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Original article

Quality of life in head and neck cancer: Patients' and family caregivers' perceptions

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ABSTRACT

Introduction: As the Quality of Life (QoL) in patients with head and neck cancer (HNC) is a significant aspect, outcomes are increasingly important to understand. We report the social/emotional and physical function outcomes in a cohort of surviving patients with HNC treated with primary surgery and/or chemoradiotherapy.

Patients and methods: Fifty-six patients with HNC treated with primary surgery and/or chemoradiotherapy, and their caregivers were identified between November 2016 and June 2017. University of Washington Quality of life (UWQoL) and EuroQoL (EQ-5D-5L) health questionnaires were given to all patients and caregivers. A paired *t* test was performed to compare the difference in the results of questionnaires between patients and caregivers.

Results: The analysis showed no significant difference between the responses of patients and caregiver, except for the anxiety domain. In the UWQoL questionnaire, patients scored higher in anxiety than caregivers ($p = .023$). On the contrary, in the EQ-5D-5L questionnaire, the anxiety/depression score was higher in caregivers than patients ($p = .019$).

Conclusions: Both patients and caregivers agreed in the perception of patients' quality of life. This final outcome supports the use of the questionnaires. The only domain that differed was the anxiety domain. The concept of anxiety may be more difficult to define due to its heterogeneity. Moreover in the EQ-5D-5L questionnaire anxiety is put together with depression, which probably is a more complex concept to look at.

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1. Introduction

Head and neck cancer (HNC) is the 10th most common cancer in the world, with an estimated over 500,000 new cases being diagnosed annually. Squamous cell carcinoma (SCC) represents more than 95% of all head and neck cancers.¹ The term "Head and Neck Cancer" encompasses a wide range of tumors that occur in several areas of the upper aerodigestive tract, including the oral cavity, pharynx and larynx. This region is the site of basic functions, such as speech, swallowing, hearing, breathing, associated with social interaction, which is of vital importance to the individual.²

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HNC can cause profound effects on all aspects of patient quality of life for many years even after treatment. Particularly, patients with head and neck cancer have to face the impact of treatment on functional and aesthetic aspects.^{3,4}

The strategies of treatment are different, mostly surgery almost always associated with radiotherapy. Adjuvant therapies include chemotherapy and immunotherapy. Surgery may cause permanent mutilations, loss of organs or changes to their functions. Changes in appearance, voice and difficulties swallowing, can cause certain limitations. Usually, pain, limitation in activity, chewing, speech and swallowing play an important role in the patient's loss of self-esteem and social isolation. All these factors, together with complications, change the perception of their life and may create a negative impact on the quality of life of these individuals.⁵

Quality of life can also be associated with the individual's degree of satisfaction found in the relationship (family, love and social life).⁶

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To assess the quality of life of the patients affected by HNC cancer is important in order to understand the impact of the disease and its treatment in the patient's daily routine and try to focus on aspects that can improve the support measures. QoL is a subjective assessment of the impact of a condition or treatment on a patient's life, incorporating his or her physical, psychological, social and somatic functioning and general wellbeing.^{7,8}

Patients with HNC report significant and persistent physical, functional and psychosocial problems. Given that, QoL assessments have been recognized as very important, often owing to the extensive functional impact of disease and treatment so, it is not surprising that QoL has become an important treatment outcome in HNC.^{9,10}

The aim of this study was to better evaluate the patient's reported QoL and relate it to how the caregiver perceives it.

2. Patients and methods

This study is a paired cohort study, analyzing QoL data of HNC patients, and their caregivers, who were treated with primary surgery and/or chemo-radiotherapy at ENT Unit – Santa Marta and Santa Venera Acireale Hospital during the period from November 2016 to June 2017. Ethical clearance was obtained from ethical committee of Unità Operativa Complessa (UOC) di Otorinolaringoiatria – ASP 3 CT, P.O. Acireale and informed consent was taken from each subject.

