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Evolution and predictive factors of quality of life in patients undergoing oncologic surgery for head and neck cancer: A prospective multicentric study

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ABSTRACT

Objectives: The purposes of this study were to assess the evolution of quality of life (QoL) in patients with head and neck squamous cell carcinoma (HNSCC) undergoing oncologic surgery and to determine the predictive factors of post-therapeutic QoL.

Methods: All HNSCC patients who underwent primary surgery, between 2012 and 2014, were enrolled in this prospective multicentric study. Patients completed the EORTC QLQ-C30 and QLQ-H&N35 questionnaires before surgery and at 6 months after treatment. Predictive factors of post-therapeutic QoL scores were determined.

Results: A total of 200 patients were included in this study. There was no significant deterioration of global QoL and no significant increase in general symptoms between the pre- and post-therapeutic periods, but a significant deterioration in role and social functioning, and an increase of most head and neck symptoms. Tumor stage, tumor site and treatment modalities (type of surgery, adjuvant therapy) were the main predictors of QoL scores. We found a negative correlation between satisfaction with the information received and global QoL score or several functioning scales.

Conclusion: HNSCC surgical treatment affects patients QoL mainly by increasing head and neck symptoms, which results in social and role functioning deterioration. These results are of great interest to improve multidisciplinary care of HNSCC patients.

1. Introduction

There are approximately 500,000 new cases of head and neck squamous cell carcinoma (HNSCC) annually worldwide [1]. HNSCC represents the 6th leading cause of cancer death [1]. Surgery has a central role in the primary therapeutic management of this disease, but can lead to significant impairments in vital functions such as swallowing, speech, and breathing and, finally, can affect patient quality of life (QoL) [2]. Provision of comprehensive and personalized information to patients undergoing surgery for HNSCC is therefore essential.

Nowadays, QoL is considered to be a crucial feature in the evaluation of any cancer therapy. In the assessment of QoL, comparison of post-therapeutic QoL to baseline QoL is critical because QoL can be impaired before any treatment by the tumor itself, comorbidities of the patient and various psychosocial factors. There are several published studies assessing QoL in HNSCC patients, in particular after radiotherapy (RT) ± chemotherapy (CT). However, there are few published studies evaluating QoL with an appropriate measure instrument in HNSCC patients undergoing different types of oncologic surgery. Moreover, predictive factors of post-treatment QoL remain insufficiently explored.

The aims of this prospective multicentric study were to assess the evolution of QoL in HNSCC patients undergoing oncologic surgery and to determine the predictive factors of post-treatment QoL.

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2. Material and methods

2.1. Patients

All patients who underwent primary surgery for a previously-untreated HNSCC between March 1, 2012, and July 31, 2014 were enrolled in this prospective multicentric study (3 tertiary care centers). Postoperative adjuvant RT, with or without concurrent CT, was administered when indicated based on the patient's general health status, tumor stage and adverse pathological features.

Patients were staged according to the 2009 American Joint Committee on Cancer (AJCC) staging system. We defined 3 levels of surgical procedures as follows: level I – minor surgical procedures without tracheotomy, surgical defect closed directly or reconstruction with small local flaps (e.g. endoscopic laser cordectomy, marginal glossectomy with direct closure with or without neck dissection etc), level II – intermediate surgical procedures requiring tracheotomy or reconstruction with regional (cervical or thoracic pedicle) flaps (e.g. open partial laryngectomy, total pharyngo-laryngectomy: TPL, oropharyngectomy with pectoralis major myocutaneous flap reconstruction …), level III – major surgical procedures requiring free-flap reconstruction (oropharyngectomy with radial forearm free-flap reconstruction, mandibulectomy with fibula free-flap reconstruction …).

2.2. QoL evaluation

Patients completed the French versions of the European Organization for Research and Treatment of Cancer (EORTC) Core QoL Questionnaire (QLQ-C30) and the EORTC Head and Neck Cancer QoL Questionnaire (QLQ-H&N35) before surgery and at 6 months after the end of treatment (including postoperative RT or RT + CT, when required). Patients who were not fluent in French or who could not answer the EORTC questionnaires for physical, psychological, or other reasons were excluded from the study. The 6-month post-treatment questionnaires were not completed in the event of death or tumor recurrence before the 6th post-treatment month.

As recommended by the EORTC, the scales and single item variables of the QLQ-C30 and H&N35 questionnaires were linearly transformed into a score from 0 to 100. A high score for a functioning scale and for the global QoL scale represents a better level of functioning, whereas a high score for a symptom scale or a single-item scale denotes a high level of symptoms or problems.

We evaluated patient satisfaction with the information received after the end of treatment using a single question in the EORTC QLQ-INFO25 questionnaire (item 52). The response format was a 4-point Likert scale (1 – not at all, 2 – a little, 3 – quite a bit, 4 – very much) and was linearly transformed into a score from 0 to 100. The higher the score, the greater the satisfaction.

