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Clinical Investigation

Patient-Reported Toxicity and Quality-of-Life Profiles in Patients With Head and Neck Cancer Treated With Definitive Radiation Therapy or Chemoradiation

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Purpose: Radiation therapy is an effective but burdensome treatment for head and neck cancer (HNC). We aimed to characterize the severity and time pattern of patient-reported symptoms and quality of life in a large cohort of patients with HNC treated with definitive radiation therapy, with or without systemic treatment.

Methods and Materials: A total of 859 patients with HNC treated between 2007 and 2017 prospectively completed the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire−Head and Neck Cancer module (QLQ-HN35) and Core Quality of Life Questionnaire (QLQ-C30) at regular intervals during and after treatment for up to 5 years. Patients were classified into 3 subgroups: early larynx cancer, infrahyoideal cancer, and suprahyoideal cancer. Outcome scales of both questionnaires were quantified per subgroup and time point by means of average scores and the frequency distribution of categorized severity (none, mild, moderate, and severe). Time patterns and symptom severity were characterized. Toxicity profiles were compared using linear mixed model analysis. Additional toxicity profiles based on age, human papillomavirus status, treatment modality, smoking status, tumor site, and treatment period were characterized as well.

Results: The study population consisted of 157 patients with early larynx cancer, 304 with infrahyoideal cancer, and 398 with suprahyoideal cancer. The overall questionnaire response rate was 83%. Generally, the EORTC QLQ-HN35 symptoms reported showed a clear time pattern, with increasing scores during treatment followed by a gradual recovery in the first

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2 years. Distinct toxicity profiles were seen across subgroups ($P < .001$), with generally less severe symptom scores in the early larynx subgroup. The EORTC QLQ-C30 functioning, quality-of-life, and general symptoms reported showed a less evident time pattern and less pronounced differences in mean scores between subgroups, although differences were still significant ($P < .001$). Differences in mean scores were most pronounced for role functioning, appetite loss, fatigue, and pain.

Conclusions: We established patient-reported toxicity and quality-of-life profiles that showed different patterns for 3 subgroups of patients with HNC. These profiles provide detailed information on the severity and persistence of various symptoms as experienced by patients during and after definitive radiation therapy. These profiles can be used to inform treatment of future patients and may serve as a benchmark for future studies.

Introduction

Radiation therapy with or without systemic treatment and surgery are the cornerstones of treatment of head and neck cancer (HNC). Patients with HNC treated with definitive (chemo)radiation therapy experience a wide spectrum of symptoms with varying severity and course over time.[1,2] Even though modern radiation therapy techniques have allowed for dose reduction to normal tissues and a reduced symptom burden, acute and late treatment-related symptoms are still considerable, significantly affecting several aspects of short- and long-term quality of life.[3-7]

In recent years, prevention and proactive management of treatment-related symptoms has gained increasing interest as the prevalence of long-term survivors of HNC with substantial toxicity burden rises.[8-12] To effectively prevent and manage symptoms, regular prospective scoring of symptoms and monitoring of their effects on quality of life are paramount. This scoring can be done by health care providers as well as by patients. As health care providers tend to underestimate patients' symptoms, there is an increasing awareness that patient-reported outcomes provide important additional information on the outcome of treatment.[13-15] The European Organization for Research and Treatment of Cancer (EORTC) has developed a series of questionnaires to examine health-related quality of life in patients with cancer. The Core Quality of Life questionnaire (EORTC QLQ-C30) measures patients' general dimensions of quality of life and daily functioning.[16] The EORTC QLQ-HN35 questionnaire examines specific HNC-related symptoms.[17] Both questionnaires have been externally validated and are widely implemented in clinical trials and in routine daily practice.[16,18,19]

Unfortunately, detailed longitudinal characterization of patient-reported symptoms and quality of life is currently lacking. Such data could provide invaluable information on the prevalence, time of onset, and recovery patterns of the toxicity burden and could be used to better inform patients about the expected symptom burden during and after treatment. Moreover, it could raise awareness among physicians of the most common and severe symptoms as perceived by patients to improve interventional decision-making. Additionally, it may attract attention to symptoms that have hitherto been studied less widely and may require further research.

Therefore, the aim of this study was to describe longitudinal patient-reported symptoms and quality-of-life profiles based on the EORTC QLQ-HN35 and QLQ-C30 questionnaires in a large cohort of patients with HNC and to identify clinically relevant subgroups.

Methods and Materials

Study population

Patients included in this study were treated with definitive radiation therapy, with or without systemic agents, between January 2007 and December 2017 at the University Medical Center Groningen. They had stage I to IV squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx, without distant metastases at the time of treatment. They were not subjected to previous HNC treatments (excluding transoral laser surgery of small glottic lesions), and they did not have synchronous tumors outside the head and neck region. Patients treated with induction chemotherapy were excluded.

Prospective data registration program

All patients were enrolled in a prospective data registration program (Clinical trials NCT 02435576) as part of routine clinical practice, collecting baseline characteristics and patient-reported outcomes (EORTC QLQ-HN35 and QLQ-C30 [version 3.0] questionnaires).[16-18] The questionnaires were completed before treatment, weekly during treatment (except for items regarding less sexuality on the QLQ-HN35 questionnaire), and after treatment. The posttreatment questionnaires were completed at 12 weeks after the start of treatment, then every 6 months for 2 years, and then annually for the subsequent 3 years. Questionnaires were completed electronically at the radiation oncology department before planned follow-up visits. Help during completion of the questionnaires was provided if needed. If a patient was unable to come to the department, paper questionnaires were mailed out, including a stamped return envelope. Returned paper questionnaires were digitalized. There was no specific policy regarding the continuation or discontinuation of follow-up in case of recurrent disease. In general, patients undergoing curative salvage treatment continued follow-up

at the radiation oncology department, whereas patients starting palliative care discontinued follow-up.