Data from the notes were recorded from all patients to identify important parameters such as patient demographics (age, sex, BMI), the presence of comorbidities, social habits, caregiver relationship to patients, tumor site and staging (in according to the AJCC Staging Manual),¹¹ histological diagnosis and type of treatment. The inclusion criteria were: 1) aged over 18 years, 2) regular follow-up at our ENT Unit, 3) completion of the self-reported questionnaire both patients and their caregivers. Patients were excluded if they were having palliative treatments on-going and mental or cognitive impairments. Two kinds of quality of life questionnaires were given to all patients and caregivers. Questionnaires included the University of Washington Quality of life Questionnaire (UWQoL)¹² and the EuroQol 5D-5L Health (EQ 5D-5L) questionnaire.¹³

UWQoL is divided into 12 questions that assess domains such as pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety. Symptom scores for the UWQoL questionnaire range from 0 to 100 (maximal function = 100). For a better evaluation of the score, as suggested in a previous paper¹², the domains were assembled into two groups: social/emotional function and physical function. The EQ-5D-5L questionnaire is divided into 5 questions that assess domains as mobility, self-care, usual activities, pain/discomfort and anxiety/depression and it has five levels of severity (no problems, slight problems, moderate problems, severe problems and extreme problems).

Primary outcome measures were to identify any difference in the results of questionnaires from patient and caregiver analyzing outcomes for individual symptoms and physical and social/emotional domains scores for UWQoL and distribution of EQ-5D-5L response calculated for each domain between the two groups. The data were analyzed with the statistical software StatsDirect 2.7.8 (StatsDirect Ltd, England), and were evaluated using paired *t* test. The results were considered significant at $p < .05$.

3. Results

Out of the 56 patients, 37 were male and 19 were female. All patients filled the questionnaires but 3 of the caregivers refused

Table 1
Demographic details of study population.

| Characteristics | Number of patients (n) | Percentage Frequency (FP) |
|--|------------------------|---------------------------|
| <i>Age, in years</i> | | |
| <55 | 11 | 19.6% |
| 55–64 | 12 | 21.4% |
| 65–74 | 24 | 42.9% |
| 75+ | 9 | 16.1% |
| <i>Gender</i> | | |
| Male | 37 | 66.1% |
| Female | 19 | 33.9% |
| <i>BMI</i> | | |
| <18 | 2 | 3.6% |
| 18–24 | 20 | 35.7% |
| 25–30 | 24 | 42.9% |
| >30 | 10 | 17.9% |
| Presence of comorbidities | 20 | 35.7% |
| <i>Social habits</i> | | |
| Smoking alone | 21 | 37.5% |
| Alcohol alone | 8 | 14.3% |
| Both | 10 | 17.9% |
| None | 17 | 30.4% |
| <i>Caregivers relationship to patients</i> | | |
| Wife/Husband/Partner | 43 | 76.8% |
| Son/Daughter | 10 | 17.9% |
| Sibling | 1 | 1.8% |
| Caregiver | 1 | 1.8% |
| Other (cousin, close friend) | 1 | 1.8% |

to fill it due to time, so the final outcomes are based on 53 couples. Full demographic details for all patients are shown in Table 1. The most represented site involved by tumor was pharynx (32.1%) followed by larynx (21.4%) and salivary glands (17.9%) and the SCC was the most common histological tumor type (60.7%).

The majority of tumors were on stage 2 or 4 (32.1% and 25%, respectively), a smaller proportion on stage 1 or 3. Out of 56 patients, a 35.7% underwent primary surgery plus radiotherapy, 25% underwent primary surgery plus chemoradiotherapy, 17.9% were treated only with radiotherapy and 16.1% underwent only primary surgery. Full cancer details for all patients are shown in Table 2.

The analysis of UWQoL outcomes found no significant difference between patients and caregivers groups for all the different domains except for the anxiety domain where, patients had a higher score than caregivers (73.52 ± 21.92 vs. 62.54 ± 26.46 , $p < .05$) (Table 3).