2.3. Ethical consideration

The protocol and all accompanying material provided to patients were reviewed and approved by institutional ethics committees prior to the start of the study. The study was conducted in compliance with the Helsinki Declaration. Informed consent was obtained from each of the participants.

2.4. Statistical analyses

We investigated potential differences in the QLQ-C30 and H&N35 scores obtained before surgery and at 6 months after the end of treatment by means of t-tests on paired measurements. We analyzed the influence on post-treatment QLQ-C30 and H&N35 scores of the following factors: age ($< vs > 65$ years), gender, education level ($\leq vs >$ high school diploma), professional activity before treatment (yes *vs* no), center of treatment, T-stage ($< vs \geq 3$), N-stage ($< vs \geq$ 2a), tumor site (oral cavity/oropharynx *vs* larynx/hypopharynx), type of surgery (total pharyngolaryngectomy *vs* other types of surgery), level of surgical procedure (I/II *vs* III), postoperative adjuvant therapy (yes *vs* no). Univariate analyses were performed using Student's t tests or Wilcoxon tests. Multivariate analyses were performed using linear regression models.

We also investigated the potential correlations between QLQ-C30 and QLQ-HN35 scores as well as between QoL (QLQ-C30 and QLQ-HN35 scores) and patient satisfaction with the information received at 6 months after the end of treatment. These correlations were determined using Pearson's test or Spearman's rank test. When $r \geq 0.30$ or $r \leq -0.30$, we need to consider the correlation between 2 scores; the closer the coefficient of correlation to 1 (or -1), the stronger the link between both variables.

All statistical analyses were performed at 5% alpha risk or 95% confidence interval by the biostatistician using R.3.0.1 software on Windows.

3. Results

3.1. Clinical characteristics of the patients

A total of 210 patients were initially included in this study. Ten patients did not complete the EORTC QoL questionnaires correctly before surgery and were secondarily excluded from the study. Thus, a total of 200 patients were included in the final analysis. There were 149 men and 51 women, mean age 63.5 ± 10.3 years (range: 29–99 years). Their main clinical characteristics are shown in Table 1.

3.2. EORTC QLQ-C30 and QLQ-HN35 scores before and after treatment

The EORTC QoL questionnaires were completed by 200 patients before treatment and by 129 patients at 6 months after the end of treatment. The post-treatment questionnaires were not completed by 71 patients for the following reasons: death (17), tumor recurrence (14) during the first 6 post-treatment months, patient refusal (15), and lost to follow-up (25). EORTC QLQ-C30 and QLQ-HN35 scores obtained by patients before and after treatment are shown and compared in Tables 2 and 3.

Regarding EORTC QLQ-C30 scores, between the pre- and post-treatment periods, we observed a significant deterioration in 2 functioning scales (role and social functioning), a significant increase in financial difficulties and a trend towards a decline in cognitive functioning. The global QoL score was remarkably stable.

Table 1
Patients' clinical characteristics.

Characteristics	All patients (n = 200)	Percentage (%)
Gender: male/female	149/51	75/25
Age: < 65/ > 65 years	104/96	52/48
Education level: ≤/ > high school diploma	147/53	73/27
Professional activity before treatment: Yes/No[a]	78/122	39/61
T-Stage: T1/T2/T3/T4	56/61/23/60	28/30/12/30
N-Stage: N0/N1/N2a/N2b/N2c/N3	130/20/9/25/14/2	65/10/4/13/7/1
Tumor site: OC/OP/HP/L	83/41/20/56	41/20/10/28
Total pharyngo-laryngectomy: Yes/No	46/153	23/67
Level of surgical procedure: I/II/II	64/92/43	32/46/22
Adjuvant treatment: None/RT/RT + CT	111/41/48	55/21/24

[a] Including retired patients; Tumor site: OC: oral cavity; OP: oropharynx; HP: hypopharynx; L: larynx; Level of surgical procedure: see complete description of the 3 levels of surgery in the material and methods section; RT: radiotherapy; CT: concurrent chemotherapy.

Table 2
EORTC QLQ-C30 scores before and after treatment.