The prospective data registration program was approved by the institutional review board. The requirement of informed consent was waived by the institutional review board, because the Dutch Medical Research Involving Human Subjects Act is not applicable to data collection as part of routine clinical practice. However, patients were able to decline participation by opting out.

Treatment

Patients were treated according to the Dutch guidelines for HNC. In general, patients younger than 70 years with stage I to II disease received accelerated radiation therapy (6 fractions per week), whereas those with locally advanced disease were treated with concomitant chemoradiation. They received 3 courses of carboplatin (day 1, 300-350 mg/m^2) and 5-fluorouracil (day 1-4, 600 mg/m^2/24 h) every 3 weeks. Patients with a T3-T4N0 larynx carcinoma received 3 courses of cisplatin (100 mg/m^2) on day 1, 22, and 43. Elderly patients (those older than 70 years) were treated with conventional fractionated radiation therapy. Accelerated radiation therapy with weekly cetuximab (400 mg/m^2 1 week before radiation therapy, followed by weekly 250 mg/m^2 during radiation therapy) was reserved for younger patients deemed unfit for chemotherapy and for some elderly patients in good general condition with locally advanced disease. Radiation treatment consisted of intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT), except for 53 patients with early-stage glottic cancer who were treated with 3-dimensional conformal radiation therapy (3D-CRT). The primary tumor and pathologic lymph nodes, if present, received 70 Gy in 2-Gy fractions. Elective lymph node regions were treated with a simultaneous integrated boost up to 54.25 Gy in fractions of 1.55 Gy. In T1N0 glottic cancer, 66 Gy to the primary tumor was prescribed.

Toxicity outcomes

All scales of the EORTC QLQ-HN35 and QLQ-C30 were assessed. Most scales consisted of 1 or more questions using a 4-point Likert scale, except for painkillers, nutritional supplements, tube feeding, weight loss, and weight gain, which were single-item binary (no or yes) scales, and global health status, which consisted of two 7-point scale questions. Scale scores (0-100) were calculated following the EORTC manual, including the management of missing data.[20] For symptom scales, higher scores represented more severe symptoms. For functional scales and global health status, higher scores represented better functioning. Subsequently, scores were categorized as none, mild, moderate, and severe. For symptoms, functional scales, and global health status, respectively, the cutoff points were scores of 0 to 100 for none, 1 to 33.33 and 99 to 66.67 for mild, 33.33 to 66.67 and 66.67 to 33.33 for moderate, and >66.67 and <33.33 for severe. Missing outcomes were attributed to recurrent disease (local, regional, metastases, or a combination thereof), death, follow-up not yet reached, or noncompliance (ie, not completing any parts of the questionnaires for any reason, including patients lost to follow-up owing to high symptom burden or patients with unknown diagnosis of recurrent disease).

Subgroup classification

Patients were classified in 3 subgroups: (1) the early larynx subgroup, consisting of patients with locally treated T1-2N0 laryngeal cancer; (2) the infrahyoideal subgroup, consisting of patients with a tumor below the hyoid bone (ie, hypopharynx or larynx); and (3) the suprahyoideal subgroup, consisting of patients with a tumor of the oral cavity, nasopharynx, or oropharynx. This separation was derived from a k-means cluster analysis that used the standardized mean radiation dose to 16 organs at risk (OARs) of the head and neck region to identify 3 clusters (Table E1). Because radiation exposure of OARs is the main contributor to toxicity, clustering patients based on radiation dose parameters was expected to lead to subgroups with distinct toxicity profiles. After the k-means cluster analysis, the main determining patient, tumor, and treatment characteristics of each cluster were identified. For example, cluster 3 contained only patients with laryngeal cancer in whom almost all tumors (99.4%) were stage T1-T2, whereas cluster 1 mainly consisted of patients with a tumor above the hyoid bone (ie, tumors of the oral cavity, nasopharynx, or oropharynx; 99.2%) (Table E1). Finally, the main determining characteristics of each cluster were used to classify the cohort into 3 subgroups.

In addition, 6 alternative classifications based on other potentially clinically relevant factors were explored: (1) age (≤70 years vs >70 years);[8,9,21-23] (2) human papillomavirus (HPV) status of oropharyngeal tumors (negative, positive, or unknown);[24-25] (3) concomitant systemic treatment (chemotherapy or cetuximab—no vs yes);[26-29] (4) smoking status (current, former, or never smoker);[30-32] (5) tumor site (oral cavity, nasopharynx, oropharynx, hypopharynx, or larynx); and (6) treatment period (2007-2013 vs 2014-2017).

