Temporal evolution of quality of life in patients endoscopically treated for sinonasal malignant tumors*

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Abstract

Background: The aim of our study is to assess which factors may affect the quality of life (QoL) and its fluctuation over time in adult patients who received endonasal endoscopic oncologic sinus surgery (EOSS) for sinonasal malignancies (SNM) in our center.

Methodology: We analyzed EOSS cases for primary SNM from January 2015 to June 2020. For each patient, we have recorded the age at treatment, gender, smoking habits, use of psychotropic drugs for mood disorders, stage, histotype, type of surgical resection, need for skull-base reconstruction, development of postoperative major complications, and the use of adjuvant intensity-modulated radiotherapy (IMRT). We evaluated the patient's performance status pre-treatment using the ECOG scale. Quality of life was measured using three questionnaires (SNOT-22; ASK-9; EORTC QLQ-C30 version 3).

Results: Fifty-five patients were enrolled in our study, of whom thirty-two (58.18%) received adjuvant IMRT. Overall, a significant improvement in all QoL outcomes was observed at eighteen months, while, female sex, higher ECOG scores, advanced stage of disease, and adjuvant IMRT were associated with worse QoL. After 18 months the delta in QoL between women and men worsened (in SNOT-22 and EORTC QLQ-GLOBAL) while if only the most fragile patients according to ECOG are considered, this difference was reduced for both tools.

Conclusion: Our analysis revealed that IMRT is the element that has the greatest impact on patient's quality of life, in association with the female sex, ECOG >2, and advanced stage of the disease.

Key words: endonasal surgery, sinonasal cancer, quality of life, skull base neoplasms

Introduction

Sinonasal malignancies (SNM) account for about 3–5% of all head and neck cancers and constitute less than 1% of all tumors[(1)]. They encompass a broad range of pathological categories with malignant epithelial tumors (sinonasal carcinomas, SNCs) accounting for more than 80% [(2)]. Current treatment options include surgery, radiotherapy, and chemotherapy, used individually or in combination. Transnasal endoscopic surgery (TNES) is the current mainstay of treatment for SNM and intensity-modulated radiotherapy (IMRT) is the preferred radiation technique as it allows to spare cranial nerves, brain, and orbital contents [(3)]. The frequent local extension of SNM to these anatomical regions may necessitate extended resections (open/transfacial or endoscopic/transnasal) and aggressive adjuvant therapies, both heavily affecting the health-related quality of life (HRQoL) of these patients [(4-7)].

The concept of quality of life (QoL) is defined by the World Health Organisation as "an individual's perception of their

position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" [8]. QoL is typically assessed through Patient Reported Outcome Measures (PROMs), which are instruments that measure outcomes reported directly by patients[9]. Chow et al. have recently published a review summarizing the most recent studies about QoL in patients with SNM. This paper confirms that the clinical assessment of SNM patients' QoL remains limited and heterogeneous because of the many different PROMs implemented by the authors [10].

Our study aims to comprehensively evaluate the QoL and its changes over time in patients treated for SNM. For this purpose, we administered three different validated PROMs, both general and disease-specific, at three different follow-up points to/in patients that were consecutively treated by EOSS at our center. In addition, we correlated the baseline patient and disease-related characteristics with the QoL scores obtained over time. Finally, we correlated the dynamic changes in the scores obtained with the demographic and clinical characteristics of the population.

Materials and methods

Patients

In the present monocentric study, we enrolled all patients with primary SNM who received endonasal endoscopic oncological sinus surgery (EOSS) at the Careggi University Hospital of Florence, Italy, which is a tertiary referral center, and in the period from January 2015 to June 2020. This study was approved by the local IRB (CEAVC, Florence, Italy) with referral number 22058. Exclusion criteria included transfacial/transcranial procedures, patients under 18 years of age, those receiving palliative treatments, and patients with persistence of disease or recurrence within 18 months from EOSS. Following the multidisciplinary board evaluation, some patients received neoadjuvant treatments before EOSS while adjuvant IMRT or chemoradiotherapy was administered in case of pathological advanced-stage disease or macroscopically/microscopically incomplete resection, as per the latest international guidelines [11]. For radiotherapy, a CT scan was acquired for radiation treatment planning purposes. A thermoplastic mask was customized for each patient. A total dose ranging between 54 and 66 Gy was delivered at conventional fractionation to the tumor bed with an IMRT technique. In selected cases with high-risk features and good clinical general conditions, concurrent chemotherapy consisting of cisplatin at a weekly dose of 40 mg/m^2 was administered with a radio-sensitizing purpose. All patients were advised to perform frequent nasal irrigations with saline solution at home and to instillate oily nasal drops twice daily. Furthermore, follow-up inpatient visits were generally scheduled at least once monthly. For each patient, we have analyzed the following demographic and clinical data: age at diagnosis; gender; smoking habits; chronic use of psychotropic drugs for mood disorders; tumor histotype; pathological tumor clinical stage according to the VIII edition of the AJCC - TNM staging system ("early" for stages I-II vs "advanced" for stages III-IV); type of surgical resection (unilateral vs bilateral) and skull-base reconstruction (yes vs no); postoperative major complications (e.g. severe bleeding, meningitis, cerebral abscess, need for reintervention). The patient's performance status at the time of diagnosis was evaluated using the ECOG scale [12].

Assessment

QoL was assessed by using three validated questionnaires: general QoL was assessed by the questionnaire developed by the European organization for research and treatment of cancer (EORTC QLQ-C30 3.0) [13-14]; the disease-specific and rhinological aspects of QoL were instead evaluated by using the sinonasal outcome test (SNOT-22) [15], and the anterior skull-base nasal inventory (ASK-9) [16].