Scales/items	Before treatment					After treatment					p-value
	Mean	SD	Cronbach's alpha	Lower CI 95%	Upper CI 95%	Mean	SD	Cronbach's alpha	Lower CI 95%	Upper CI 95%	
Global quality of life (items 29, 30)	62.7	22.1	0.9	0.8	0.94	61.0	20.5	0.89	0.77	0.94	0.48
Physical functioning (items 1–5)	82.1	22.4	0.82	0.78	0.86	79.4	22.6	0.85	0.79	0.89	0.31
Role functioning (items 6, 7)	80.6	27.4	0.79	0.67	0.87	72.4	30.9	0.89	0.84	0.93	0.02
Emotional functioning (items 21–24)	65.5	26.2	0.82	0.76	0.86	69.5	27.7	0.89	0.85	0.92	0.19
Cognitive functioning (items 20, 25)	85.0	21.1	0.55	0.4	0.68	79.9	24.7	0.67	0.49	0.8	0.06
Social functioning (items 26, 27)	86.0	24.4	0.77	0.6	0.86	75.89	30.7	0.84	0.74	0.9	< 0.001
Fatigue (items 10, 12, 18)	32.2	29.5	0.89	0.86	0.92	36.5	29.2	0.92	0.88	0.94	0.2
Nausea and vomiting (items 14, 15)	4.9	14.5	0.71	0.48	0.88	6.6	17.3	0.75	0.51	0.91	0.37
Pain (items 9, 19)	26.6	29.4	0.79	0.69	0.85	24.4	28.2	0.82	0.71	0.88	0.5
Dyspnea (item 8)	23.5	31.6	~	~	~	27.8	33.4	~	~	~	0.25
Insomnia (item 11)	36.4	36.3	~	~	~	34.7	33.7	~	~	~	0.66
Appetite loss (item 13)	27.5	34.4	~	~	~	27.4	34.4	~	~	~	0.98
Constipation (item 16)	22.1	31.5	~	~	~	20.6	28.6	~	~	~	0.66
Diarrhoea (item 17)	7.2	19.2	~	~	~	10.8	23.7	~	~	~	0.16
Financial difficulties (item 28)	11.7	26.4	~	~	~	18.6	30.2	~	~	~	0.04

SD: standard deviation; CI: confidence interval; p-value: comparison between pre- and post-treatment scores, statistically significant p-values are underscored; ~: not applicable.
A high score for a functioning scale and for the global QoL scale represents a better level of functioning, whereas a high score for a symptom scale or a single-item scale denotes a high level of symptoms or problems.

Regarding EORTC QLQ-HN35 scores, a significant increase in symptoms and problems was observed between the pre- and post-treatment periods for most symptom scales or single-item scales except for pain, sexuality, coughing, feeling ill and weight loss.

3.3. Predictive factors of EORTC QLQ-C30 and QLQ-HN35 scores after treatment

Predictive factors of EORTC QLQ-C30 and QLQ-HN35 scores after treatment in univariate and multivariate analysis are shown in Tables 4 and 5.

We found no predictive factors of global QoL. After univariate and multivariate analyses, N-stage (≥2a) and type of surgery (TPL) were significant predictors of poor physical functioning. Type of surgery (TPL) was a significant predictor of poor role functioning. T-stage (≥3) and type of surgery (TPL) were significant predictors of poor emotional functioning. Adjuvant treatment (postoperative RT or RT + CT) was a significant predictor of poor cognitive functioning. T-stage (≥3), N-stage (≥2a) and type of surgery (TPL) were significant predictors of poor social functioning.

Regarding general symptoms, after univariate and multivariate analyses, N-stage (≥2a) and surgical procedure level (≥II) were significant predictors of fatigue and nausea/vomiting. Surgical procedure level (≥II) and adjuvant treatment (postoperative RT or RT + CT) were significant predictors of pain. Gender (women), education level (> high school diploma) and type of surgery (TPL) were significant predictors of dyspnea. Professional activity (no activity before treatment) and N-stage (≥2a) were significant predictors of appetite loss. Adjuvant

Table 3
EORTC QLQ-HN35 scores before and after treatment.

Scales/items	Before treatment					After treatment					p-value
	Mean	SD	Cronbach's alpha	Lower CI 95%	Upper CI 95%	Mean	SD	Cronbach's alpha	Lower CI 95%	Upper CI 95%	
Pain (items 1–4)	26.4	26.3	0.82	0.77	0.86	23.4	25.4	0.84	0.77	0.89	0.31
Swallowing (items 5–8)	20.2	23.9	0.78	0.72	0.83	29.5	31.3	0.86	0.81	0.9	< 0.001
Senses (items 13, 14)	10.2	21.3	0.65	0.45	0.82	28.2	32.2	0.72	0.54	0.82	< 0.001
Speech (items 16, 23, 24)	22.5	24.2	0.66	0.54	0.75	36.0	28.3	0.66	0.5	0.75	< 0.001
Social eating (items 19–22)	21.4	27.4	0.85	0.8	0.9	34.3	32.7	0.89	0.83	0.92	< 0.001
Social contact (items 18, 25–28)	11.4	16.4	0.69	0.59	0.77	21.3	25.7	0.89	0.85	0.93	< 0.001
Sexuality (items 29, 30)	37.5	41.6	0.96	0.92	0.98	43.6	40.2	0.93	0.86	0.97	0.21
Teeth (item 9)	19.0	32.8	~	~	~	32.0	39.6	~	~	~	< 0.001
Mouth-opening (item 10)	21.6	35.5	~	~	~	35.9	40.0	~	~	~	< 0.001
Dry mouth (item 11)	32.3	35.1	~	~	~	41.2	39.7	~	~	~	0.04
Sticky saliva (item 12)	27.0	35.1	~	~	~	41.1	40.2	~	~	~	< 0.001
Coughing (item 15)	31.1	31.1	~	~	~	29.2	33.2	~	~	~	0.6
Feeling ill (item 17)	11.3	22.7	~	~	~	12.7	23.8	~	~	~	0.61
Pain killers (item 31)	56.9	49.7	~	~	~	42.4	49.6	~	~	~	0.01
Nutritional supplement (item 32)	23.6	42.6	~	~	~	36.2	48.3	~	~	~	0.02
Feeding tube (item 33)	10.3	30.4	~	~	~	21.3	41.1	~	~	~	0.01
Weight loss (item 34)	29.2	45.6	~	~	~	29.4	45.7	~	~	~	0.98
Weight gain (item 35)	22.7	42.0	~	~	~	36.6	48.4	~	~	~	0.01

