tools, scales, and indexes that condenses many variables in a single score. In our opinion, the benefits from this approach are twofold: a simplification of data analysis and a minimization of omitted variable biases. In this regard, an interesting investigation was performed by Tribius et al. [78] regarding the influence of sociodemographic variables on HRQOL in HNC patients. This study used an adapted version of a composite social class indicator [79] that considered three different sociodemographic variables (educational level, type of occupation, and household income) to differentiate the socio-economic status as high, moderate, or low. Other examples were reported within the discussion of this review (G8, ACE-27, KFI, HADS), but those were related to sociodemographic and psychological variables. To the best of our knowledge, no scoring systems that condense the selected DT-specific variables have been developed yet. Our recommendation for future research is to consider these features simultaneously, rather than individually, addressing the baseline confounding described above, and to select cohorts that are as homogeneous as possible. An example of this protocol is given by Ferri et al. [29] and Canis et al. [28], who performed some accurate cohort selections resulting in quite a small sample size, but one that was highly homogeneous and reproducible.

As observed by Borggreven et al. [35], patients usually present compromised HRQOL at the baseline, probably due to preexisting impairments related to comorbidity status or cancer diagnosis. We believe that this issue could be addressed by evaluating only the differences between baseline and post-treatment questionnaires in a longitudinal study design, rather than in absolute scores compared to a reference population in a cross-sectional fashion, even though the interquestionnaire analysis may highlight interesting insights [80].

As a result of this approach, more homogeneous, reproducible, and comparable cohorts will be expected, enhancing the level of evidence in the field.

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