Likewise, the analysis of the distribution of responses to mobility, self-care, usual activities and pain/discomfort EQ-5D-5L dimensions didn't show any significant difference between the two groups except for the anxiety/depression domain where, caregivers are reported to have higher number of cases than patients ($p = .019$) (Table 4).

4. Discussion

Recently, after the recognition of the huge impact of head and neck cancer has on patients' life, increased research has focused on better investigation about their quality of life, as it is recognised that both the diagnosis and treatment for HNC can have a significant impact on QoL.¹⁴ Much of the recent articles have focused on the management of QoL according to the patient's point of view⁵ or the impact of cancer in caregivers' life.¹⁵

Currently, there are few studies that address the quality of life of caregivers of patients with head and neck cancer and there are even fewer comparative studies between the two groups.

Table 2
Tumour site, histology, stage of disease and treatment modalities.

| Tumour Site | Number of patients (n) | Percentage Frequency (FP) |
|--|------------------------|---------------------------|
| Aerodigestive Tract | 38 | 67.9% |
| Oral cavity | 7 | 12.5% |
| Pharynx | 18 | 32.1% |
| Larynx | 12 | 21.4% |
| Sinonasal | 1 | 1.8% |
| Head and Neck | 18 | 32.1% |
| Salivary glands (parotid/submandibular) | 10 | 17.9% |
| Mandible | 1 | 1.8% |
| Face | 1 | 1.8% |
| Brain | 1 | 1.8% |
| Others (eye, neck, thyroid) | 5 | 8.9% |
| <i>Hystology</i> | | |
| Squamous cell carcinoma | 34 | 60.7% |
| Adenocarcinoma | 12 | 21.4% |
| Adenocystic carcinoma | 6 | 10.7% |
| Sarcoma | 1 | 1.8% |
| Others | 3 | 5.4% |
| <i>Stage of disease (TNM)</i> | | |
| Stage 0 | – | – |
| Stage 1 | 13 | 23.2% |
| Stage 2 | 18 | 32.1% |
| Stage 3 | 11 | 19.6% |
| Stage 4 | 14 | 25% |
| <i>Treatment modalities</i> | | |
| Radiotherapy | 10 | 17.9% |
| Surgery | 9 | 16.1% |
| Radiotherapy + surgery | 20 | 35.7% |
| Combination therapy (radio-, chemo- and surgery) | 17 | 25% |

Table 3
UWQoL domain scores for patients and caregivers groups.

| Domains | Patients Group (n = 53) Mean ± DS | Caregivers Group (n = 53) Mean ± DS | p |
|--------------------------------|--------------------------------------|--|------|
| <i>Emotional Function</i> | | | |
| Pain | 71.69 ± 26.51 | 65.66 ± 23.45 | .139 |
| Activity | 57.53 ± 20.32 | 55.31 ± 23.27 | .744 |
| Recreation | 66.62 ± 20.03 | 65.68 ± 23.95 | .911 |
| Shoulder | 72.61 ± 32.47 | 75.36 ± 35.11 | .327 |
| Mood | 71.31 ± 26.23 | 68.59 ± 22.87 | .272 |
| Anxiety | 73.52 ± 21.92 | 62.54 ± 26.46 | .023 |
| <i>Physical Function</i> | | | |
| Appearance | 73.23 ± 17.26 | 75.62 ± 15.22 | .467 |
| Swallowing | 55.51 ± 31.72 | 58.23 ± 26.43 | .681 |
| Chewing | 49.09 ± 31.38 | 55.98 ± 32.24 | .117 |
| Speech | 69.72 ± 23.09 | 73.28 ± 26.18 | .627 |
| Taste | 52.42 ± 34.18 | 53.13 ± 30.32 | .793 |
| Saliva | 56.64 ± 36.24 | 53.34 ± 36.64 | .464 |
| <i>Composite Soc/Emot Func</i> | 68.88 ± 24.58 | 65.52 ± 25.85 | .559 |
| <i>Composite Phys Func</i> | 59.44 ± 28.98 | 61.6 ± 27.84 | .453 |

* p ≤ .05.

