The Laryngoscope

Risk Factors for Fear of Recurrence in Head and Neck Cancer Patients

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Objective: Fear of recurrence (FoR) affects the quality of life of head and neck cancer survivors. Identification of factors predisposing to FoR may help to recognize and treat patients at risk.

Materials and Methods: For this exploratory study, 101 disease-free head and neck cancer survivors completed a cross-sectional survey in 2017 that included the FoR questionnaire at a random point in time during their follow-up. Additionally, the patients were asked to choose their favorite among four follow-up schedules with or without systematic imaging and varying frequency of visits.

Results: Elevated FoR was present in 36.6% of patients. Females and patients ≤65 years showed significantly higher FoR overall scores than males (score difference 3.40; CI 0.49–6.32; $p = 0.022$) and patients >65 years (score difference 4.25; CI 1.58–6.92; $p = 0.002$). A history of cancer recurrence or second primary malignancy increased the relative risk (RR) for elevated FoR (RR 1.7; CI 1.01–2.86; $p = 0.046$). Tumor stage and treatment modality were not significantly associated with elevated FoR or FoR overall score. Higher FoR overall scores were recorded in patients who favored intensive follow-up plans (mean overall FoR score 18 vs. 15; SD 7.7; $p = 0.076$) and systematic imaging in follow-up (17 vs. 13, SD 7.1; $p = 0.034$).

Conclusion: Fear of recurrence in head and neck cancer patients is associated with female sex, younger age, and history of a past recurrence or second primary malignancy. Due to its high prevalence, it should be addressed in clinical practice and future research.

Key Words: cancer follow-up, cancer recurrence, cancer survivors, fear of recurrence, head and neck cancer.

Level of Evidence: NA

***Laryngoscope*, 133:1630–1637, 2023**

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide and is associated with significant morbidity and mortality.[1] HNSCC patients have a comparably high risk of developing recurrences and second primary malignancies (SPM).[2] Depending on the initial tumor stage, loco-regional recurrence occurs in 15%–50% and is a major factor contributing toward HNSCC-related death.[3–5] Furthermore, patients with head and neck cancer have one of the highest rates of depression among all cancer patients.[6,7] It is therefore not surprising that these patients are vulnerable to develop clinically relevant fear of recurrence (FoR), which describes an "anxiety, worry or fear that cancer may return or progress."[8]

The exact definition of clinically relevant FoR has not yet been standardized in the literature and a globally accepted tool to measure FoR with validated cut-off levels is lacking, which is reflected in a variety of measurements and interpretations of cut-off values. The missing standardization makes it difficult to discern "normal" concerns from clinically relevant FoR and to quantify its prevalence and compare studies. A recent study[9] attempted to define the presence of clinically relevant FoR as follows: (a) high levels of preoccupation, (b) high levels of worry, (c) that are persistent, and (d) hypervigilance to bodily symptoms. Despite the lack of standardization, published research suggests that the prevalence of FoR in HNSCC survivors is high. Using a variety of scores, studies have reported the prevalence as high as 30%–67%.[10–14] Yet FoR is not only common but it has also been demonstrated to be one of the most important issues patients wish to discuss with their physicians.[10–14] Nevertheless, FoR is given little attention in clinical practice let alone in follow-up guidelines.[15–17] One of the challenges in tackling FoR is the difficulty to identify affected patients. Therefore, a better understanding of risk factors is paramount to develop and implement protocols capable to anticipate, identify and treat FoR.

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Editor's Note: This Manuscript was accepted for publication on July 25, 2022.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.30340

Studies published so far suggest that objective factors like tumor stage and prognosis play a minor role in FoR, whereas socio-demographic characteristics (e.g., age, sex) and psychological factors (e.g., pessimism) may represent risk factors.[10–12,18–21]

In this exploratory study, we investigated to what extent FoR was present among our HNSCC survivor cohort undergoing follow-up. The aim was to describe possible associations with clinical and socio-demographic factors. Furthermore, the study investigated if the level of FoR was associated with preferences in regard to the frequency of follow-up consultations and radiologic exams.