SD: standard deviation; CI: confidence interval; p-value: comparison between pre- and post-treatment scores, statistically significant p-values are underscored; ~: not applicable. A high score for a symptom scale or a single-item scale denotes a high level of symptoms or problems.

Table 4
Predictive factors of EORTC QLQ-C30 scores after treatment.

Scales/items	P values for each factor in univariate/multivariate analyses									
	Gender	Age	Ed level	Prof act	T-Stage	N-Stage	Tum site	TPL	SP level	Adj trt
Global quality of life	0.58	0.89	0.89	0.66	0.51	0.5	0.99	0.45	0.34	0.3
Physical functioning	0.07	0.1	0.06	0.14	0.04/NS	0.05/0.02	0.76	0.05/0.01	0.05/NS	0.33
Role functioning	0.37	0.88	0.49	0.9	0.21	0.13	0.44	0.03/0.02	0.03/NS	0.72
Emotional functioning	0.95	0.41	0.81	0.31	< 0.001/0.01	0.15	0.13	0.02/0.005	0.01/NS	0.2
Cognitive functioning	0.78	0.71	0.76	0.73	0.24	0.16	0.8	0.19	0.28	0.02
Social functioning	0.05/NS	0.52	0.12	0.83	< 0.001/0.04	0.02/0.02	0.17	0.01/0.005	0.01/NS	0.01/NS
Fatigue	0.51	0.42	0.09	0.32	0.17	0.01/0.03	0.87	0.17	< 0.001/0.01	< 0.001/NS
Nausea and vomiting	0.4	0.06	0.35	0.33	0.59	0.01/0.002	0.35	0.12	< 0.001/0.02	0.11
Pain	0.58	0.43	0.86	0.34	0.05/NS	0.08	1	0.27	< 0.001/0.01	0.02/ < 0.001
Dyspnea	< 0.001/0.03	0.91	< 0.001/0.007	0.47	0.01/NS	0.19	0.03/NS	< 0.001/0.001	< 0.001/NS	0.54
Insomnia	0.58	0.14	0.59	0.91	0.29	0.74	0.96	0.21	0.81	0.63
Appetite loss	0.87	0.91	0.11	< 0.001/0.04	0.79	< 0.001/0.02	0.9	0.97	0.44	0.02/NS
Constipation	0.91	0.13	0.52	0.46	0.36	0.14	0.83	0.24	0.24	< 0.001
Diarrhoea	0.33	0.12	0.55	0.49	0.76	0.43	0.33	0.06	0.29	0.88
Financial difficulties	0.1	0.09	0.22	0.15	0.05/0.02	0.04/0.04	0.55	0.3	0.01	0.87

Statistically-significant p-values are underscored. Multivariate analyses were performed when multiple significant p-values were found in univariate analysis. NS: non-significant p-values in multivariate analysis. Age: < vs. > 65 years; education level (Ed level): ≤ vs. > high school diploma, professional activity before treatment (Prof act): yes vs. no, T-stage: < vs. ≥ 3, N-stage: < vs. ≥ 2a, tumor site (Tum site): oral cavity/oropharynx vs. larynx/hypopharynx, total pharyngolaryngectomy (TPL): yes vs. no, surgical procedure level (SP level): level I/II vs. III, Adjuvant treatment (Adj trt): yes vs. no.

treatment (postoperative RT or RT + CT) was a significant predictor of constipation. T-stage (≥3) and N-stage (≥2a) were significant predictors of financial difficulties.