Statistical analyses

Per subgroup, the mean score, standard deviation (SD), and standard error of the mean (SEM) of all scales were calculated. For single-question binary scales, the mean score indicated the percentage of patients who responded to that item. For example, a mean score of 62 for painkiller use at week 6 of treatment meant that 62% of the patients used painkillers at that time point. Differences in mean scores over time between subgroups were evaluated and tested for statistical significance per outcome scale with random-intercept linear mixed models and likelihood ratio tests. For

each outcome scale, a linear mixed model with random effects for time and patient was compared with a linear mixed model that also included a fixed effect for subgroup. A significant difference in likelihood between both models, evaluated with a likelihood ratio test, indicated that subgroups exhibited different toxicity profiles. In addition, for the 3 main subgroups, the proportional frequency distribution of the categorized scales was calculated. All subgroup scores were based on a complete case analysis per scale and time point.

Furthermore, mean scale scores using imputed data (10 imputations) were calculated to assess the effect of bias owing to missing data in the complete case analysis. Imputed data were obtained using multiple imputation by chained equation.[33,34]

Results

In total, 859 patients with HNC were included and classified in 3 subgroups: early larynx (157 patients), infrahyoideal (304 patients), and suprahyoideal (398 patients). Baseline characteristics are listed in Table 1. The patients in the early larynx subgroup had a mean age of 68 years; 40% were current smokers and 50% were former smokers. They were all treated with radiation alone (33% conventional and 67% accelerated) without elective neck irradiation. The patients in the infrahyoideal subgroup had a mean age of 64 years, and 61% were current smokers. Of patients in this subgroup, 72% had a tumor located in the larynx and 28% had a tumor in the hypopharynx. The majority of these patients (69%) had T3 or T4 tumors, and 51% had pathologic lymph nodes. They were mostly treated with radiation alone (22% with conventional and 45% with accelerated radiation) and bilateral neck irradiation (99%). The patients in the suprahyoideal subgroup had a mean age of 62 years; 54% were current smokers and 32% were former smokers. The majority (78%) had oropharyngeal tumors. Other primary tumor sites included the oral cavity (14% of the patients) and the nasopharynx (8% of the patients). Most of these patients (61%) had T3 or T4 tumors, and 81% had pathologic lymph nodes. The main treatment modality was chemoradiation (53% of patients), and 95% of these patients received bilateral neck irradiation.

Missing data were more prevalent at later time points owing to an increasing number of deceased patients, patients with recurrent disease, and patients with shorter follow-up times (Table E2). Of the patients in follow-up, the questionnaire response rate for all scales ranged from 91% at early time points to 71% at 5 years (Table E3). The overall response rate was 83%.

The mean EORTC QLQ-HN35 scores per subgroup are shown in Figure 1. All mean scores, SDs, and SEMs are listed in Table E4. Most symptoms showed a clear time pattern with rapidly increasing scores reaching a maximum at the end of treatment (week 6-7), followed by recovery until 24 months. For weight gain, a different pattern was seen, as patients tended to gain weight after treatment. For some symptoms, no clear time pattern was observed because the symptoms had a constant low prevalence (eg, problems with teeth and problems with social contact). Some symptoms improved in almost all cases (eg, tube-feeding use, for which scores returned to baseline levels in all patients by 24 months), whereas other symptoms only partially improved (eg, dry mouth, for which the mean scores for all patients ranged from 36-40 at 12-60 months, compared with 25 at baseline). Use of nutritional supplements and painkillers peaked early during treatment. From week 4 to 7, an average of 63% and 81% of patients used nutritional supplements and painkillers, respectively. At later time points (12-60 months), these were reduced to 17% and 29% on average, which is lower compared with baseline use (26% and 57% for use of nutritional supplements and painkillers, respectively). Symptom severity varied among the subgroups and was generally less pronounced in the early larynx subgroup, except for coughing and speech problems, which were lowest in the suprahyoideal subgroup. Overall, the mean symptom scores were 15, 25, and 30 for the early larynx, infrahyoideal, and suprahyoideal subgroups, respectively. The highest differences between subgroups were seen for opening the mouth at week 6 (mean score of 5 in the early larynx subgroup vs 45 in the suprahyoideal subgroup) and tube feeding use at week 7 (mean score of 3 in the early larynx subgroup vs 64 in the suprahyoideal subgroup) for nonbinary and binary items, respectively. The proportions of patient complaints ranging from none to severe are presented in Figure 2 and Table E5.

The mean EORTC QLQ-C30 scores per subgroup are shown in Figure 3. All mean scores, SDs, and SEMs are listed in Table E6. For global health and functional scales, high mean scores were seen, with an overall mean score of 83 (Fig. 3A). In general, functional-scale scores decreased slightly at 12 weeks compared with baseline, with an average decline of 5 points. The largest decrease was seen for role functioning (15-point decline compared with baseline in all patients). The early larynx subgroup had a slightly better level of physical, role, and social functioning as well as a better global health status compared with the other subgroups. The largest difference was seen for role functioning at 12 weeks between the early larynx and the suprahyoideal subgroups (mean score of 82 in the early larynx subgroup vs 64 in the suprahyoideal subgroup). For general symptoms, low mean scores were observed, with an overall mean score of 13 (Fig. 3B). Fatigue was the most severe symptom at all time points. For some general symptoms, scores decreased at week 12 compared with baseline, such as appetite loss (14-point decrease), constipation (8-point decrease), fatigue (18-point decrease), nausea and vomiting (9-point decrease), and pain (6-point decrease). Otherwise, scores were relatively constant over time. The early larynx subgroup had less appetite loss, fatigue, and pain. The largest difference was seen for appetite loss at 12 weeks between the early larynx and suprahyoideal subgroups (mean score of 10 in the early larynx subgroup vs 35 in the