MATERIALS AND METHODS

Study design, setting, and patient selection

This assessment is an extrapolation of a previous study on HNSCC patients' preferences in post-treatment follow-up conducted at the Department of Oto-Rhino-Laryngology, Head and Neck Surgery, Inselspital, Bern University Hospital, Bern, Switzerland, a tertiary anticancer center.[22] We conducted a cross-sectional survey between July and September 2017. Participants were undergoing routine post-treatment follow-up for HNSCC. Patients treated with curative intent (any treatment modality) with complete remission at the initial clinical and radiologic assessment of treatment response at 3–4 months after treatment were eligible. Patients who had received successful salvage treatment for recurrence or SPM were also included. Patients with persistent disease, suspected recurrence, and/or cognitive deficits were excluded. The TNM classification of Malignant Tumors 7th edition of the Union for International Cancer Control manual was used for tumor staging.[23]

A single interviewer, a medical student (J.R.), conducted the survey. After participants had provided written consent, the questionnaire was explained to each participant in detail and completed without additional aid from the interviewer. Socio-demographic and clinical data were extracted from medical charts (Table I). The Bernese Cantonal Ethics Committee (Ref. 2017-00854) approved the study. Strengthening the reporting of observational studies in epidemiology guidelines for reporting cross-sectional studies are applied.[24]

Fear of recurrence questionnaire

The questionnaire used in this study was developed by Rogers et al.[10] and contains seven statements to be rated. It has high internal consistency and convergent validity in HNSCC patients.[11] Six questions (Q1–Q6) are rated on a 5-point Likert scale (1 = not at all; 5 = all the time), whereas a scale from 1 to 10 (1 = not at all; 10 = a great deal) applies to Q7 (Tables II and III). As proposed by the authors of the questionnaire, the presence of elevated FoR was defined if the score in any items Q1–Q6 was ≥4, or the score of Q7 was ≥7.[11] For this study, we have also calculated an FoR overall score, which we defined as the sum of scores of Q1–Q7 (range: 7–40), to quantify FoR.

The original English questionnaire was translated to German according to the European Organization for Research and Treatment of Cancer standards.[25] After translation by a native German speaker, the questionnaire was back-translated to English by an independent bilingual speaker. Deviations from the original were conciliated by a third party, and the final German version was approved by consensus.

TABLE I.
Socio-Demographic, Disease, and Treatment Characteristics.

Feature		Number of patients	%
Mean age ± standard deviation (range)	64.3 years ± 9.1 (47–86)		
Gender	Female	30	29.7
	Male	71	70.3
Highest education	Compulsory school (until 9th grade)	11	11.0
	Vocational training	79	79.0
	A-Level	10	10.0
Smoking habits	Active	36	35.6
	Ceased	42	41.6
	Never	23	22.8
Alcohol	≥1 unit/day	34	33.7
	<1 unit/day	67	66.3
Tumor site	Oral cavity	39	38.6
	Larynx	21	20.8
	Oropharynx	25	24.8
	Hypopharynx	4	4.0
	Nasopharynx	2	2.0
	Nose and paranasal sinus	4	4.0
	CUP*	4	4.0
	Multiple	2	2.0
T-stage	T0	4	4.0
	Tis	1	1.0
	T1	37	36.6
	T2	24	23.8
	T3	17	16.8
	T4	18	17.2
N-stage	N0	49	49.0
	N1	15	14.9
	N2	34	33.6
	N3	3	3.0
UICC tumor stage†	0 (CIS‡)	1	1.0
	I	30	29.7
	II	12	11.9
	III	18	17.8
	IVA-B	40	39.6
Treatment	(C)RT§ alone	34	33.7
	Surgery alone	31	30.7
	Surgery + adjuvant (C)RT§	36	35.6
Recurrence	No	93	92.1
	Yes	8	7.9
Other primary malignancies	No	63	62.4
	Upper aero-digestive tract	16	15.8
	Lung	6	5.9
	Other	16	15.8

*CUP, carcinoma of unknown primary.
†UICC, Union for International Cancer Control.[18]
‡CIS, carcinoma in situ.
§(C)RT, (chemo)radiotherapy.