According to us, the point of view of the caregiver is as important as the patient's one due to the role that the caregiver has in the patient's life. Any differences in QoL scores between these two groups may mean that an aspect of their care is being underreported. For this reason, we asked the patients followed at our clinic, and with caregivers present at that time, to fill two validated questionnaires for use in head and neck cancer patients: the UWQoL and EQ-5D-5L questionnaires,^{16,12} aiming to determine more details regarding their thought about patients' QoL.

In the present study, the results of UWQoL showed us an overall agreement between the two groups. Particularly, as regards physical functions and the results showed us no significant differences

Table 4
Distribution of EQ-5D-5L dimension responses for patients and caregivers groups.

| Domains | Patients Group (n = 53) n (%) | Caregivers Group (n = 53) n (%) | p |
|---------------------------------|----------------------------------|------------------------------------|-------|
| <i>Mobility</i> | | | |
| No problems | 18 (34) | 23 (43.4) | .457 |
| Slight problems | 12 (22.6) | 14 (26.4) | |
| Moderate problems | 14 (26.4) | 12 (22.6) | |
| Severe problems | 6 (11.3) | 5 (9.4) | |
| Unable to walk about | 3 (5.7) | – | |
| <i>Self-care</i> | | | |
| No problems | 33 (62.3) | 38 (71.7) | .442 |
| Slight problems | 9 (17) | 8 (15.1) | |
| Moderate problems | 9 (17) | 6 (11.3) | |
| Severe problems | 1 (1.9) | 1 (1.9) | |
| Unable to wash or dress | 1 (1.9) | – | |
| <i>Usual activities</i> | | | |
| No problems | 9 (17) | 7 (13.2) | .791 |
| Slight problems | 23 (43.4) | 25 (47.2) | |
| Moderate problems | 12 (22.6) | 11 (20.8) | |
| Severe problems | 9 (17) | 10 (18.9) | |
| Unable to do usual activities | – | – | |
| <i>Pain/discomfort</i> | | | |
| No pain or discomfort | 10 (18.9) | 14 (26.4) | .658 |
| Slight pain or discomfort | 12 (22.6) | 10 (18.9) | |
| Moderate pain or discomfort | 26 (49.1) | 25 (47.2) | |
| Severe pain or discomfort | 5 (9.4) | 4 (7.5) | |
| Extreme pain or discomfort | – | – | |
| <i>Anxiety/depression</i> | | | |
| Not anxious or depressed | 17 (32.1) | 5 (9.4) | .019* |
| Slightly anxious or depressed | 19 (35.8) | 13 (24.5) | |
| Moderately anxious or depressed | 10 (18.9) | 14 (26.4) | |
| Severely anxious or depressed | 6 (11.3) | 7 (13.2) | |
| Extremely anxious or depressed | 1 (1.9) | 14 (26.4) | |

* p ≤ .05.

between the group of patients and the group of caregivers. As regards social/emotional functions the results showed us an overall agreement between the two groups except for the anxiety domain in which patients scored higher than caregivers. Again, from the results of the EQ-5D-5L instrument, there was a high level of overall agreement between the two groups except for the anxiety/depression domain whom score was higher in caregivers than patients. This was different to the outcome from the UWQoL questionnaire assessing the same domain.