Regarding head and neck symptoms, after univariate and multivariate analyses, adjuvant treatment (postoperative RT or RT + CT) was a significant predictor of swallowing difficulties and sense problems. Gender (women) was a significant predictor of speech problems. T-stage (≥3) was a significant predictor of trouble with social eating. Age (≥65 years) was a significant predictor of less sexuality. T-stage (≥3), N-stage (≥2a) and tumor site (oral cavity and oropharynx) were significant predictors of teeth problems. Professional activity (no activity before treatment) and tumor site (oral cavity and oropharynx) were significant predictors of mouth-opening limitation. T-stage (≥3) and adjuvant treatment (postoperative RT or RT + CT) were significant predictors of dry mouth. Adjuvant treatment (postoperative RT or RT + CT) was a significant predictor of sticky saliva. Gender (women) was a significant predictor of pain killer prescription. Surgical procedure level (≥2) was significant predictor of nutritional supplementation, feeding tube dependence and weight loss.

3.4. Correlations between EORTC QLQ-C30 scores, QLQ-HN35 scores and satisfaction with the information received after treatment

Correlations between EORTC QLQ-C30 scores, QLQ-HN35 scores and satisfaction with the information received after treatment are shown in Table 6. We found some negative correlations between global QoL score or functioning scales and several QLQ-HN35 scores (sticky saliva, coughing, feeling ill, pain killers, nutritional supplement and feeding tube). We found some positive correlations between different general symptoms and several QLQ-HN35 scores.

After treatment, satisfaction with the information received score was 58.1 ± 28.8 and was negatively correlated with the global QoL

Table 5
Predictive factors of EORTC QLQ-HN35 scores after treatment.

Scales/items	P values for each factor in univariate/multivariate analyses									
	Gender	Age	Ed level	Prof act	T-Stage	N-Stage	Tum site	TPL	SP level	Adj trt
Pain	0.83	0.34	0.51	0.09	0.19	0.26	0.71	0.59	0.45	0.55
Swallowing	0.8	0.02/NS	0.67	0.01/NS	0.15	0.07	0.26	0.69	0.03/NS	0.02/0.05
Senses	0.28	0.52	0.29	0.58	0.82	0.22	0.67	0.12	0.31	0.03
Speech	0.04	0.53	0.64	0.09	0.9	0.4	0.14	0.12	0.5	0.15
Social eating	0.96	0.09	0.11	0.01/NS	0.04/0.02	0.2	0.23	0.34	0.05/NS	0.08
Social contact	0.52	0.74	0.7	0.64	0.9	0.94	0.41	0.99	0.89	0.88
Sexuality	0.62	0.05	0.09	0.09	0.74	0.63	0.38	0.34	0.94	0.07
Teeth	0.74	0.31	0.83	0.11	0.02/0.03	0.03/0.04	< 0.001/0.005	0.93	0.01/NS	0.01/NS
Mouth-opening	0.75	0.1	0.04/NS	< 0.001/0.02	0.06	0.17	< 0.001/0.001	0.34	0.49	0.26
Dry mouth	0.06	0.57	0.64	0.88	0.01/0.005	0.13	0.2	0.75	0.14	0.01/0.04
Sticky saliva	0.79	0.52	0.91	0.03/NS	0.06	0.28	0.28	0.35	< 0.001/NS	0.04/0.02
Coughing	0.59	0.79	0.37	0.84	0.98	0.91	0.26	0.51	0.79	0.37
Feeling ill	0.64	0.07	0.13	0.28	0.63	0.25	0.29	0.14	0.53	0.07
Pain killers	0.02	0.07	0.54	0.31	0.76	0.67	0.76	0.35	0.5	0.51
Nutritional supplement	0.63	0.18	0.74	0.06	0.29	0.52	0.82	0.8	0.01	0.11
Feeding tube	0.18	0.5	0.56	0.08	0.42	0.28	0.42	0.15	0.05	0.42
Weight loss	0.47	0.3	0.47	0.34	0.14	0.99	0.88	0.59	0.03	0.1
Weight gain	0.09	0.77	0.67	0.8	0.07	0.3	1	0.56	0.66	0.64

Statistically-significant p-values are underscored. Multivariate analyses were performed when multiple significant p-values were found in univariate analysis. NS: non-significant p-values in multivariate analysis. Age: < vs. > 65 years; education level (Ed level): ≤ vs. > high school diploma, professional activity before treatment (Prof act): yes vs. no, T-stage: < vs. ≥ 3, N-stage: < vs. ≥ 2a, tumor site (Tum site): oral cavity/oropharynx vs. larynx/hypopharynx, total pharyngolaryngectomy (TPL): yes vs. no, surgical procedure level (SP level): level I vs. II/III, Adjuvant treatment (Adj trt): yes vs. no.

Table 6
Correlations between QLQ-C30 scores, QLQ-HN35 scores and satisfaction with the information received after treatment.