Follow-up preferences

Patients were additionally asked to choose their favorite among four different follow-up schedules (schedules A, B, C, and D), which differed in the frequency of clinical follow-up and the inclusion of imaging, as previously published.[22]

- Schedule A: 3-monthly visits and annual loco-regional imaging during 2 years after treatment, 4-monthly visits in year 3, 6-monthly visits in years 4 and 5
- Schedule B: Same as schedule A in terms of visits, without loco-regional imaging; lung screening by low-dose CT for patients with substantial smoking history only
- Schedule C: Biannual visits for 5 years after treatment and annual loco-regional imaging during the first 2 years
- Schedule D: Same as schedule C in terms of visits, without loco-regional imaging; lung screening by low-dose CT for patients with substantial smoking history only

Statistical analysis

Categorical data are presented as a number with a percentage. Continuous variables are summarized as median with interquartile range (IQR), or as mean and standard deviation in case of the normal distribution as indicated by the respective label. To investigate the association of socio-demographic, disease-specific characteristics, and patient preferences with elevated FoR, we derived risk ratios using Poisson regression with robust standard errors for each variable, without further adjustment. Associations with FoR overall score were analyzed using linear regression analogously, hence for each variable separately without further adjustment. All analyses were done using Stata 16 (StataCorp LLC, College Station, TX, USA). Results were considered significant if the p-value was ≤0.05%.

RESULTS

Of 110 approached patients, eight patients refused participation and one was excluded due to cognitive deficits. Table I shows the socio-demographic and clinical characteristics of the 101 included patients. Mean age was 64.3 years (range 47–86 years; SD 9.1 years) and there was no significant difference in age between the sexes (females, mean 63.5 years, range 47–86 years; males, mean 64.6 years, range 51–84 years, $p = 0.42$). Patients were predominantly male (70.3%), and the majority had a history of smoking (77.2%). Over half of the patients (57.4%) presented with advanced-stage disease at first diagnosis. Recurrence occurred in eight (8%) patients. Sixteen (16%) patients suffered a previous or metachronous SPM of the upper aerodigestive tract (HNSCC: 11; esophagus: 3; trachea: 2), whereas 22 (22%) were diagnosed with other malignancies before or after treatment of the HNSCC, including patients with multiple cancers ($n = 26$ cancers: lung: 6; skin: 6; breast: 3; thyroid: 2; ovary: 2; prostate: 2; others: 5). Mean follow-up time after the initial diagnosis was 3.8 years (range: 3 months–19.6 years; median: 2.6 years).

FoR and clinical associations

Results of the study questionnaire are presented in Tables II and III. Table IV shows the relative risk (RR) for elevated FoR and the FoR overall score in association with clinical variables.

The mean FoR overall score was 16.2 (range 7–38; median IQR 14.8, 17.6). Elevated FoR as per the definition in the methods applied to 36.6% of the participants and those had significantly higher mean FoR overall scores than patients without elevated FoR (21.7 vs. 13.0; $p < 0.001$). Females demonstrated significantly higher FoR overall scores than males (score difference 3.40; CI 0.49–6.32; $p = 0.022$), and the RR for elevated FoR was higher in females but not statistically significant (47% vs. 32%, $p = 0.16$). The FoR overall score was significantly higher in patients ≤65 years than in patients >65 years (score difference 4.25; CI 1.58–6.92; $p = 0.002$), whereas RR for elevated FoR was also increased but not statistically significant (41% vs. 30%, $p = 0.264$). FoR overall score continuously and significantly decreased with increasing age (score difference per 10 years increase −2.37; CI −3.81 to −0.93; $p = 0.001$) (Table IV, Figure 1). None of the other clinical variables were

TABLE II.
Fear of Recurrence Questionnaire Items Q1–Q6.

