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Long-term health-related quality of life in head and neck cancer survivors: A large multinational study

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Abstract

Head and neck cancer (HNC) patients suffer from a range of health-related quality of life (HRQoL) issues, but little is known about their long-term HRQoL. This study explored associations between treatment group and HRQoL at least 5 years' post-diagnosis in HNC survivors. In an international cross-sectional study, HNC survivors completed the European Organization for Research and Treatment of Cancer (EORTC) quality of life core questionnaire (EORTC-QLQ-C30) and its HNC module (EORTC-QLQ-H&N35). Meaningful HRQoL differences were examined between five treatment groups: (a) surgery, (b) radiotherapy, (c) chemo-radiotherapy, (d) radiotherapy ± chemo-therapy and neck dissection and (e) any other surgery (meaning any tumour surgery that is not a neck dissection) and radiotherapy ± chemotherapy. Twenty-six sites in 11 countries enrolled 1105 survivors. They had a median time since diagnosis of 8 years, a mean age of 66 years and 71% were male. After adjusting for age, sex, tumour site and UICC stage, there was evidence for meaningful differences (10 points or more) in HRQoL between treatment groups in seven domains (*Fatigue*, *Mouth Pain*, *Swallowing*, *Senses*, *Opening Mouth*, *Dry Mouth* and *Sticky Saliva*). Survivors who had

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single-modality treatment had better or equal HRQoL in every domain compared to survivors with multimodal treatment, with the largest differences for *Dry Mouth* and *Sticky Saliva*. For *Global Quality of Life*, *Physical and Social Functioning*, *Constipation*, *Dyspnoea and Financial Difficulties*, at least some treatment groups had better outcomes compared to a general population. Our data suggest that multimodal treatment is associated with worse HRQoL in the long-term compared to single modality.

KEYWORDS
cross-sectional, head and neck cancer, quality of life, survivor, treatment

What's new?

Head and neck cancer and its treatments can cause side reffects that negatively affect health-related quality of life (HRQoL). Little is known about the long term HRQoL of survivors of head and neck cancer beyond 1 year. Here, the authors examined the association between treatment and HRQoL at least 5 years after diagnosis. For symptoms concerning dry mouth, sticky saliva, problems swallowing, mouth pain, problems opening the mouth, problems with senses, and fatigue, they found that patients who had undergone a single mode of treatment had better outcomes than those who had had multimodal treatment.

1 | INTRODUCTION

Head and neck cancer (HNC) encompasses a range of neoplasms with heterogeneous clinical presentation arising from the mucosal epithelia of the head and neck. It is usually treated in multidisciplinary teams involving head and neck surgeons, radiation oncologists and medical oncologists. The disease and its treatment cause considerable sequelae with negative effects on health-related quality of life (HRQoL) due to the structures involved, which are critical for breathing, eating and speaking, and unsatisfied body image due to facial alterations, which can affect patient's social and sexual life.[1–3] Worldwide, ~19.3 million cases were diagnosed in 2020, making HNC the seventh most frequent cancer diagnosis that year.[4] Mortality ranges depending on the specific cancer site and the stage.[5–7] Risk factors include tobacco and alcohol consumption, particularly in combination, and more recently the role of human papilloma virus has been established as a risk factor.[8–10] For early stage disease, curative treatment can include conservative surgery or radiotherapy, with later stages necessitating definitive concurrent chemo-radiotherapy or surgery with adjuvant (chemo)-radiotherapy.[11]

The effect of the disease and the treatment on patients' HRQoL has been studied in the first year following diagnosis and treatment, and there is evidence showing that physical, social, emotional and role functioning, pain, fatigue, nausea, dyspnoea, dysphagia, problems with senses, problems with teeth, opening mouth, dry mouth and sticky saliva are negatively affected.[12–18] Studies examining HRQoL beyond 1 year following diagnosis and/or treatment have shown that HNC patients may still face problems with oral health, physical and emotional functioning, dyspnoea, trismus, dry mouth and sticky saliva.[17,19–24] At 5 years' postdiagnosis, HNC patients are no longer routinely followed up.[16] However, the long-term HRQoL effects, occurring after 5 years, have not been sufficiently examined, and for the studies that do exist, the number of survivors included is limited.[25–29] Very little evidence on these survivors' long-term HRQoL is available, despite the fact that approximately half of patients with this diagnosis will reach this important milestone.

Through a project called 'Late Toxicity and Long-term Quality of Life in Head and Neck Cancer Survivors' (EORTC 1629), we aimed to address this by describing the HRQoL of a large, international collective of HNC survivors. We also explored differences in the HRQoL found in this survivor population in light of the type of treatment received.