The exception is the anxiety domain. This perhaps is a difficult domain to compare as anxiety/depression is the only domain in which the caregiver can give a real subjective opinion without relating it to what the patients' thought could be. According to the DSM-V, depressive symptomatology, includes the follow: depressed mood; loss of interest and enjoyment in usual activities; reduced energy and decreased activity; reduced self-esteem and confidence; ideas of guilt and unworthiness; pessimistic thoughts; disturbed sleep; diminished appetite; ideas of self harm.¹⁷

It seems to be straightforward that the concept of depression includes many aspects and is a snapshot of symptoms that may be clearer to the person who cares the patient rather than the patient itself. A diagnosis of HNC has a profound impact not only on patients' life but also on family members who play a crucial role in their care. Having someone who sympathizes the conditions helps the HNC patient to accept the disease and loss of function.¹⁸

Frequently, the caregivers spend all the energies to improve the patients' QoL, taking a crucial role in patients' life, sometimes at the cost of their QoL.¹⁹

We can postulate that cancer is a sort of battle that, usually, patients fight due to two reasons: the attachment to life and the

wish to continue to live alongside those they love. By contrast, caregivers, especially partners, live actively and with compassion the illness of their loved ones. HNC is considered to be one of the most traumatic types of cancer. The prevalence of major depression is estimated to be 15–50% and the suicide rate has shown to be particularly high.^{20–22}

Researchers have demonstrated increased levels of distress in cancer patients after diagnosis, during active treatment and until 4 years after treatment.²³ Many research studies have focused on the impact of depression on treatment outcomes, such as mortality or disease progression, among cancer patients. However, depression is frequently underdiagnosed and consequently undertreated.²⁴ Therefore, early identification or prediction of depression is crucial and caregivers are the most critical figure to better understand the patients' progress. Both the questionnaires have proved to be very useful, as both the physical and the social/emotional experiences were taken into account. The concept of QoL is not monodimensional, but includes a number of life domains. It is generally considered that QoL is best defined and measured from the individual's perspective. Without the person's assessment of the meaning of his current situation, there is no way of balancing the experience.²⁵

The concept of QoL directs attention to "complete social and psychological being: the individual's performance of social roles, mental acuity, emotional state, sense of well-being and relationships with others".²⁶ QoL is a parameter that should always be considered in the assessment of patients with cancer due to its impact on the patients' life but is also important to keep in mind the perception of the most implicated people: caregivers.

5. Conclusions

This paired cohort study aimed to compare perceptions of QoL of between patients, all of whom have been treated for Head and Neck cancer, and their caregivers. Data from the UWQoL questionnaire and EQ-5D-5L health questionnaire reflect both the patient's perception and the caregiver's perception. All the items have received similar score both in patients and caregivers with the exception of the anxiety domain. Precisely, in the UWQoL questionnaire patients had a higher score in anxiety than caregivers. Contrarily, in the EQ-5D-5L the anxiety/depression score was higher in caregivers than patients. This queer result, opposite outcome in two apparently similar domains, led us to find a possible explanation. The concept of anxiety may be more difficult to define due to the heterogeneity of aspect involved in this word, moreover in the EQ-5D-5L questionnaire anxiety is put together with depression, which probably is a more complex concept to look at. This raises the possibility that this domain is not a good reflection on the caregiver's perception and may need further studies to evaluate its importance on QoL.

References

1. Chen YJ, Chang JT, Liao CT, et al.. Head and neck cancer in the betel quid chewing area: recent advances in molecular carcinogenesis. *Cancer Sci.* 2008;99:1507–1514.