			Score value *N* (%)					
Item	Statement	*N*	1 (Not at all)	2 (A little)	3 (Sometimes)	4 (A lot)	5 (All the time)	Median (IQR*)
Q1	I am afraid that my cancer may recur.	101	31 (30.7%)	24 (23.8%)	34 (33.7%)	8 (7.9%)	4 (4.0%)	2 (2, 3)
Q2	I am worried or anxious about the possibility of cancer recurrence.	101	23.8 (24%)	31 (30.7%)	35 (34.7%)	9 (8.9%)	2 (2.0%)	2 (2, 3)
Q3	How often have you worried about the possibility of getting cancer again?	100†	34 (34.0%)	26 (26.0%)	25 (25.0%)	11 (11.0%)	4 (4.0%)	2 (2, 3)
Q4	I get strong waves of strong feelings about cancer coming back.	101	40 (39.6%)	29 (28.7%)	21 (20.8%)	9 (8.9%)	2 (2.0%)	2 (2, 3)
Q5	I think about cancer returning when I did not mean to.	101	48 (47.5%)	30 (29.7%)	15 (14.9%)	4 (4.0%)	4 (4.0%)	2 (2, 2)
Q6	I examine myself to see if I have any physical signs of cancer.	101	38 (37.6%)	11 (10.9%)	26 (25.7%)	18 (17.8%)	8 (7.9%)	3 (3, 4)

*IQR, interquartile range.
†($N = 100$), one patient did not provide this information.

TABLE III.
Fear of Recurrence Questionnaire—Item Q7.

Item	Statement	*N*	Score value *N* (%)										
			1	2	3	4	5	6	7	8	9	10	Median (IQR*)
Q7	To what extent does worry about getting cancer again spill over or intrude on your thoughts and activities?	101	34 (33.7%)	22 (21.8%)	19 (18.8%)	11 (10.9%)	1 (1.0%)	4 (4.0%)	3 (3.0%)	4 (4.0%)	0 (0.0%)	1 (1.0%)	2 (2, 4)

*IQR, interquartile range.

associated with a significant difference in FoR overall score (Table IV).

Compared to oral cavity HNSCC, RR for elevated FoR was significantly lower in patients with laryngeal cancer (RR 0.38; CI 0.15–0.97; $p = 0.044$), and trended lower in pharyngeal cancer (RR 0.53; CI 0.27–1.05; $p = 0.067$).

Patients who had suffered from a recurrence, SPM, or both, ($n = 44$, 44%) had a significantly increased RR for elevated FoR (RR 1.70; CI 1.01–2.86; $p = 0.046$), whereas the increase in mean FoR overall score was not significant (score difference 1.63; CI −1.11 to 4.37; $p = 0.24$).

Tumor stage, treatment modality, and the elapsed time between diagnosis and the survey were neither significantly associated with the FoR overall score nor with the relative risk of elevated FoR (Table IV).

Follow-up preferences

Patients who favored intensive follow-up plans (schedules A and B; see Materials and Methods) trended toward higher FoR overall scores (mean overall FoR score 18 vs. 15; SD 7.7; $p = 0.076$). Those patients who favored follow-up plans that included regular imaging had significantly higher FoR overall scores than those favoring follow-up plans without systematic imaging (mean overall score 17 vs. 13; SD 7.1; $p = 0.034$). Females showed a tendency toward intensive follow-up plans compared to men, but this result did not reach statistical significance (schedules A and B; 59% vs. 37%; $p = 0.074$).

DISCUSSION

This study performed among HNSCC patients undergoing follow-up after curative treatment aimed to determine factors that predispose patients to elevated FoR and to elicit the follow-up preferences of patients suffering from FoR. Our results showed that elevated FoR is associated with female sex, age ≤65 years, and history of a past recurrence or SPM, whereas other tumor- and treatment-related factors play a secondary role.

Prevalence of FoR in HNSCC patients

It is important to distinguish between "normal" worries and a clinically relevant FoR.[8,9] Only seven patients in our cohort (7%) claimed to have no FoR in all of the seven items. To some degree, "normal" FoR may even have a positive effect on patients' vigilance toward new symptoms and prompt early self-referral in case of a recurrence.[26] Clinically relevant FoR, on the other hand, has a serious impact on patients' quality of life.[8–14,27–32] Our study confirmed that FoR is a common problem among HNSCC patients, with 36.6% of our cohort affected by elevated FoR. This number is in line with earlier reports by Ghazali et al.[11] (35%) and Rogers et al.[10] (40%), who used the same questionnaire. Unfortunately, there is still no standardized, globally accepted measurement of FoR.

TABLE IV.
Relative Risk for Elevated Fear of Recurrence and Total Score in Relation to Clinical Variables.