SNOT-22 is a questionnaire that was initially developed for patients with chronic rhinosinusitis. It includes twenty-two items scored from 0 to 5, higher scores representing worse symptoms. Items 1-12 investigate physical symptoms (rhinological as well as ear and facial symptoms), and items 13-22 explore global health and QoL (sleep function and psychological issues) [15].

ASK Nasal Inventory is another instrument used to assess QoL before and after endonasal surgery. It consists of nine questions about symptoms of sinusitis, nasal functioning, crusting, satisfaction, and nasal care techniques. For each question, patients have to grade the severity and frequency of their symptoms on a five-point scale. More severe symptoms are indicated by higher scores [16]. The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health-related quality of life (QoL) of patients with malignant tumors. It includes five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and some items assessing additional symptoms (dyspnoea, loss of appetite, insomnia, constipation, and diarrhea), and the financial impact of the disease. All these items are measured by a 4-point Likert-like method. It also includes a global health status scale, which is assessed by a 7-point Likert-like system. We calculated a summary score for each scale according to the EORTC manual[13,14].

For statistical purposes, we have examined the total scores of SNOT-22 and ASK-9; for EORTC QLQ-C30 instead, we considered only items 29 and 30, which better summarize the global health status of patients (QLQ GLOBAL). Each questionnaire was administered to the patients at one (t0), six (t1), and eighteen (t2) months intervals after the completion of treatment (EOSS or EOSS+IMRT). Higher scores in SNOT-22 and ASK-9 are associated with a lower level in terms of QoL, whereas the latter improves with higher scores in EORTC QLQ-C30 [13-16].

Table 1. Characteristics of study cohort.

Variable	N°	%
Total Sample	55	100%
Sex		
M	44	80%
F	11	20%
Age at surgery		
<60 years	20	36.36%
≥60 years	35	63.64%
Smoking		
never	38	69.10%
former	10	18.18%
current	7	12.72%
Psychotropic drug		
no	52	94.55%
yes	3	5.45%
ECOG		
0	25	45.45%
1	14	25.45%
2-4	16	29.1%
Stage		
early	20	36.36%
advanced	35	63.64%
Histotype		
ITAC	23	41.82%
SCC	18	32.72%
MM	4	7.27%
ESTH	4	7.27%
ADK no-ITAC	3	5.45%
SNUC	2	3.63%
RHAB	1	1.81%
Type of resection		
unilateral	35	63.64%
bilateral	20	36.36%
Skull base reconstruction		
no	36	65.45%
yes	19	34.55%
Major complications		
no	50	90.90%
yes	5	9.10%
IMRT		
no	23	41.82%
yes	32	58.18%

Male (M); Female (F); Adenocarcinoma intestinal-type (ITAC); Squamous cell-carcinoma(SCC); Mucosal melanoma (MM); Esthesioneuroblastoma (ESTH); Adenocarcinoma non-intestinal-type (ADK no-ITAC); Sinonasal Undifferentiated Carcinoma (SNUC); Rhabdomyosarcoma (RHAB); intensity-modulated radiotherapy (IMRT)

Statistical analysis

Standard descriptive statistics (means and proportions for continuous and categorical variables, respectively) were used to describe the distribution of the features of patients and tumors as well as the scores in the three QoL scales that were used (SNOT-22, ASK-9, and QLQ-GLOBAL). The association of the characteristics of both patients and tumors with the different

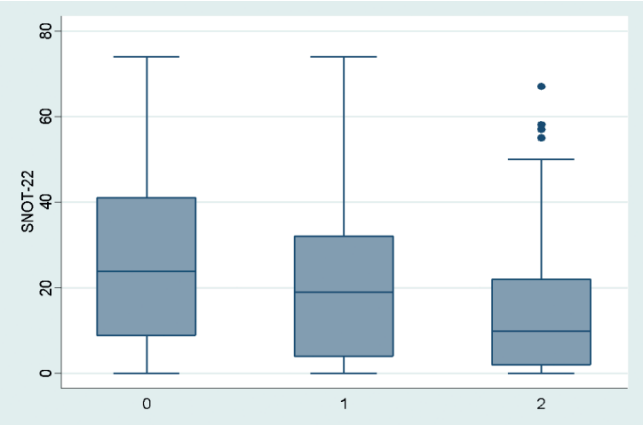

Figure 1. SNOT-22 mean scores in our total sample. X-axis: 1 month after treatment, t0 (0); 6 months after treatment, t1 (1); 18 months after treatment, t2 (2). Y-axis: SNOT-22 scores.

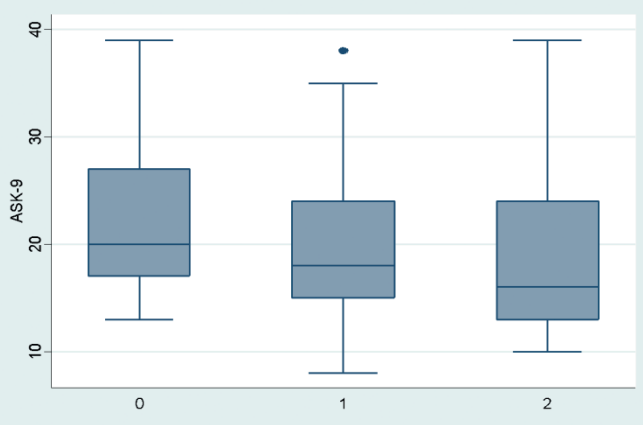

Figure 2. ASK-9 mean scores in our total sample. X-axis: 1 month after treatment, t0 (0); 6 months after treatment, tl (l); 18 months after treatment, t2 (2); Y-axis: ASK-9 scores.