Table 1 Baseline characteristics of all patients and per subgroup*

Characteristic	All patients (N = 859)		Early larynx (n = 157)		Infrahyoideal (n = 304)		Suprahyoideal (n = 398)	
Mean (SD) age, y	64 (10.2)		68 (10.3)		64 (9.5)		62 (10.2)	
Sex								
Male	650	(75.7)	140	(89.2)	243	(79.9)	267	(67.1)
Female	209	(24.3)	17	(10.8)	61	(20.1)	131	(32.9)
Smoking status								
Current smoker	462	(53.8)	63	(40.1)	186	(61.2)	213	(53.5)
Former smoker	296	(34.5)	78	(49.7)	90	(29.6)	128	(32.2)
Never smoker	101	(11.8)	16	(10.2)	28	(9.2)	57	(14.3)
Tumor site								
Oral cavity	55	(6.4)	0	(0)	0	(0)	55	(13.8)
Oropharynx	310	(36.1)	0	(0)	0	(0)	310	(77.9)
HPV positive	111	(35.8)	-		-		111	(35.8)
HPV negative	164	(52.9)	-		-		164	(52.9)
HPV unknown	35	(11.3)	-		-		35	(11.3)
Nasopharynx	33	(3.8)	0	(0)	0	(0)	33	(8.3)
Hypopharynx	86	(10.0)	0	(0)	86	(28.3)	0	(0)
Larynx	375	(43.7)	157	(100)	218	(71.7)	0	(0)
T-stage								
Tis-T2	407	(47.4)	157	(100)	94	(30.9)	156	(39.2)
T3-4	452	(52.6)	0	(0)	210	(69.1)	242	(60.8)
N-stage								
N0	380	(44.2)	157	(100)	148	(48.7)	75	(18.8)
N+	479	(55.8)	0	(0)	156	(51.3)	323	(81.2)
Treatment modality								
Conventional RT	195	(22.7)	51	(32.5)	68	(22.4)	76	(19.1)
Accelerated RT	315	(36.7)	106	(67.5)	137	(45.1)	72	(18.1)
Chemoradiation	283	(32.9)	0	(0)	72	(23.7)	211	(53.0)
Accelerated RT with cetuximab	66	(7.7)	0	(0)	27	(8.9)	39	(9.8)
Neck irradiation								
No	162	(18.9)	157	(100)	0	(0)	5	(1.3)
Unilateral	18	(2.1)	0	(0)	2	(0.7)	16	(4.0)
Bilateral	679	(79.0)	0	(0)	302	(99.3)	377	(94.7)
Treatment technique								
3D-CRT	53	(6.2)	53	(33.8)	0	(0)	0	(0)
IMRT	550	(64.0)	59	(37.6)	212	(69.7)	279	(70.1)
VMAT	256	(29.8)	45	(28.7)	92	(30.3)	119	(29.9)
Median (IQR) mean dose, Gy								
Brain	1.9	(0.7-3.5)	0.1	(0.0-0.2)	1.3	(0.9-2.8)	3.0	(2.0-4.3)
Brain stem	6.7	(1.9-12.8)	0.1	(0.1-0.4)	3.5	(2.1-10.6)	11.0	(7.2-16.4)
Buccal mucosa high†	37.9	(16.2-54.1)	0.6	(0.3-1.1)	29.2	(19.2-37.4)	55.0	(45.5-64.7)
Buccal mucosa low‡	29.3	(12.7-40.0)	0.5	(0.3-1.0)	24.4	(14.8-33.0)	39.1	(31.4-48.7)
Crico	47.5	(38.2-55.7)	47.7	(39.0-55.4)	56.6	(48.9-62.8)	41.6	(34.3-48.1)
Body	13.4	(8.7-16.6)	2.1	(1.8-2.8)	13.4	(10.9-16.2)	15.3	(12.9-17.7)
Glottic area	64.7	(44.1-68.5)	67.5	(66.1-70.2)	68.3	(67.0-69.3)	43.2	(36.6-49.8)
Oral cavity	42.9	(23.6-54.5)	0.9	(0.6-1.4)	33.4	(25.8-42.4)	55.0	(49.8-61.0)
Parotid gland high†	29.5	(18.7-40.2)	0.6	(0.4-1.2)	26.3	(20.9-34.5)	38.0	(30.6-47.2)
Parotid gland low‡	23.0	(14.0-29.6)	0.6	(0.3-1.1)	23.2	(18.1-27.5)	26.8	(21.0-34.6)
PCM inferior	56.4	(43.7-65.5)	60.7	(54.1-64.6)	65.9	(60.2-68.3)	43.6	(36.9-51.4)
PCM middle	54.9	(40.0-63.6)	9.8	(5.3-21.4)	60.7	(49.7-65.9)	57.4	(49.4-64.1)
PCM superior	50.8	(29.7-62.0)	1.0	(0.6-1.5)	41.4	(32.3-52.3)	62.0	(56.8-66.6)
Subm gland high†	62.8	(48.4-68.1)	4.0	(2.0-10.4)	59.3	(50.3-65.7)	67.5	(63.8-69.2)
Subm gland low‡	52.5	(43.7-60.8)	2.6	(1.6-6.3)	51.9	(47.9-58.8)	56.2	(51.8-64.9)
Supraglottic larynx	56.7	(44.5-66.3)	46.3	(38.4-56.5)	66.4	(61.3-68.3)	51.0	(41.3-60.5)

3D-CRT = 3D conformal radiation therapy; crico = cricopharyngeal inlet muscle; HPV = human papillomavirus; IMRT = intensity modulated radiation therapy; IQR = interquartile range; PCM = pharyngeal constrictor muscle; RT = radiation therapy; subm = submandibular; VMAT = volumetric modulated arc therapy.