Clinical variable	Elevated FoR			FoR overall score		
	No. of patients with elevated FoR	RR* (95% CI†)	*p*-value (*p*-value per category)	Mean score ± SD‡	Mean score difference (95% CI†)	*p*-value
Gender						
Male, *n* = 71	23 (32.4%)	Reference	0.16	15 ± 6.1	Reference	0.022
Female, *n* = 30	14 (46.7%)	1.44 (0.86 to 2.40)		19 ± 8.4	3.40 (0.49–6.32)	
Age						
Age >65 years, *n* = 43	13 (30.2%)	Reference	0.264	14 ± 5.3	Reference	0.002
Age ≤65 years, *n* = 58	24 (41.4%)	1.37 (0.79–2.37)		18 ± 7.6	4.25 (1.58 to 6.92)	
Age per 10 years increase	na§	0.78 (0.57–1.07)	0.12	na§	−2.37 (−3.81 to −0.93)	0.001
UICC tumor stage‖						
0-I, *n* = 31	12 (38.7%)	Reference	(0.19)	17 ± 8.5	Reference	(0.26)
II, *n* = 12	4 (33.3%)	0.86 (0.34–2.16)	0.75	14 ± 4.6	−2.51 (−7.19 to 2.17)	0.29
III, *n* = 18	10 (55.6%)	1.44 (0.78–2.64)	0.24	19 ± 6.4	1.96 (−2.12 to 6.04)	0.34
IV, *n* = 40	11 (27.5%)	0.71 (0.36–1.39)	0.32	15 ± 6.4	−1.40 (−4.70 to 1.89)	0.40
UICC tumor stage‖						
0-II, *n* = 33	16 (48.5%)	Reference	0.92	16 ± 7.6	Reference	0.81
II-IV, *n* = 58	21 (36.2%)	0.97 (0.58–1.64)		16 ± 6.5	0.34 (−2.42 to 3.11)	
Tumor site						
Oral cavity, *n* = 40	20 (50.0%)	Reference	(0.079)	16 ± 7.3	Reference	(0.98)
Nose, nasopharynx, CUP¶, *n* = 10	5 (50.0%)	1.00 (0.50–2.01)	1	17 ± 7.2	0.77 (−4.19 to 5.74)	0.76
Oropharynx, hypopharynx, *n* = 30	8 (26.6%)	0.53 (0.27–1.05)	0.067	16 ± 6.6	−0.18 (−3.57 to 3.22)	0.92
Larynx, *n* = 21	4 (19.0%)	0.38 (0.15–0.97)	0.044	16 ± 7.3	−0.37 (−4.15 to 3.42)	0.85
Treatment						
(C)RT alone, *n* = 34	9 (26.5%)	Reference	(0.31)	16 ± 6.8	Reference	(0.86)
Surgery alone, *n* = 31	14 (45.2%)	1.71 (0.86–3.38)	0.13	16 ± 8.0	0.41 (−3.06 to 3.88)	0.82
Surgery + adjuvant (C)RT#, *n* = 36	14 (38.9%)	1.47 (0.73–2.95)	0.28	17 ± 6.3	0.92 (−2.42 to 4.26)	0.59
Recurrence or second primary malignancies						
Neither, *n* = 57	16 (28.1%)	Reference	0.046	15 ± 6.2	Reference	0.24
Recurrence or second primary malignancies, *n* = 44	21 (47.7%)	1.70 (1.01–2.86)		17 ± 7.8	1.63 (−1.11 to 4.37)	
Smoking habits						
Never, *n* = 23	7 (30.4%)	Reference	0.61	14 ± 5.5	Reference	0.13
Active or ceased smoker, *n* = 78	30 (38.5%)	1.19 (0.61–2.35)		17 ± 7.3	2.55 (−0.73 to 5.82)	
Alcohol**						
<1 unit/day, *n* = 67	23 (34.3%)	Reference	0.74	16 ± 6.8	Reference	0.93
≥unit/day *n* = 34	13 (38.2%)	1.10 (0.64–1.89)		16 ± 7.3	−0.13 (−3.03 to 2.77)	
Highest education**						
Compulsory school (until 9th grade), *n* = 11	2 (18.2%)	Reference	(0.45)	16 ± 7.1	Reference	(0.96)
Vocational training, *n* = 79	31 (39.2%)	2.16 (0.59–7.84)	0.24	16 ± 7.0	0.43 (−4.07 to 4.93)	0.85
A-level, *n* = 10	3 (30.0%)	1.65 (0.34–8.00)	0.53	17 ± 7.3	0.88 (−5.23 to 6.99)	0.78
Time since first cancer diagnosis (per 1-year increase)	na§	1.03 (0.97–1.09)	0.35	na§	0.09 (−0.30 to 0.47)	0.65