QoL scores and their changes over time (at 1, 6, and 18 months after treatment) was investigated by means of univariate and multivariate random-effect mixed models (which are instrumental in order to correctly modeling the within-person correlation); a term for interaction with time was added to all the models to test the hypothesis that the strength of observed associations may vary (either strengthen or weaken) over time. The statistical analyses were performed using Stata software version 16. All tests were two-sided, and the threshold of statistical significance was set to 0.05.

Results

Study population

A total of 55 patients were enrolled in the present study, with the large majority being male (80%). The mean age was 63.13 years (standard deviation, SD, 13.47). 29.1% of patients had a poor performance status (ECOG score ≥ 2) and 5.5% took mood-stabilizing medications at the time of PROMs submission. In our

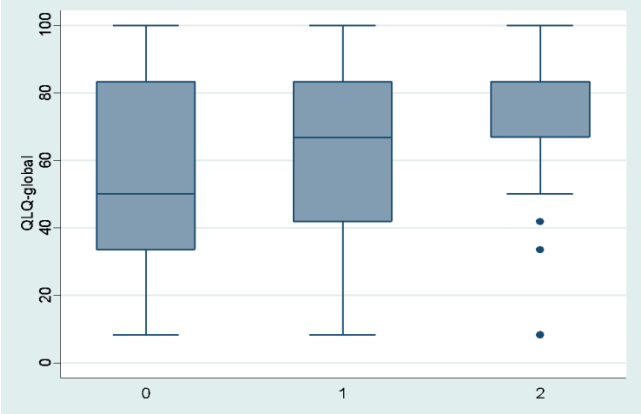

Figure 3. QLQ GLOBAL mean scores in our total sample. X- axis: 1 month after treatment, t0 (0); 6 months after treatment, t1 (1); 18 months after treatment, t2 (2). Y-axis: QLQ-GLOBAL scores.

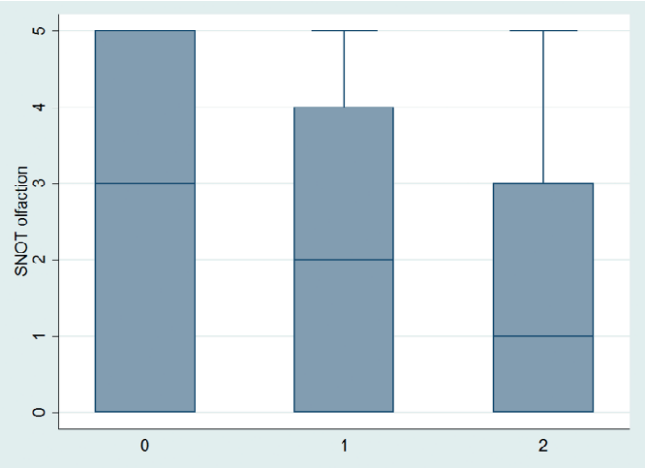

Figure 4. SNOT-22 item 12 (loss of taste/smell) mean scores in our total sample. X- axis: 1 month after treatment, t0 (0); 6 months after treatment, t1 (1); 18 months after treatment, t2 (2). Y- axis: SNOT-22 item 12 (loss of taste/smell) scores.

cohort, 63.64% of subjects presented with an advanced stage of the disease. 41.82% of our population was diagnosed with intestinal-type adenocarcinoma (ITAC) histotype, while squamous-cell carcinomas (SCC) occurred in 32.72% of our cohort. Overall, only 3 patients required neoadjuvant treatment, while 58.18% of patients received adjuvant IMRT (only 5 of these subjects received adjuvant chemoradiotherapy) because of pathological advanced-stage disease or macroscopically/microscopically incomplete resection. A more detailed view of the demographic and clinical characteristics of the cohort is given in Table 1.

Quality of life

Considering the whole population, SNOT-22 mean scores were 25.7, 20.9, and 15.9 at t0, t1, and t2, respectively (Figure 1); ASK-9 mean scores were 21.9 at t0, 19.5 at t1, and 18.5 at t2 (Figure 2); finally, QLQ-GLOBAL mean scores were 55.5 at t0, 61.2 at t1, and 77.3 at t2 (Figure 3). Mean scores of all three questionnaires at 18 months after the completion of oncological treatment revealed a general improvement in the perceived QoL of SNM patients, and in Table 2 the changes of PROMs over time are reported.
QoL according to SNOT-22 (Table 3) appeared to be statistically worse in women than men, and after 18 months the delta in SNOT-22 scores between men and women tended to increase (interaction with time coefficient is 3.33, p=0.047 at multivariate analysis), and in patients with ECOG scores over 1 or advanced stage of disease, or subjects treated also with adjuvant IMRT (p<0.001; but only at univariate). Interestingly, the difference in SNOT-22 scores between patients with higher ECOG scores and ECOG scores <2 showed a significant tendency towards obliteration after the end of the treatment (the coefficient for interaction with time was - 6.32, p<0.001 at the multivariate analysis). A similar trend in the time-dependent association with the SNOT-22 scores (i.e., attenuation of the association over time) was also registered in patients treated with IMRT (interaction with time coefficient is - 3.57, p=0.009) and in those with advanced stage of disease (interaction with time coefficient is - 3.11, p<0.001, univariate).
QoL according to ASK-9 (Table 4) was statistically worse in non-smokers (p<0.05; univariate) and in patients with ECOG scores > 2 (p = 0.002; univariate) or with an advanced stage of disease (p<0.001; univariate) or treated with adjuvant IMRT (p<0.001; multivariate).
Table 5 reported QoL according to EORTC-QLQ GLOBAL evaluation: only adjuvant IMRT (p<0.001; univariate and multivariate) and the ECOG score (p<0.001 in univariate analysis, p<0.05 in multivariate analysis) were significantly associated with QoL scores. In particular, the QLQ GLOBAL scores were lower among patients with ECOG equal to 1 or 2-4 compared to those with ECOG equal to 0; however, the difference tended to attenuate over time (p for interaction with time 0.022 and 0.085). A similar trend towards decreasing difference in QLQ GLOBAL scores with time also occurred in patients who were vs. those who were not treated with IMRT (interaction with time coefficient in multivariate models was 5.46, p = 0.063) (Table 5).