* Data are presented as No. (%) unless otherwise noted.

† High indicates the side (left or right) of the organ with the highest mean radiation dose.

‡ Low indicates the side (left or right) of the organ with the lowest mean radiation dose.

BSL = baseline; W = week since start of treatment; M = month since end of treatment; * = binary (no/yes) items; Nutr suppl = nutritional supplements
P–values were obtained with linear mixed models and likelihood ratio test

Fig. 1. Mean scores on the Head and Neck Cancer module of the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-HN35).

suprahyoideal subgroup). The proportion of patients per complaint score are shown in Figure 4 and Table E7.

The EORTC QLQ-HN35 toxicity profiles of the alternative subgroups were generally less distinctive compared with those of the 3 main subgroups. Baseline characteristics of the alternative subgroups are shown in Table E8. The toxicity profiles based on age showed minor differences, except for less tube feeding use in older patients, with an overall mean use of 6% in older patients compared with 25% in younger patients (Fig. E1). The patients with HPV-positive oropharyngeal cancer had lower scores at baseline, with a mean score of 18, compared with 26 for patients with HPV-negative cancer (Fig. E2). In addition, patients with HPV-positive cancer had better recovery from tube feeding, nutritional supplement, and painkiller use. Patients receiving concomitant systemic treatment had more severe symptoms, with an overall mean symptom score of 32, compared with 23 in the patients treated with radiation alone (Fig. E3). However, when excluding the early larynx subgroup from the cohort, the differences in symptom severity between the 2 groups were reduced (Fig. E4). Use of tube feeding remained clearly different in both groups (overall mean scores of 8 and 43 for radiation alone and concomitant systemic treatment, respectively; $P < .001$). The profile of current smokers showed higher symptom scores for coughing after treatment, with a mean score of 29 from month 6 to 60 compared with 21 in former and never smokers (Fig. E5). Also, current smokers used more tube feeding, nutritional supplements, and painkillers during and after treatment (overall mean scores of 22, 42, and

Fig. 2. Proportion of patients with no complaints to severe complaints on the Head and Neck Cancer module of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ−HN35).

56 in current smokers compared with 15, 30, and 47 in former and never smokers for the use of tube feeding, nutritional supplements, and painkillers, respectively). The toxicity profiles per tumor site are shown in Figure E6. In general, the lowest mean scores were for the larynx subsite. For some symptoms, large differences in mean scores were seen between subsites (eg, use of feeding tube and nutritional supplements and opening the mouth). The toxicity profiles per treatment period are shown in Figure E7, largely corresponding to treatment technique, that is, IMRT from 2007 to 2013 and VMAT from 2014 to 2017 (Table E8). The toxicity profiles of both treatment groups were very similar. A significant difference was seen only for tube-feeding use, speech problems, and weight gain. The imputed toxicity profile showed a different time pattern compared with the complete case profile, with increasing scores at later time points after initial recovery in the first 24 months (Fig. E8).

Discussion

This study's findings present longitudinal patient-reported symptoms and quality-of-life profiles, based on the EORTC QLQ-HN35 and QLQ-C30 questionnaires, for a large prospective cohort of patients with HNC treated with definitive radiation therapy with or without systemic treatment. To facilitate the interpretability of such a profile for an individual patient and promote its use in clinical practice, we classified the study cohort into 3 subgroups: early larynx,