QLQ-HN35 scores	Correlation coefficients (r)															
	QLQ-C30 scores															
	S/Info	GQoL	PF	RF	EF	CF	SF	Fa	NV	Pa	Dy	In	AL	Co	Di	FD
Pain	0	0	0	0	0	0	0	0	0	+0.3	0	+0.3	0	0	0	+0.3
Swallowing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	+0.3
Senses	0	0	0	0	0	0	0	0	0	0	+0.3	0	0	+0.3	0	0
Speech	0	0	0	0	0	0	+0.3	0	0	+0.6	+0.3	+0.3	+0.3	+0.3	0	+0.3
Trouble with social eating	0	0	0	0	0	0	0	0	0	+0.3	+0.3	+0.3	+0.3	+0.3	+0.3	+0.3
Trouble with social contact	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sexuality	0	0	0	+0.3	0	0	0	0	0	0	0	0	0	0	0	0
Teeth	0	0	0	0	0	0	0	0	0	+0.3	0	0	0	+0.3	0	0
Mouth-opening	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dry mouth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Sticky saliva	0	- 0.3	- 0.3	- 0.3	- 0.3	0	0	0	0	0	0	0	0	0	0	0
Coughing	0	- 0.3	- 0.3	- 0.6	- 0.3	- 0.3	- 0.3	- 0.3	0	0	0	0	0	0	0	0
Feeling ill	0	0	- 0.3	- 0.6	- 0.3	- 0.3	- 0.3	0	0	0	0	0	0	0	0	0
Pain killers	0	0	- 0.3	- 0.3	- 0.3	0	0	- 0.3	- 0.3	0	0	0	0	0	0	0
Nutritional supplement	0	- 0.3	- 0.3	- 0.3	- 0.3	- 0.3	- 0.3	- 0.3	- 0.3	0	0	0	0	0	0	0
Feeding tube	0	0	- 0.6	- 0.3	- 0.3	- 0.3	- 0.3	0	0	0	0	0	0	0	0	0
Weight loss	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Weight gain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
S/Info	NA	- 0.3	- 0.3	0	- 0.3	- 0.3	0	0	0	0	0	0	0	0	0	0

S/Info: satisfaction with the information received, GQoL: global quality of life, PF: physical functioning, RF: role functioning, EF: emotional functioning, CF: cognitive functioning, SF: social functioning, Fa: fatigue, NV: nausea and vomiting, Pa: pain, Dy: dyspnea, In: insomnia, AL: appetite loss, Co: constipation, Di: diarrhoea, FD: financial difficulties. Significant correlation between two variables exists when r (Pearson's test or Spearman's rank test) is superior to 0.30 or inferior to −0.30; this correlation increases as r approaches 1 or -1.

score, and physical, emotional and cognitive functioning.

4. Discussion

In this prospective multicentric study on HNSCC patients undergoing oncologic surgery with or without postoperative RT or RT + CT, we showed that there was no significant deterioration of global QoL and no significant increase in general symptoms between the pre- and post-therapeutic periods. In contrast, the impact of treatment on QoL scores was evident for role and social functioning scales and for most head and neck symptoms.

After treatment, tumor stage (T or N stage), tumor site and treatment modalities (type of surgery, adjuvant therapy) were the main predictors of QoL scores. Female sex, high education level and absence of professional activity before treatment also had a negative impact on various QoL scores. In addition, we found a negative correlation between satisfaction with the information received and the global QoL score or several functioning scales. Indeed, patients with a better global QoL or a better level of functioning, were less satisfied with the information they received.

A significant proportion of patients did not complete the post-operative questionnaire and the rate of patients (25/200, i.e. 12.5%) who were lost to follow-up may appear to be relatively high for a prospective database. However, a significant number of patients, which live far from the tertiary care center where they have been treated, are followed in a local institution (primary/secondary care center) or by a private specialist, after the end of the treatment. This is particularly true for elderly patients or patients with severe comorbidities. In such cases, completion of the postoperative questionnaire could be difficult to obtain.

In the present study, the EORTC QoL questionnaires detected the classical changes in HNSCC patients' QoL after treatment [2,3]. As previously described by several authors, there were no significant changes in global QoL and no drastic increase in general symptoms after curative treatment for HNSCC [4–6]. This can be explained by the fact that HNSCC surgical treatment does not generate major changes in general health status and general symptoms but also by the fact that general health status and general symptoms were already impaired before treatment by the cancer itself. Regarding functioning scales, there was a significant deterioration in role and social functioning after treatment. This highlights the main consequences of HNSCC treatment affecting the patients' appearance and their ability to communicate, finally leading to a poorer social life. Similarly, Veldhuis et al. in a series of 67 HNSCC patients treated by surgery alone or surgery followed by RT ± CT, showed that, among the different functioning scales, the decrease between the pre- and post-treatment scores was most acute for role and social functioning [7].