Loss of smell/taste

In Table 6, mean scores of the SNOT-22 single item number 12 (loss of smell/taste) are reported. Considering the whole sample, olfactory and gustatory impairment decreased significantly (p-value < 0.001) over time: at t0 mean score was 2.8 and at t2 was 1.7, as shown in Figure 4. Patients with advanced stages of the disease reported a statistically significant worse mean score at univariate analysis (p<0.001) but not at multivariate analysis. Finally, IMRT harmed subjective smell and taste perception in univariate and multivariate analysis, (p<0.001 and p=0.006, respectively), even though this difference decreased over time.

Table 2. Mean scores of the three questionnaires.

Variable	SNOT-22 (mean)			ASK-9 (mean)			QLQ GLOBAL (mean)		
	t0	t1	t2	t0	t1	t2	t0	t1	t2
Total sample	25.7	20.9	15.9	21.9	19.5	18.5	55.5	61.2	77.3
Gender									
M	23.9	18.5	13.3	21.3	18.7	18.0	59.1	63.5	78.4
F	33.0	30.5	26.5	24.3	22.4	20.6	40.9	52.3	72.7
Age at surgery									
<60 years	24.0	17.9	11.2	20.9	18.8	18.6	60.0	65.8	80.8
≥60 years	26.7	22.6	18.7	22.5	19.8	18.5	52.9	58.6	75.2
Smoking									
never	28.7	24.1	18.9	23.5	20.8	19.4	51.1	57.0	74.3
former	20.4	14.0	9.3	18.9	16.4	16.0	68.3	75.0	81.7
current	16.9	13.0	9.4	17.7	16.4	17.4	60.7	64.3	86.9
Psychotropic drug									
no	26.2	20.9	15.6	22.1	19.6	18.5	55.1	60.6	76.9
yes	17.3	19.7	22.3	18.3	17.7	19.0	61.1	72.2	83.3
ECOG									
0	14.1	10.2	8.1	19.6	17.0	16.7	69.0	74.7	81.0
1	26.9	24.5	20.4	21.1	20.3	18.6	47.0	53.6	78.6
2-4	42.8	20.9	15.9	26.4	22.6	21.3	41.7	46.9	70.3
Histotype									
ITAC	30,7	24,3	17,4	24,2	21,0	20,1	56,9	56,2	73,5
SCC	18,0	14,7	13,3	18,3	13,3	13,0	47,2	69,4	80,5
other	22,6	18,8	15,1	20,5	18,9	17,8	55,2	64,4	79,9
Type of surgery									
unilateral resection	22.9	19.1	15.1	20.6	18.1	17.6	58.8	65.7	79.3
bilateral resection	31.6	24.3	17.2	23.8	21.2	19.6	51.8	55.7	77.2
Skull base reconstruction									
no	24.4	20.5	16.0	20.9	19.1	18.2	52.7	60.4	76.6
yes	28.2	21.6	15.8	23.9	20.2	19.1	60.5	62.7	78.5
Major complications									
no	24.2	20.1	15.8	21.4	19.6	18.8	55.3	61.2	77.3
yes	40.4	28.4	17.4	27.0	18.2	15.6	56.7	61.7	76.6
IMRT									
no	11.6	6.2	6.0	18.3	14.3	14.7	73.2	83.0	85.5
yes	35.9	31.4	23.1	24.5	23.1	21.3	42.7	45.6	71.3

Male (M); Female (F); Intensity-modulated radiotherapy (IMRT); Sino-nasal outcome test (SNOT-22); Anterior skull-base nasal inventory (ASK-9); Item 29-30 EORTC QLQ-C30 (EORTC-QLQ GLOBAL); 1 month after treatment (t0); 6 months after treatment (t1); 18 months after treatment (t2), Adenocarcinoma intestinal-type (ITAC); Squamous cell-carcinoma(SCC).

Discussion

The management of SNM is complex because it requires strong expertise in many fields from pathology to both surgical and non-surgical treatments [7]. Because of the frequent involvement of adjacent orbital or brain structures, SNM and their treatments almost inevitably affect in various degrees visual function, nasal respiration, the sense of smell and taste, and some functions of the peripheral and central nervous system [17]. Therefore, it is unsurprising that this population shows an important reduction in QoL [10]. The present study has shown that such a deterioration

Table 3. SNOT-22 univariate and multivariate analysis.