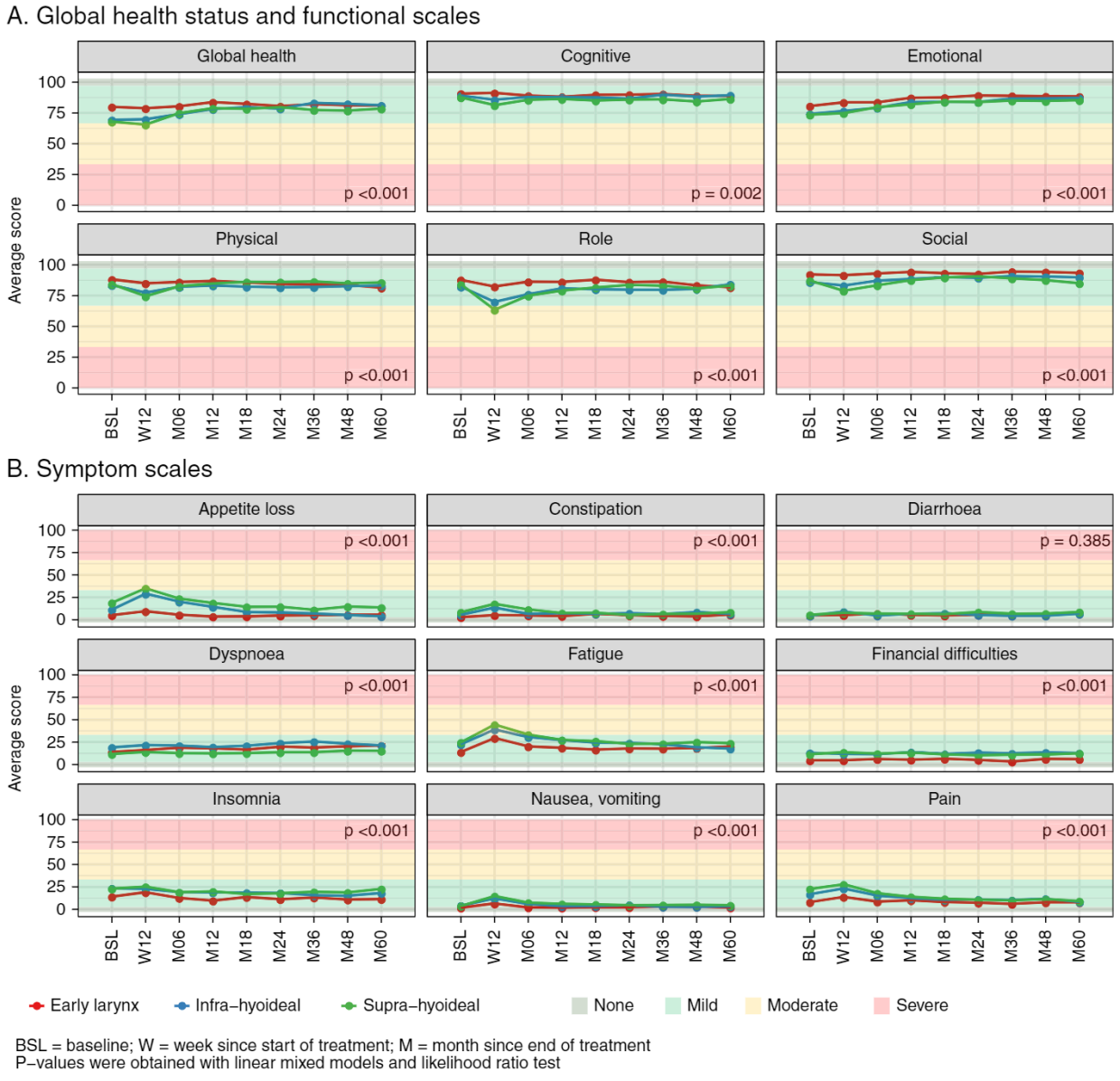

Fig. 3. Mean scores on the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ−C30). (A) Global health status and functional scales. (B) Symptom scales.

infrahyoideal, and suprahyoideal. The extent of the data presented in this study is unique. The toxicity profiles contain information about acute as well as long-term symptom burden, up to 5 years after treatment. In addition, all data were scored prospectively using validated questionnaires, and a high overall response rate of 83% was achieved, all of which contribute to the quality of the data.

The EORTC QLQ-HN35 profiles showed a clear time pattern, with the highest symptom scores being reported at the end of treatment, followed by recovery in the first 2 years after treatment. All symptom scores except weight gain were significantly different between the subgroups. Overall, the early-stage larynx subgroup had milder symptoms. This is very likely owing to the less intense treatment (that is, no elective neck irradiation and smaller target volumes), resulting in less healthy-tissue irradiation. The differences in toxicity severity between the infrahyoidal and suprahyoideal subgroups were less pronounced and may be attributed to the different tumor sites and, consequently, the location of the high-dose region. This might explain why complaints of a dry mouth and the use of a feeding tube and nutritional supplements, as well as pain and problems with opening the mouth, were more frequently observed in the suprahyoideal subgroup, whereas coughing and speech problems were more pronounced in the infrahyoideal subgroup. The highest questionnaire scores during treatment were for the use of a feeding tube, nutritional supplements, and painkillers. However, the severity of these scales might be overestimated because of the binary scoring, with maximum scores assigned even to sporadic aid. Specifically, in the case of painkillers, the use of painkillers was surveyed with no further specification for