This degradation of role and social functioning after treatment may explain the significant increase in financial difficulties reported in the present study. The financial difficulties encountered in HNSCC patients after treatment have already been reported by several authors in studies conducted in other countries with different health care systems. In the study by Vedhuis et al. mentioned above and conducted in Germany, a drastic increase in financial difficulties was reported 10 months after therapy [7]. In another study, conducted in India, examining long-term QoL in HNSCC survivors 1 year after completion of their treatment, Chaukar et al. showed that financial difficulties constituted the items of the EORTC QLQ-C30 for which patients reported having most problems [8]. Interestingly, the present study showed that these financial difficulties also affect HNSCC patients in France, which is acknowledged for its highly-protective social and health care system.

In a previous prospective study analyzing the evolution of QoL in HNSCC patients undergoing surgery with free-flap reconstruction, we reported remarkably similar results regarding EORTC QLQ-C30 scores except for fatigue, which was found to be increased after therapy [2]. In comparison with this earlier study, the present study also included patients undergoing lower levels of surgical procedure, which could explain the non-significant increase in fatigue level after treatment. This is supported by our results showing that surgical procedure level was an independent predictor of fatigue after treatment. Moreover, patients undergoing free-flap reconstruction most often have a locally-advanced disease requiring postoperative adjuvant therapy, which can contribute to the fatigue reported by the patients a long time after treatment. Interestingly, our results showed that adjuvant treatment

adversely impacted both fatigue and cognitive function. In this regard, Powell et al. showed a significant association between fatigue and mean dose to the cerebellum in nasopharyngeal cancer patients undergoing chemoradiotherapy [9]. In fact, intensity-modulated radiotherapy techniques for HNSCC have been associated with a net increase in irradiated brain volumes [10]. The increasing use of chemoradiotherapy has additionally exposed this patient population to potential neurotoxicity due to cytotoxic drugs. Moreover, HNSCC patients may be particularly at risk for impaired neurocognitive function as risk factors for the development of HNSCC include smoking and excess alcohol consumption which are also associated with impaired neurocognitive function [10].

Among functioning scales, emotional functioning was the most deteriorated function both before and after treatment. This finding should encourage health-care professionals to evaluate the psychological status of HNSCC patients throughout their management and to provide them with appropriate psychological support. However, although the change observed was non-significant, emotional functioning was the only functioning scale that tended to improve after treatment. This suggests that the preoperative period is the most anxiety-generating phase in the therapeutic management of HNSCC patients. This also highlights the need for appropriate management of patient anxiety and fear in the preoperative period. After therapy, the long-term side effects of treatment, the changes in physical appearance, the deterioration of social life and the anxiety related to cancer and the risk of recurrence and death may all affect patients' emotional status. In a study analyzing psychosocial effects in long-term HNSCC survivors, Holloway et al. showed that both psychosocial and physiologic factors influenced QoL in patients with HNSCC, but that many QoL measures were most strongly influenced by psychosocial considerations [11]. Moreover, in a recent prospective study, Barber et al. demonstrated that the incidence and severity of preoperative depressive symptoms in HNSCC patients treated with surgery was high (54%) and that patients with moderate or severe preoperative depressive symptoms had significantly decreased postoperative functional performance status, increased narcotic use, decreased completion of adjuvant therapy, and a longer length of hospital stay [12].

The EORTC QLQ-H&N35 module revealed the typical functional impairment affecting HNSCC patients after therapy that mainly involves the senses, mouth opening, dental status, salivary, speech and swallowing functions [13]. Indeed, for all these functions the related-EORTC QLQ-H&N35 score significantly increased after treatment, thus denoting a higher level of problems or symptoms. Similarly, Chaukar et al. found that dry mouth, sticky saliva, dental problems and mouth opening were the domains with poorer scores [8]. Interestingly, although surgery can also contribute to mouth-opening problems, all these disorders are generally considered to be long-term side-effects of RT. In the present study, sticky saliva was also inversely correlated to global QoL and several functioning scales. This suggests that, even in HNSCC patients treated with primary surgery, long-term side effects of adjuvant RT were the main factors affecting patients' QoL.

In the head and neck region, the level of pain was remarkably stable despite a significant reduction in pain-killer consumption. Tumor-related pain was replaced by pain related to the sequelae of surgery which can be increased in cases of postoperative RT ± CT. In this regard, and curiously, we found that adjuvant treatment significantly impacts post-treatment pain measured by the EORTC QLQ-C30 questionnaire but not the pain evaluated by the specific QLQ-H&N35 module. We also found that pain-killer consumption was inversely correlated to physical, role and emotional functioning. This highlights the importance of post-therapeutic pain management in patients with HNSCC and supports the conclusions of the French Otorhinolaryngology and Head and Neck Surgery Society guidelines stipulating that, to improve patients' QoL, particular care should be given to detection and early-adapted treatment of pain induced by HNSCC treatment [14–16].