*RR, risk ratio.
†CI, confidence interval.
‡SD, standard deviation.
§na, Age per 10y increase and time since diagnosis as continuous variables do not induce groups of patients, hence proportion of elevated FoR and mean FoR could not be calculated.
‖UICC, Union for International Cancer Control.[18]
¶CUP, carcinoma of unknown primary.
#(C)RT, (chemo)radiotherapy.
**(N = 100), one patient did not provide this information.

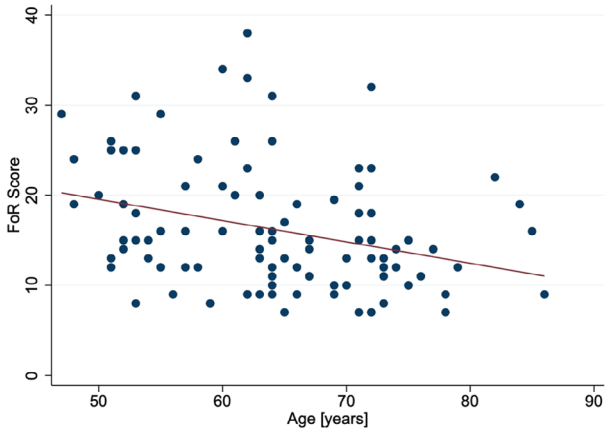

Fig. 1. FoR overall score per 10 years increase. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Impact of socio-demographic factors

A predisposition for FoR in females and young patients has been described across multiple cancer types,[11,12,18,33–36] but Simard et al.[19] concluded that this association disappears when controlled for cancer site. In contrast, a recent meta-analysis by Pang and Humphris[37] found an association between female gender and higher levels of FoR. In our study, the significantly higher FoR overall scores in females suggest that such an association is likely in HNSCC, although the increase in the RR did not reach statistical significance, which we attribute to the limited sample size. The role of gender in FoR warrants further investigation. There is less controversy on the association between young age and FoR,[19] where our study also found significantly higher FoR overall scores. We can only speculate, but the endangering of familial or career planning may present a higher psychological impact on young patients. Our study did not find a significant association between educational levels and elevated FoR. Existing literature on this association is controversial, with both high-level and low-level educational backgrounds being associated with FoR.[21,34,38]

Although not statistically significant, the relative risk for elevated FoR and mean FoR overall score was higher in current and ex-smokers than in never-smokers in our cohort. A study by Asen et al.[39] found that an internal attribution of the cause of cancer (e.g., smoking) predisposed patients to FoR. This is corroborated by other studies.[27,40,41]

Impact of tumor- and treatment-related factors

Neither tumor stage nor treatment modality exhibited any association with FoR. This is surprising because the treatment of advanced HNSCC is more invasive, rehabilitation takes longer and the lasting functional consequences are more severe. Indeed, studies reported that pain, functional impairment, or complaints related to side effects of treatment were associated with FoR.[13,33] On the other hand, studies including various types of cancer agreed that tumor stage and FoR do not correlate.[36,42] This reflects the fact that the severity of symptoms, as perceived by the patients, does not necessarily correspond with objective findings and may in some cases even be an expression of underlying anxiety or depression.[43]

Impact of follow-up duration and course of disease

Although negatively correlated with age, there was no statistically significant decline in FoR with the increased time between first diagnosis in our survey, which is in line with results from studies across the whole cancer spectrum.[33,36]

The course of the disease, on the other hand, may have an impact on FoR. Patients who suffered a recurrence or an SPM more often had elevated FoR ($p = 0.046$) and tended to have higher FoR overall scores ($p = 0.24$). This association has not been addressed in hitherto published HNSCC-specific literature but is described in other cancers.[44,45]