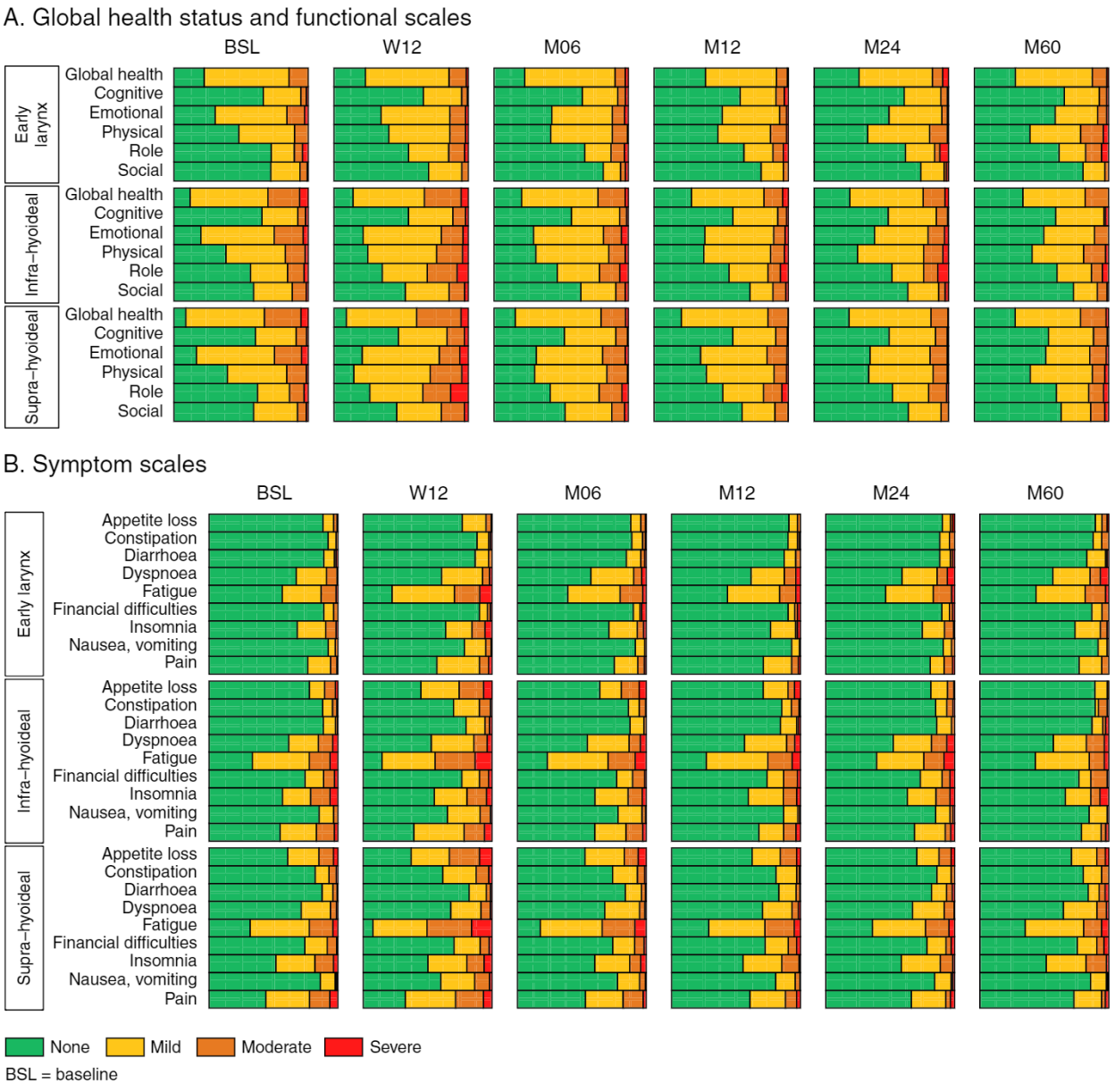

Fig. 4. Proportion of patients with no complaints to severe complaints on the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ−C30). (A) Global health status and functional scales. (B) Symptom scales.

the type and dosage used. Frequently used painkillers included paracetamol and opioids. In addition, use of tube feeding might be influenced by the institutional practice of prophylactic percutaneous endoscopic gastrostomy tube placement in patients receiving chemoradiation therapy, probably lowering the threshold for actual use. The EORTC QLQ-C30 profile showed a less pronounced time pattern, with limited worsening of some items reported at 12 weeks and recovery to baseline levels reported in the first year after treatment. Global health, functioning, and general symptom scales, except for diarrhea, were significantly different between the subgroups. However, the differences in mean scores were less pronounced. This might be owed to a "response shift," that is, the theory that patients tend to adapt to their new normal.[35] In addition, global health, functioning, and general symptoms are likely to be less directly affected by the irradiation of healthy tissue but may rely more on other factors.

Of course, there are various ways to classify patients and generate insight into the symptom burden of specific subgroups. Although the toxicity profiles of alternative classifications, based on age, HPV status of oropharyngeal tumors, administration of systemic therapy, smoking status, and tumor site, also showed significant differences for many symptoms, the differences in mean scores between groups were often less pronounced. However, exploring these profiles can be of value in clinical practice. It is important to stress that the toxicity profiles based on age were influenced

by the different treatment regimens. This was clearly reflected in the higher use of tube feeding in younger patients, many of whom were treated with chemoradiation therapy. Remarkably, other symptoms showed minor differences, despite the less intense treatment in elderly patients. In patients with HPV-positive oropharyngeal tumors, lower scores for tube feeding and use of nutritional supplements and painkillers were reported after treatment. These patients are generally in better condition (ie, fewer are active smokers, and they have fewer symptoms at baseline). Moreover, HPV-positive tumors are less likely to relapse, which in turn can cause symptoms. Patients treated with concurrently administered systemic agents reported more symptoms than did patients treated with radiation alone. Similar results were found by other investigators.[27,28] However, when we excluded the early larynx subgroup from the cohort, the effect of systemic treatment on toxicity severity almost disappeared, with often overlapping mean scores. This suggests that the difference in toxicity severity in the study cohort was mainly associated with early-stage larynx patients, a subgroup with substantially fewer symptoms. Current smokers showed a slightly worse toxicity profile compared with former and never smokers. Previous studies also reported higher late toxicity outcomes in smokers.[30-32] The largest differences were seen for coughing and use of tube feeding, nutritional supplements, and painkillers. Toxicity profiles per tumor site allowed for the evaluation of site-specific symptoms. For example, the highest mean scores for opening the mouth and for teeth were for the oral-cavity subsite. Overall, the lowest mean scores were for the larynx subsite. For some tumor sites (eg, oral cavity and nasopharynx), the number of patients was limited. In addition, the toxicity profile reported was from a more modern cohort (2014-2017). This profile was very similar to that of patients treated earlier (2007-2013), even though most patients of the current study's cohort were treated with contemporary techniques (VMAT), whereas patients in the earlier cohort were treated with 3D-CRT or IMRT. This suggests that differences in toxicity burden between patients individually are larger than differences between treatment periods. Similar results were found by Dahele et al.[36] They investigated patient-reported outcomes (EORTC QLQ-HN35 and EORTC QLQ-C30) of patients with HNC treated in 4 subsequent periods. They also did not find a significant difference in outcomes for the whole population, except for dry mouth in the periods 2000 to 2005 and 2012 to 2016. The toxicity profiles in the current study reflect the average toxicity on a population level, whereas individual patients might benefit from a more conformal radiation technique. In addition, in this study, the case mix of the more recent cohort was different compared with the earlier cohort (Table E8). We are currently investigating the effect of increased OAR sparing on the acute toxicity burden in a population including patients treated with both photon and proton therapy.