				univariate								multivariate							
	SNOT-22 (mean)			random effects mixed models				interaction with time				random effects mixed models				interaction with time			
	t0	t1	t2	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p
Total sample	25.7	20.9	15.9	-4,88	-6,24	-3,52	<0.001					-2,64	-4,79	-0,49	0,016				
Gender																			
M	23.9	18.5	13.3	ref				ref				ref				ref			
F	33.0	30.5	26.5	11,48	0,56	22,41	0,039				0,231	5,75	-3,12	14,63	0,204	3,33	0,04	6,63	0,047
Age at surgery																			
<60 years	24.0	17.9	11.2	ref				ref				ref				ref			
≥60 years	26.7	22.6	18.7	2,55	-7,19	12,30	0,608	2,39	-0,41	5,18	0,094								
Smoking																			
never	28.7	24.1	18.9	ref				ref				ref				ref			
former	20.4	14.0	9.3	-9,35	-20,87	2,16	0,111				0,731								
current	16.9	13.0	9.4	-10,83	-24,14	2,50	0,111				0,568								
Psychotropic drug																			
no	26.2	20.9	15.6	ref				ref				ref				ref			
yes	17.3	19.7	22.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG performance																			
0	14.1	10.2	8.1	ref				ref				ref				ref			
1	26.9	24.5	20.4	13,44	3,74	23,13	0,007				0,865	5,15	-3,89	14,18	0,264				0,833
2-4	42.8	20.9	15.9	29,35	20,05	38,65	<0.001	-6,30	-9,28	-3,32	<0.001	18,94	9,86	28,01	<0.001	-6,32	-9,68	-2,95	<0.001
Histotype																			
ITAC	30,7	24,3	17,4	ref				ref				ref				ref			
SCC	18,0	14,7	13,3	-13,10	-34,30	8,20	0,228	4,30	-1,77	10,36	0,165								
other	22,6	18,8	15,1	-8,10	-17,80	1,50	0,098	2,87	0,11	5,63	0,041								
Stage																			
early	13.7	10.9	7.9	ref				ref				ref				ref			
advanced	32.5	26.6	20.5	18,79	9,88	27,70	<0.001	-3,11	-5,88	-0,34	0,028								
Type of surgery																			
Unilateral resection	22.9	19.1	15.1	ref				ref				ref				ref			
Bilateral resection	31.6	24.3	17.2	8,63	-1,24	18,50	0,087	-3,30	-6,05	-0,54	0,019								

	SNOT-22 (mean)			univariate							multivariate						
				random effects mixed models				interaction with time			random effects mixed models				interaction with time		
	t0	t1	t2	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p
Skull base reconstruction																			
no	24.4	20.5	16.0	ref				ref				ref				ref			
yes	28.2	21.6	15.8	3,52	-6,43	13,46	0,488				0,170								
Major complications																			
no	24.2	20.1	15.8	ref				ref				ref				ref			
yes	40.4	28.4	17.4	15,96	-0,29	32,21	0,054	-7,28	-11,82	-2,74	0,002								
IMRTw																			
no	11.6	6.2	6.0	ref				ref				ref				ref			
yes	35.9	31.4	23.1	25,82	18,26	33,38	<0.001	-3,57	-6,25	-0,89	0,009	20,05	12,44	27,67	<0.001				0,244

Male (M); Female (F); Intensity-modulated radiotherapy (IMRT); Sino-nasal outcome test (SNOT-22); 1 month after treatment (t0); 6 months after treatment (t1); 18 months after treatment (t2), Adenocarcinoma intestinal-type (ITAC); Squamous cell-carcinoma (SCC).

improves over time, and this is true for the many faces of QoL captured by the administered tools.

In our opinion, nasal irrigations and frequent follow-up appointments may have played a significant role in improving QoL. Moreover, frequent endoscopic evaluations were aimed at detecting possible treatment-related complications or early tumor recurrences.

QoL and HRQoL are usually interchangeable in both research and clinical practice, and the latter is generally divided into two broad domains: physical and nonphysical. Post-treatment symptoms in patients with SNM might be separated into these categories: physical and psychological consequences [18]. Starting from the former ones, it is possible to identify nasal, ocular, endocrine, and neurological impairments. Nasal complications such as obstruction or frequent epistaxis are not uncommon [19]. Anosmia is another frequent side effect of surgical treatment [20]. Our findings revealed that olfactory and gustatory impairment was often reported by patients in the immediate post-surgical period. Notwithstanding, subjective smell and taste perception improved over time. Interestingly, preservation of smell is possible in particular cases, even for esthesioneuroblastoma originating from the olfactory cleft [21]. Ocular symptoms may occur because of tumor extension, but diplopia, globe malposition, enophthalmos, persistent epiphora, recurrent dacryocystitis, and loss of visual acuity are often the effect of surgical resection [22-24]. Finally, keratopathy, visual field defects, and visual acuity impairments may occur because of postoperative radiation [6, 24]. Endocrine impairment can be traced back to irradiation of the hypothalamic-pituitary axis [25,26]. Intracranial extension of tumors through the dura or foramina at the base of the skull causes particular neurological impairments and complications [27]. Tumors can also invade the pterygopalatine and infratemporal fossae, with symptoms such as trismus, face discomfort, and numbness [22]. A cerebrospinal fluid leak is a common postoperative complication in patients who had extensive resections, and it can culminate in meningitis or an intracranial abscess. Pneumocephalus, hemorrhage, frontal syndrome, and consciousness impairment are only a few of the postoperative neurological problems [22-24].

Patients with SNM frequently present also nonphysical, i.e. psychiatric symptoms [28]. This could be due to the impairment of basic activities such as eating, speaking, working, and socializing, including the socio-economic and economic burden that comes with it [28-29].

For the first time in the literature, to the best of our knowledge, these three questionnaires (SNOT-22; ASK-9; EORTC-QLQ) are

Table 4. ASK-9 univariate and multivariate analysis.