Follow-up preferences and FoR

Our results suggest that those patients, who prefer intensive follow-up schedules and systematic imaging, are affected by more elevated levels of FoR than patients favoring less intensive follow-up schedules and no systematic imaging. One could argue that patients suffering from FoR may find reassurance in more frequent exams and indeed, studies looking at cancer patients, in general, show a tendency for patients with FoR to have significantly more self-initiated follow-up.[46] On the other hand, some studies demonstrate that FoR may be triggered by extrinsic factors such as medical consultations.[34,47–49] Our study cannot conclude whether the preference for more frequent follow-up visits reflects a desire of patients with FoR for close surveillance, or whether such frequent consultations are actually a driver of FoR. Literature also shows that patients with FoR, those who use disengaging coping strategies (avoidance coping), avoid medical visits to prevent facing their FoR.[50] We are not aware of any other study that investigated the follow-up preferences of HNSCC patients considering FoR.

Implications for clinical practice

Although patients consider FoR the most important topic they wish to discuss with their physician,[15] this discussion is commonly forgone during consultation.[16] It is a challenge to identify patients with FoR, especially in high-throughput follow-up centers. Here, patients are often seen by different physicians, and the development of a relationship where patients feel comfortable in communicating their fears is difficult. Several studies indicate that patients feel that they are not given enough opportunity to express their fears.[16,17] There is thus significant potential for improvement if clinicians recognize and address the issue. This exploratory study augments the limited existing literature on FoR and provides evidence for some indicators, whereas its design does not

allow to provide definitive clinical recommendations. Taking into account these results and published literature, we suggest the following measures: (1) the sensitization of clinicians on FoR and its consequences. It is important to convey the message that FoR is independent of disease severity, stage, or treatment. Physicians need to be particularly aware of the increased risk of relevant FoR of female and younger patients and patients with recurrent disease or an SPM; (2) the establishment of a setting that allows patients to communicate their concerns. In high-throughput cancer centers, many patients will find it hard to speak about their fears; therefore, (3) systematic screening at specific consultations (e.g., after confirmation of treatment response) may be applied to identify patients at risk. Tools such as the nine-item Fear of Cancer Recurrence Inventory severity subscale can be used for screening,[38] but even a single item questionnaire may suffice[12]; (4) provision of timely access to professional psychological support. A variety of therapeutic interventions have proven to be effective in reducing anxiety and FoR.[51] Such interventions should ideally take place early in the follow-up.[52]

Limitations

The cohort size of this study was limited, and the study population was heterogeneous concerning certain variables (e.g., age, sex, time after diagnosis), whereas some tumor localizations were underrepresented, resulting in large confidence intervals and thus, some weaker but real associations may not have reached statistical significance. In addition, a study in a single institution may not be representative of an international population. The assessment was not longitudinal; there was only a single assessment at a random time in follow-up. The study did not include assessments of anxiety in general, which would have been of interest concerning follow-up preferences. Finally, we cannot fully exclude that factors that were not assessed may have an impact on FoR. The used FoR questionnaire has several limitations, as it does not allow to gauge the severity of FoR. The FoR overall score we have used in this study to quantify FoR lacks a defined cut-off point and does not allow us to clearly identify patients whose FoR is clinically relevant and warrants treatment. Although the severity of FoR correlates with the quality of life of HNSCC patients,[13] it remains to be proven that this correlation is replicated by the FoR overall score.

CONCLUSION

This exploratory study identified females, younger patients, and patients who suffered a recurrence or SPM as risk groups for elevated FoR, whereas FoR appears to occur independently of cancer- and treatment-related factors and may manifest even in patients with good prognosis. Research on FoR in HNSCC patients is in its infancy and further hypothesis-testing studies will be needed to explore this topic. To provide a basis for further research in this area, the development of a universally accepted measurement tool for FoR is essential.

ACKNOWLEDGMENT

We would like to thank PD Dr. med. Sven Trelle, Director of the Clinical Trials Unit, University of Bern, Bern, Switzerland, for the assistance and support by him and his team. Open access funding provided by Universitat Zurich.

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