The toxicity profile using imputed data showed increasing symptom scores at later time points after initial recovery compared with our complete case analysis. This indicates the presence of selection bias in the complete case analysis. Long-term survivors (>2 years) completing the questionnaires probably had early-stage tumors with a more favorable prognosis and consequently received less intense treatment, resulting in less toxicity. In contrast, patients with advanced disease treated with extensive radiation fields and concomitant systemic treatment, who consequently experienced more symptoms, are likely underrepresented at late time points, owing to a higher risk of recurrent disease, death, or nonresponse to the questionnaires because of high symptom burden. This hypothesis is supported by the observed differences in characteristics between patients who completed the questionnaire 5 years after treatment and those who were lost to follow-up (Table E9). The influence of selection bias on the complete case-toxicity profile increased at later time points, owing to the increasing attrition rate during follow-up, as shown in Tables E2 and E3. As a result of selection bias, long-term outcome data became skewed, suggesting that symptoms tended to recover at later time points. However, this may have been the effect of the selection bias rather than a real recovery of symptoms. Although the complete case-toxicity profiles were influenced by selection bias, they are representative of and reflect clinical practice, as natural patient selection also occurs there.

This study adds to the existing literature on toxicity burden and quality of life after primary radiation therapy.[3,7,27-29,36-39] Some of the studies mainly aimed to characterize either acute[27] or long-term toxicity burden.[29,37] Other studies aimed to compare the toxicity burden of 3D-CRT with IMRT.[3,7,36,38,39] In addition to these studies, we mapped the complete longitudinal course of multiple prospectively scored symptoms and quality-of-life items of a large cohort, making this one of the most comprehensive reports to date, to our knowledge. Overall, this study's results are consistent with those reported in the existing literature. However, some differences were noted. First, in a study by Rathod et al,[38] in which patients were randomly assigned to either 3D-CRT or IMRT, substantially higher scores were observed for the use of tube feeding and nutritional supplements as well as weight gain in the patients treated with IMRT, compared with this study's cohort. Because of the binary scoring of these items, the mean scores may increase when answered positively by only a few patients. Moreover, different policies regarding the prophylactic use of feeding tubes and/or nutritional supplements could lead to distinct scores across centers. A difference was also noted between the current study and that of Rosenthal et al,[27] who described the acute symptom burden, using the MD Anderson Symptom Inventory Head and Neck Module, of patients treated with radiation alone (77 patients) or chemoradiation (72 patients). Their study observed more problems with taste, compared with problems with senses observed in the current study's cohort. However, in the current study, the item "problems with senses" evaluated changes in both taste and smell, whereas the MD Anderson Symptom

Inventory Head and Neck Module evaluates problems with taste only. In the current study's cohort, problems with smell were less severe than problems with taste (Fig. E9), which explains the lower scores of the combined item "problems with senses." Rosenthal et al also observed fewer speech problems in patients treated with radiation alone, compared with that subgroup of the current study's cohort. This could be attributed to the higher percentage of patients with laryngeal cancer in our cohort (65% vs 9%). However, in general, the observed differences are limited, and this study's results are consistent with those of previous studies, supporting the generalizability of our results. Furthermore, because our center is one of the eight certified HNC centers in The Netherlands, because the study was conducted in accordance with national and international guidelines, and because of the high rate of patient-reported outcomes, the results of this study can be considered representative for the general HNC population.

The longitudinal toxicity profiles of this study provide information about the onset, time pattern, and severity for a wide spectrum of symptoms, functioning, and quality of life. The detailed reporting of mean scores, as well as frequency distributions of categorized symptom severities per subgroup, enable readers to further explore this data as they wish, either to use in daily practice or for research purposes. In daily practice, these data may help clinicians estimate patient-reported outcomes for newly referred patients. The data may also raise awareness of symptoms that might be overlooked by clinicians but that are commonly experienced by patients (eg, nausea, vomiting, and fatigue). For research purposes, these profiles may serve as benchmark data of current radiation-induced toxicity against which comparisons with outcomes of other institutions or of emerging treatment techniques, such as proton therapy, can be performed. Furthermore, the profiles may guide future research concerning toxicity prevention by indicating possible interesting symptoms to further explore and by providing data needed for power and sample-size calculations.

In conclusion, this study characterized the symptom burden and quality of life of a large cohort of patients with HNC treated with definitive (chemo)radiation therapy. The comprehensive longitudinal toxicity and quality-of-life profiles of 3 clinically relevant subgroups (patients with early-larynx, infrahyoideal, and suprahyoideal HNC) provide valuable information on onset, time pattern, and severity of a wide range of symptoms, functioning, and quality of life.

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