Variable	univariate											multivariate							
	ASK-9 (mean)			random effects mixed models				interaction with time				random effects mixed models				interaction with time			
	t0	t1	t2	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p
Total sample	21.9	19.5	18.5	-1,71	-2,29	-1,12	<0.001					-1,71	-2,30	-1,12	<0.001				
Gender																			
M	21.3	18.7	18.0	ref				ref				ref				ref			
F	24.3	22.4	20.6	3,08	-0,95	7,10	0,135				0,855	3,41	0,06	6,76	0,046				0,868
Age at surgery																			
<60 years	20.9	18.8	18.6	ref				ref				ref				ref			
≥60 years	22.5	19.8	18.5	0,78	-2,63	4,19	0,654				0,173								
Smoking																			
never	23.5	20.8	19.4	ref				ref				ref				ref			
former	18.9	16.4	16.0	-4,74	-9,14	-0,35	0,034				0,424								
current	17.7	16.4	17.4	-5,96	-11,05	-0,87	0,022	1,92	0,17	3,67	0,031								
Psychotropic drug																			
no	22.1	19.6	18.5	ref				ref				ref				ref			
yes	18.3	17.7	19.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG performance																			
0	19.6	17.0	16.7	ref				ref				ref				ref			
1	21.1	20.3	18.6	2,23	-1,53	5,99	0,245				0,794								
2-4	26.4	22.6	21.3	5,67	2,07	9,27	0,002				0,119								
Histotype																			
ITAC	24,2	21,0	20,1	ref				ref				ref				ref			
SCC	18,3	13,3	13,0	-6,90	-14,00	0,31	0,061				0,655	-3,80	-10,28	2,75	0,257				0,922
other	20,5	18,9	17,8	-2,70	-5,90	0,58	0,107				0,229	-3,00	-6,06	0,13	0,060				0,150
Stage																			
early	18.2	15.4	15.5	ref				ref				ref				ref			
advan-ced	24.0	21.7	20.2	5,60	2,52	8,68	<0.001				0,397								
Type of surgery																			
Unilateral resection	20.6	18.1	17.6	ref				ref				ref				ref			
Bilateral resection	23.8	21.2	19.6	2,75	-0,53	6,02	0,101				0,336								

Variable	ASK-9 (mean)			univariate								multivariate							
				random effects mixed models				interaction with time				random effects mixed models				interaction with time			
	t0	t1	t2	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p
Skull base reconstruction																			
no	20.9	19.1	18.2	ref				ref				ref				ref			
yes	23.9	20.2	19.1	2,71	-0,93	6,35	0,144	-1,05	-2,26	0,17	0,091								
Major complications																			
no	21.4	19.6	18.8	ref				ref				ref				ref			
yes	27.0	18.2	15.6	4,72	-1,29	10,74	0,124	-4,39	-6,26	-2,52	<0,001								
IMRTw																			
no	18.3	14.3	14.7	ref				ref				ref				ref			
yes	24.5	23.1	21.3	7,19	4,45	9,93	<0,001				0,694	7,29	4,57	10,01	<0,001				0,702

Male (M); Female (F); Intensity-modulated radiotherapy (IMRT); Sino-nasal outcome test (SNOT-22); 1 month after treatment (t0); 6 months after treatment (t1); 18 months after treatment (t2), Adenocarcinoma intestinal-type (ITAC); Squamous cell-carcinoma (SCC).

used simultaneously to assess QoL in patients affected by SNM. Actually, none of the aforementioned questionnaires has ever been validated to assess sinonasal cancer patients' QoL. In fact, SNOT-22 and ASK-9 were initially designed to evaluate the QoL of patients who underwent endonasal surgery for chronic rhinosinusitis or skull base lesions, respectively [30-32, 16]. On the other hand, EORTC-QLQ is a general PROM that is commonly used to evaluate the QoL of patients affected by any malignancies, regardless of the site of the primary tumor [13,14]. Thus, we opted to administer the three questionnaires at the same time to capture the entire load of the symptom burden relevant to this patient population. In our cohort, the most frequent histotype presented is ITAC (41.82%), which is not in line with other series where the most common SNM is SCC [2]. The prevalence of ITAC in our population, may be explained by the geographic location of our University Hospital: Tuscany, an Italian region that is known to be rich in leather and wood manufacturers, which could explain such a great incidence of ITAC, a histotype which is strongly associated with leather and wood dust professional exposure [2,33]. On multivariate analysis, QoL is not significantly influenced by histotype, even if patients affected by ITAC had reported worse scores in ASK-9 (0.05 ≤ p-value ≤ 0.1). Data are shown in Tables 3, 4, and 5.

Many studies examined outcomes in patients with benign and malignant skull base diseases after open or endoscopic endonasal surgery, with a few getting RT [34]. Our results confirmed that IMRT is a negative prognostic factor for QoL, and adjuvant radiotherapy may exacerbate local symptomatology (anosmia, crusts, xerostomia, xerophthalmia) and it can also affect patients' mood [3,35,36]. Over time the QoL of our patients improved in all administered questionnaires, and even the differences between irradiated and non-irradiated subjects decreased over time, although this was not statistically significant (Tables 3, 4, and 5). Our experience lines up with other series: more than a year following surgery, patients who underwent adjuvant RT experience only a partial and slow recovery of QoL [37]. Aware of the higher difficulties complained by RT patients, we use to intensify in-patient visits to clean sinonasal cavities from mucus and crusting.

Instead, we noticed a conflicting result as to the impact of the type of EOSS on QoL: our data do not agree with the literature where more extensive surgical approaches (transnasal craniectomy with skull base reconstruction) are related to worse QoL [37,38]. In the work from Castelnuovo et al. [37], these differences in QoL between subjects who had and subjects who had not undergone transnasal craniectomy with skull base reconstruc-

Table 5. QLQ GLOBAL univariate and multivariate analysis.