2 | METHODS

2.1 | Study design and inclusion criteria

The EORTC 1629 study is a multinational cross-sectional study carried out by members of the Quality of Life Group and the HNC Group of the EORTC and coordinated at the University Hospital in Mainz, Germany. Survivors who fulfilled the inclusion criteria were identified at each participating centre and asked to participate by mailed invitation letter, at their follow-up appointment in hospital, or by telephone. Eligibility criteria were: ≥18 years old, confirmed carcinoma of the larynx, lip, oral cavity, salivary glands, oropharynx, hypopharynx, nasopharynx, nasal cavity, nasal sinuses or unknown primary in the head and neck area, and the diagnosis more than 5 years in the past. Exclusion criteria were eye, thyroid or orbit tumours, skin cancers or lymphoma in the head and neck region. Survivors with current evidence of disease or who had experienced a second primary were not excluded from the study, as these are occurrences reflecting the reality of some cancer survivors.

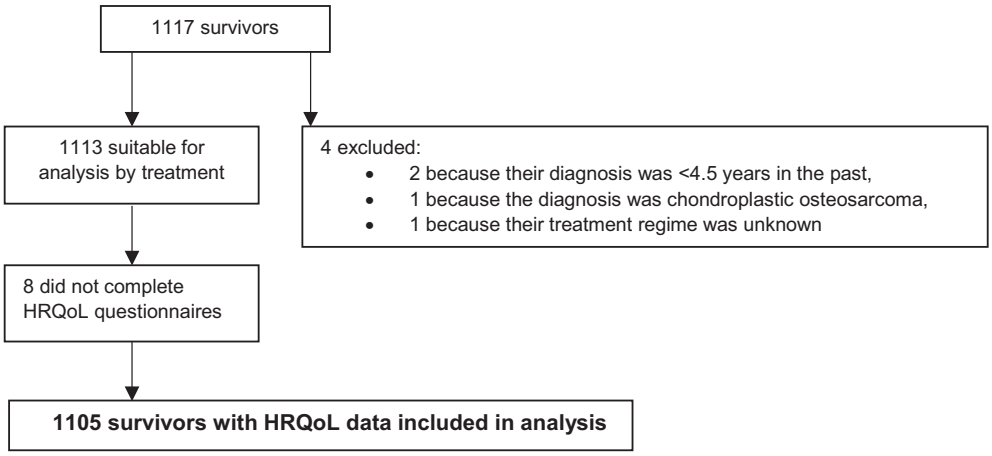

FIGURE 1 Flow of survivors enrolled in the EORTC 1629 study.

2.2 | Treatment groups

Five broad treatment groups were defined a priori: surgery only; radiotherapy (RT) only; chemo-radiotherapy (CRT); radiotherapy ± chemotherapy and neck dissection (RT ± CT and ND); and any other type of surgical intervention plus radiation ± chemotherapy (surgery and RT ± CT). The last two groups were separated to make a distinction between less extensive and more extensive surgeries. In the 'RT ± CT and ND' group, the assumption was that neck dissection was less extensive than the surgeries in the group that had any other kind of surgery plus RT or CT. The order of treatments was not considered in the multimodal treatment groups.

2.3 | Data collection

Consenting survivors were invited to the local researcher's clinic to complete questionnaires. All documentation was completed with article and pencil and then either scanned and emailed or the documents were shipped via post to the coordinating centre in Mainz, where the data were entered into the Computer-Based Health Evaluation System (CHES®), a web-based database developed by the Evaluation Software Development company in Austria.[30] The collaborators from Portugal and Greece chose to enter the data into the database themselves rather than send the documents to Mainz.

2.4 | Questionnaires

The questionnaires were the EORTC quality of life core questionnaire (EORTC QLQ-C30) and its head and neck cancer module (EORTC QLQ-H&N35).[1,31] The EORTC QLQ-C30 consists of five functional scales, nine symptom scales and one global quality of life (QoL) scale, and has been validated in an international setting.[1,31] The EORTC QLQ-H&N35 covers issues specific to HNC patients and includes 18 symptom scales; it has been validated in an international setting and is used extensively in HRQoL research.[1,15,32,33] Both questionnaires use a four-point Likert scale to indicate the extent of problems experienced, ranging from 'not at all' to 'very much'. The answers for each domain are converted to a score ranging from 0 to 100; for functional scales, high scores represent a high level of QoL, and for symptom scales high scores indicate a poor QoL. A difference in score of 10 or more points is considered to be a clinically relevant difference and was the cut-off we regarded in our study.[34]

2.5 | Clinical data

Physicians completed a Case Report Form for each survivor and recorded the survivor's sex, age, education, smoking status, diagnosis and treatment details, Karnofsky index and Charlson Comorbidity Score.[35] Some clinicians reported UICC stage using version 7 and some using version 8, but all TNM values were reassessed using the version 7 classification, which are the values reported here.

2.6 | Statistical analysis

The survivor characteristics are reported for the entire study population according to treatment group as frequencies and percentages. Chi-square test for independence, Fisher's test or analysis of variance was used depending on the type of data to explore the distribution of demographic and clinical characteristic over the treatment groups.