2. Connor NP, Cohen SB, Kammer RE, et al.. Impact of conventional radiotherapy on health-related quality of life and critical functions of the head and neck. *Int J Radiat Oncol Biol Phys.* 2006;65:1051–1062.
3. Broglie MA, Soltermann A, Haile SR, et al.. Quality of life of oropharyngeal cancer patients with respect to treatment strategy and p16-positivity. *Laryngoscope.* 2013;123:164–170.
4. Grillo C, Saita V, Grillo CM, et al.. Candida colonization of silicone voice prostheses: evaluation of device lifespan in laryngectomized patients. *Otorinolaringol.* 2017;67:75–80.
5. Rathod S, Livergant J, Klein J, Witterick I, Ringash J. A systematic review of quality of life in head and neck cancer treated with surgery with or without adjuvant treatment. *Oral Oncol.* 2015;51:888–900.
6. Loewe N, Bagherzadeh M, Araya-Castillo L, Thieme C, Batista-Foguet JM. Life domain satisfactions as predictors of overall life satisfaction among workers: evidence from Chile. *Soc Indic Res.* 2014;118:71–86.
7. Ware Jr JE, Keller SD, Gandek B, Brazier JE, Sullivan M. Evaluating translations of health status questionnaires. Methods from the IQOLA project. *International Quality of Life Assessment. Int J Technol Assess Health Care.* 1995;11:525–551.
8. WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychol Med.* 1998;28:551–558.
9. Bjordal K, Bottomley A. Making advances in quality of life studies in head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2017;97:659–661.
10. Murphy BA, Ridner S, Wells N, Dietrich M. Quality of life research in head and neck cancer: a review of the current state of the science. *Crit Rev Oncol Hematol.* 2007;62:251–267.
11. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer; 2010.
12. Rogers SN, Gwanne S, Lowe D, Humphris G, Yueh B, Weymuller Jr EA. The addition of mood and anxiety domains to the University of Washington quality of life scale. *Head Neck.* 2002;24:521–529.
13. Pickard AS, De Leon MC, Kohlmann T, Cella D, Rosenbloom S. Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. *Med Care.* 2007;45:259–263.
14. Terrell JE, Ronis DL, Fowler KE, et al.. Clinical predictors of quality of life in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2004;130:401–408.
15. Richardson AE, Morton RP, Broadbent EA. Changes over time in head and neck cancer patients' and caregivers' illness perceptions and relationships with quality of life. *Psychol Health.* 2016;31:1203–1219.
16. Rogers SN, Miller RD, Ali K, Minhas AB, Williams HF, Lowe D. Patients' perceived health status following primary surgery for oral and oropharyngeal cancer. *Int J Oral Maxillofac Surg.* 2006;35:913–919.
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, D.C.: APA; 2013.
18. Katz MR, Irish JC, Devins GM, et al.. Psycho-social adjustment in head and neck cancer: the impact of disfigurement, gender and social support. *Head Neck.* 2003;25:103–112.
19. Verdonck-de Leeuw IM, Eerenstein SE, der Linden V, et al.. Distress in spouses and patients after treatment for head and neck cancer. *Laryngoscope.* 2007;117:238–241.
20. Misono S, Weiss NS, Fann JR, Redman M, Yueh B. Incidence of suicide in persons with cancer. *J Clin Oncol.* 2008;26:4731–4738.
21. Hammerlid E, Ahlner-Elmqvist M, Bjordal K, et al.. A prospective multicentre study in Sweden and Norway of mental distress and psychiatric morbidity in head and neck cancer patients. *Br J Cancer.* 1999;80:766–774.
22. Lydiatt WM, Moran J, Burke WJ. A review of depression in the head and neck cancer patient. *Clin Adv Hematol Oncol.* 2009;7:397–403.
23. Stanton AL. What happens now? psychosocial care for cancer survivors after medical treatment completion. *J Clin Oncol.* 2012;30:1215–1220.
24. de Leeuw JR, de Graeff A, Ros WJ, Blijham GH, Hordijk GJ, Winnubst JA. Prediction of depressive symptomatology after treatment of head and neck cancer: the influence of pre-treatment physical and depressive symptoms, coping, and social support. *Head Neck.* 2000;22:799–807.
25. Bloom J, Kang S, Petersen D, Stewart S. Quality of life in long-term cancer survivors. In: Feuerstein M, ed. *Handbook of Cancer Survivorship.* New York, NY: Springer; 2007:43–63.
26. Levine S. The changing terrain of medical sociology: emergent concern with quality of life. *J Health Soc Behav.* 1987;28:1–6.