Variable	univariate											multivariate							
	QLQ-GLOBAL (mean)			random effects mixed models				interaction with time				random effects mixed models				interaction with time			
	t0	t1	t2	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p
Total sample	55.5	61.2	77.3	10,91	8,20	13,61	<0.001					4,03	-0,32	8,38	0,069				
Gender																			
M	59.1	63.5	78.4	ref				ref				ref				ref			
F	40.9	52.3	72.7	-17,94	-31,87	-4,00	0,012	6,25	-0,41	12,92	0,066	-10,54	-19,42	-1,67	0,020				0,172
Age at surgery																			
<60 years	60.0	65.8	80.8	ref				ref				ref				ref			
≥60 years	52.9	58.6	75.2	-6,67	-17,02	3,68	0,206				0,785								
Smoking																			
never	51.1	57.0	74.3	ref				ref				ref				ref			
former	68.3	75.0	81.7	14,19	1,51	26,86	0,028				0,170								
current	60.7	64.3	86.9	9,82	-4,85	24,48	0,190				0,722								
Psychotropic drug																			
no	55.1	60.6	76.9	ref				ref				ref				ref			
yes	61.1	72.2	83.3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG performance																			
0	69.0	74.7	81.0	ref				ref				ref				ref			
1	47.0	53.6	78.6	-24,94	-37,46	-12,42	<0.001	9,78	3,41	16,14	0,003	-12,05	-23,30	-0,81	0,036	7,84	1,15	14,54	0,022
2-4	41.7	46.9	70.3	-30,26	-42,27	-18,25	<0.001	8,32	2,22	14,43	0,008	-14,12	-25,36	-2,87	0,014	5,85	-0,80	12,50	0,085
Histotype																			
ITAC	56,9	56,2	73,5	ref				ref				ref				ref			
SCC	47,2	69,4	80,5	3,53	-19,32	26,38	0,762				0,179								
other	55,2	64,4	79,9	4,27	-6,12	14,67	0,420				0,154								
Stage																			
early	69.2	76.2	85.8	ref				ref				ref				ref			
advan-ced	47.6	52.6	72.4	-19,55	-28,69	-10,41	<0.001				0,154								
Type of surgery																			
Unilateral resection	58.8	65.7	79.3	ref				ref				ref				ref			
Bilateral resection	51.8	55.7	77.2	-6,38	-16,01	3,24	0,194				0,391								

Variable	QLQ-GLOBAL (mean)			univariate								multivariate							
				random effects mixed models				interaction with time				random effects mixed models				interaction with time			
	t0	t1	t2	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p
Skull base reconstruction																			
no	52.7	60.4	76.6	ref				ref				ref				ref			
yes	60.5	62.7	78.5	3,99	-6,58	14,55	0,460				0,310								
Major complications																			
no	55.3	61.2	77.3	ref				ref				ref				ref			
yes	56.7	61.7	76.6	0,39	-17,18	17,95	0,965				0,834								
IMRTw																			
no	73.2	83.0	85.5	ref				ref				ref				ref			
yes	42.75	45.6	71.3	-35,51	-44,47	-26,54	<0.001	8,16	2,89	13,43	0,002	-30,26	-39,80	-20,72	<0.001	5,46	-0,29	11,21	0,063

tion decreased during the first year after surgery, and this issue should be further explored in the future.

In our experience, all patients have reported a significant improvement in QoL over time as shown in Figures 1, 2, and 3. In particular, considering SNOT-22, the delta of our total sample between scores at t0 and t2 is higher than Minimal Clinically Important Difference - MCID [39], therefore this variation may be considered clinically meaningful. We found this MCID specifically in the following categories: male, those under 60 years, never or former smokers, ECOG > 2, advanced stage, bilateral resection, skull base reconstruction, experiencing major complications, and undergoing IMRT.

Analyzing the independent predictors of QoL, we noticed that the female sex was significant in all questionnaires (Tables 3, 4, 5): this confirms the trend reported in the literature [40] and the reasons behind this increased susceptibility by females are complex and still poorly understood [41]. Differences between females and males in SNOT-22 scores tended to grow significantly after 18 months, whereas according to ASK-9 and QLQ-GLOBAL these variations were not significant.

Unexpectedly, we have found that smokers showed better ASK-9 scores than non-smokers (Table 4). Smoking is known to disrupt ciliary activity in the respiratory epithelium, to induce mucous hypersecretion and viscoelastic alteration; in addition, it favours the depletion of airway surface fluids, an increased oxidative stress, and the degradation of the inflammatory and immunological systems [42]. In our opinion, the chronic effects of smoking on respiratory mucosa could have led to a lower perception of the effects of cancer treatments rather than a summation of the effects. This represents an uncommon finding, as smoking habits are usually an irrelevant or even detrimental factor to QoL recovery after endonasal surgery [43,44].

Our results showed that age at treatment did not affect QoL significantly, and this is in line with other recent papers [45]. Notoriously, poor performance status was predictable of worst oncological outcomes in head and neck patients as they are usually older and with several comorbidities [46,47]. Even in our experience pre-treatment performance status had a greater impact on QoL in all three administered questionnaires. Fragile patients, with ECOG > 2, registered statistically significant worse scores in SNOT-22, ASK-9, and QLQ-GLOBAL. Curiously after 18 months, the differences between fragile patients and not ones according to SNOT-22 tended to decrease, while they increased considering QLQ-GLOBAL (Tables 3, 4, and 5).

The present study has some limitations: SNM are rare tumors and multicentric studies should be conducted to include a

Male (M); Female (F); Intensity-modulated radiotherapy (IMRT); Sino-nasal outcome test (SNOT-22); 1 month after treatment (t0); 6 months after treatment (t1); 18 months after treatment (t2), Adenocarcinoma intestinal-type (ITAC); Squamous cell-carcinoma (SCC).