Our results demonstrate a significant increase in nutritional support measures after therapy. This is explained by the deterioration of post-therapy swallowing function. Although head and neck surgery obviously affects swallowing function, post-operative RT also has a major impact on this function. Indeed, our results show that, after multivariate analysis, adjuvant therapy remained the only factor impacting swallowing function. Moreover, several studies have shown the major role, long after treatment, of pre- or postoperative radiotherapy in the limitation of mouth-opening [17]. The role of radiotherapy is also obvious in dental problems and salivary dysfunction, which were among the main head and neck symptoms of our patients. These problems all contribute to restrict oral feeding long-term after therapy. Furthermore, altered sense of taste, restricted diet, and changed physical appearance can all bother the patient while eating in public. This explains why, in our study as in most published QoL studies in head and neck oncology, social eating was more deteriorated than swallowing function after therapy [3,4]. The present study shows that, compared to the pre-operative period, a significant proportion of patients put on weight 6 months after therapy. This suggests that the nutritional support procedures engaged in the post-therapeutic phase are effective and highlights the need of an individualized nutritional follow-up in the multidisciplinary management of head and neck patients. Interestingly, in a study assessing swallowing function following postchemoradiotherapy neck dissection, Chapuy et al. reported gastrostomy tube dependence at 12 and 24 months in 25% and 10% of patients, respectively [18]. Therefore, it is very likely that the oral diet of the patients included in our study, which was evaluated 6 month after therapy, continues to improve during the first 2 post-therapeutic years. The relatively short follow-up period constitutes a weakness of this study because a slight evolution of QoL scores has been reported for head and neck cancer patients between the 6th and the 12th post-therapeutic months [2]. However, delaying the post-therapeutic QoL evaluation time inevitably leads to an increase in the number of non-evaluable patients due to deaths, tumor recurrences, intercurrent diseases or loss to follow-up. Hence, a post-therapeutic evaluation performed 6 months after the end of the treatment seemed to us to offer an acceptable compromise.

It was not surprising that tumor stage and site, as well as treatment modalities, were the main predictors of QoL in the present study. In a recent prospective study on 67 patients with either oropharyngeal or laryngeal cancer, Veldhuis et al. also showed the impact of tumor site and disease stage on QoL [7]. It is interesting to note that laryngectomized patients had the worst level of functioning and that TPL had a greater impact on functioning scales (cognitive functioning excepted) compared with the level of surgical procedure or adjuvant therapy. The advances made in speech and pulmonary rehabilitation have undoubtedly contributed to improve psycho-social well-being and quality of life of laryngectomized patients. Nevertheless, as highlighted by Babin et al. among head and neck cancer patients, laryngectomized patients are those who have the highest need of global and multidisciplinary management including intensive functional rehabilitation procedures and psycho-social supportive interventions [19,20].

Although the influence of patient age on sexuality is easily understandable, the negative impact of female gender on dyspnea, speech, and pain killer prescription needs to be highlighted. However, we can assume that a hoarse voice, a frequent result of head and neck cancer treatment, is accepted less easily by women than by men. The significant effect of professional inactivity before treatment on certain QoL scores and, in particular, on appetite loss, is important to note and could be explained, at least in part, by a decline in physical activity. Interestingly, in a recent study analyzing QoL in long-term head and neck cancer survivors, Wells et al. showed that, among other factors, lower socio-economic status and unemployment independently contributed to poorer generic and cancer-specific QoL [21].

Finally, we observed significant negative correlations between several head and neck symptoms and global QoL score or various functioning scales. This suggests that reduction of post-therapeutic head and neck symptoms by the use of less invasive surgical procedures,

more accurate reconstructive surgery and modern techniques of RT should be the best way to improve patient QoL. Moreover, we found that patients with a better global QoL or a better level of functioning were less satisfied with the information they received. This result seems surprising since we might expect that patients with a poor QoL would be more critical in their assessment of the information delivered by healthcare professionals. It follows, therefore, that patients with a better global QoL were less satisfied with the information they received and that satisfaction with the information received had no positive impact on QoL. In this regard, we also found a positive correlation between social functioning and speech problems suggesting that a similar impairment of speech function would have a greater impact on patients with a high social functioning than on patients with a poor social functioning. QoL is a complex construct involving multiple parameters, including psychosocial factors. It may be that patients with a higher global QoL are those with less severe disease and are thus more concerned with function and more demanding of complete and accurate medical information.

5. Conclusion

In this prospective multicentric longitudinal study, we evaluated the evolution of QoL in HNSCC patients undergoing primary oncologic surgery. Although the global QoL score remained stable, we found a deterioration of role and social functioning, as well as an increase in financial difficulties and most head and neck symptoms. We also found that, after treatment, tumor stage, tumor site and treatment modalities were the main predictors of QoL scores. In addition, we found a negative correlation between satisfaction with the information received and global QoL score or several functioning scales. These findings could be useful to improve post-therapeutic supportive care procedures and, ultimately, the global management of HNSCC patients. These results are also of great interest to help adjust the multidisciplinary care of these patients to their individual needs.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.01.012.

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