Table 6. SNOT-22 item 12 (loss of taste/smell) univariate and multivariate analysis.

Variable	univariate											multivariate							
	SNOT-item 12 (mean)			random effects mixed models				interaction with time				random effects mixed models				interaction with time			
	t0	t1	t2	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p
Total sample	2,8	2,2	1,7	-0,58	-0,77	-0,38	<0.001					-0,58	-0,77	-0,38	<0.001				
Gender																			
M	2,9	2,2	1,8	ref				ref				ref				ref			
F	2,6	2,1	1,2	-0,32	-1,51	0,87	0,595				0,432								
Age at surgery																			
<60 years	2,6	2,0	1,2	ref				ref				ref				ref			
≥60 years	2,9	2,3	1,9	0,48	-0,53	1,50	0,350				0,388								
Smoking																			
never	3,0	2,5	1,9	ref				ref				ref				ref			
former	2,8	2,1	2,0	-0,14	-1,36	1,08	0,824				0,501								
current	1,9	1,1	0,1	-1,39	-2,80	0,01	0,052				0,331								
Psychotropic drug																			
no	2,8	2,2	1,6	ref				ref				ref				ref			
yes	2,3	2,0	2,3	0,00	-2,09	2,09	0,998				0,147								
ECOG performance																			
0	1,8	1,4	1,1	ref				ref				ref				ref			
1	3,6	2,8	2,1	1,42	0,32	2,53	0,012				0,120								
2-4	3,6	2,9	2,0	1,40	0,34	2,47	0,010	-0,44	-0,89	0,01	0,056								
Histotype																			
ITAC	3,4	3,0	2,3	ref				ref				ref				ref			
SCC	3,7	1,7	1,7	-0,56	-2,60	1,48	0,590				0,300	0,35	-1,69	2,38	0,738				0,307
other	2,2	1,7	1,1	-1,23	-2,18	-0,27	0,012				0,961	-0,78	-1,68	0,12	0,089				0,961
Stage																			
early	2,0	1,1	0,4	ref				ref				ref				ref			
advan-ced	3,3	2,8	2,4	1,65	0,75	2,56	<0.001				0,100	1,09	-0,16	2,33	0,087				0,103
Type of surgery																			
Unilateral resection	2,7	2,0	1,5	ref				ref				ref				ref			
Bilateral resection	3,2	2,7	2,1	0,64	-0,35	1,64	0,206				0,809	-0,60	-1,66	0,45	0,264				0,812

Variable	SNOT-item 12 (mean)			univariate						multivariate					
				random effects mixed models				interaction with time			random effects mixed models			interaction with time	
	t0	t1	t2	coeff	lower	upper	p	coeff	lower	upper	p	coeff	lower	upper	p
Skull base reconstruction															
no	2,7	2,1	1,5	ref				ref				ref			
yes	3,0	2,4	2,0	0,37	-0,67	1,40	0,488				0,589				
Major complications															
no	2,7	2,2	1,6	ref				ref				ref			
yes	4,3	2,5	2,0	0,75	-1,07	2,57	0,419				0,107				
IMRTw															
no	1,6	1,0	0,8	ref				ref				ref			
yes	3,7	3,1	2,3	1,86	1,01	2,71	<0.001				0,207	1,51	0,42	2,60	0,006	0,212

Male (M); Female (F); Intensity-modulated radiotherapy (IMRT); Sino-nasal outcome test (SNOT-22); 1 month after treatment (t0); 6 months after treatment (t1); 18 months after treatment (t2), Adenocarcinoma intestinal-type (ITAC); Squamous cell-carcinoma (SCC).

larger number of patients, as well as a pre-operative QoL assessment and a longer follow-up period, to gain more accurate outcomes about the factors that influence the subjects' QoL. Finally, QoL also depends on many cultural aspects, and our results from a European cohort may not be generalizable. In our opinion, with longer follow-up, QoL scores could be compared between the IMRT group vs non-IMRT and advanced vs early stages.

Conclusion

Sinonasal malignancies may heavily affect patients' QoL. As of today, satisfactory outcomes in terms of both disease-specific survival and overall survival may be expected, for those patients presenting with an early-stage tumor. It is therefore imperative for rhinologists to focus also on the best possible QoL. Practically, we need to offer close outpatient visits to constantly monitor patients' psychophysical status. For the first time in the literature, to the best of our knowledge, these three questionnaires (SNOT-22; ASK-9; EORTC-QLQ) have been used simultaneously to assess the quality of life of patients treated for nasosinusal neoplasms and how QoL changes over the time. Our analysis revealed that, besides the female sex, ECOG >2, and advanced stage, IMRT is the element that has the greatest impact on QoL. Because the delta between the QoL scores between these two groups decreased over time, these patients should be offered constant supportive care, especially in the initial months after surgery. Depending on their clinical conditions and questionnaire scores, we may tailor post-surgical steps and possibly identify patients who need multidisciplinary management and/or specialistic psychological support.

Authorship contribution

Conceptualization: OG, GM, PB, LGL, GF, AG; Data curation: GF, AG; Formal analysis: LGL, MC, SC; Investigation: OG, GM, LGL, GF, AG, PO; Methodology: GM, LGL, MC, SC; Supervision: GM, PB; Validation: GM, OG; Visualization: OS, GM, PB, LGL, SC; Roles/Writing – original draft: GF, AG, PO, LGL; Writing, review and editing: OG, GM, PB, MC, LGL.

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Conflict of interest

All authors declare they have no conflict of interest.

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