Each of the HRQoL domain scores is reported for each treatment group as means with 95% confidence intervals (CI) and standard deviations (SD) for the raw data. Analysis of covariance (ANCOVA) was used to calculate adjusted means with 95% CI for all HRQoL domains and to assess statistical evidence for differences of 10 points or more between treatment groups and Tukey–Kramer post hoc tests were used to determine where the differences were. Age, sex, UICC stage and tumour sub-site were included as covariables, as we expected these to be the main sources of potential confounding. If adjusted means or CI for a HRQoL domain were less than 0 or more than 100, these was recorded as '0' and '100', respectively, as these are the limits of the HRQoL scores. As current evidence of disease or the occurrence of a second primary at some point since the HNC diagnosis were not an exclusion criteria, we also looked at whether our

TABLE 1 Characteristics of the 1105 survivors by type of treatment.

	Surgery		RT		CRT		RT ± CT and ND[a]		Surgery and RT ± CT[a]		Totals	
Totals	**128**	**12%**	**134**	**12%**	**310**	**28%**	**111**	**10%**	**422**	**38%**	**1105**	**100%**
Age (years)[b]												
Mean (range)	67 (23–93)		70 (43–92)		64 (27–88)		66 (47–86)		66 (23–90)		66 (23–93)	
Sex[c]												
Male	78	61%	107	80%	233	75%	76	68%	289	68%	783	71%
Female	50	39%	27	20%	77	25%	35	32%	133	32%	322	29%
Geographic area[c]												
Northern Europe	20	16%	22	16%	78	25%	45	41%	85	20%	250	23%
Central/Western Europe	66	52%	65	49%	95	31%	52	47%	192	45%	470	43%
Southern Europe	23	18%	39	29%	95	31%	6	5%	75	18%	238	22%
Israel	2	2%	0	0%	2	1%	1	1%	5	1%	10	1%
Japan	3	2%	0	0%	11	4%	1	1%	15	4%	30	3%
Brazil	14	11%	8	6%	29	9%	6	5%	50	12%	107	10%
Smoking status												
Never smoker	40	31%	28	21%	99	32%	33	30%	115	27%	315	29%
Former smoker	69	54%	91	68%	171	55%	64	58%	237	56%	632	57%
Current smoker	14	11%	15	11%	35	11%	13	12%	62	15%	139	13%
Missing	5	4%	0	0%	5	2%	1	1%	8	2%	19	2%
Total years of education												
<10	48	38%	54	40%	105	34%	20	18%	144	34%	371	34%
10	13	10%	27	20%	44	14%	15	14%	64	15%	163	15%
>10	61	48%	52	39%	154	50%	73	66%	203	48%	543	49%
Missing	6	5%	1	1%	7	2%	3	3%	11	3%	28	3%
Tumour subsite[d]												
Oropharynx	11	9%	39	29%	147	47%	63	57%	115	27%	375	34%
Oral cavity	66	52%	7	5%	15	5%	5	5%	147	35%	240	22%
Larynx	34	27%	68	51%	31	10%	5	5%	68	16%	206	19%
Nasopharynx	0	0%	6	4%	71	23%	4	4%	4	1%	85	8%
Salivary gland	11	9%	0	0%	0	0%	1	1%	48	11%	60	5%
Unknown primary	0	0%	3	2%	11	4%	31	28%	7	2%	52	5%
Hypopharynx	2	2%	6	4%	24	8%	2	2%	16	4%	50	5%
Nasal cavity and sinuses	4	3%	5	4%	11	4%	0	0%	17	4%	37	3%
Histology[c]												
Squamous cell	110	86%	125	93%	277	89%	110	99%	347	82%	969	88%
Other	17	13%	7	5%	29	9%	1	1%	71	17%	125	11%
Missing/unknown	1	1%	2	1%	4	1%	0	0%	4	1%	11	1%
UICC Stage (version 7)[d]												
I	85	66%	59	44%	1	0%	4	4%	71	17%	220	20%
II	29	23%	37	28%	30	10%	11	10%	68	16%	175	16%
III	6	5%	19	14%	80	26%	50	45%	91	22%	246	22%
IV	4	3%	14	10%	194	63%	39	35%	177	42%	428	39%
Missing/unknown	4	3%	5	4%	5	2%	7	6%	15	4%	36	3%
Karnofsky												
<50	0	0%	0	0%	1	0%	0	0%	2	0%	3	0%
50 or 60	4	3%	4	3%	12	4%	1	1%	13	3%	34	3%
70 or 80	28	22%	37	28%	76	25%	26	23%	139	33%	306	28%

(Continues)

TABLE 1 (Continued)

	Surgery		RT		CRT		RT ± CT and ND[a]		Surgery and RT ± CT[a]		Totals	
Totals	**128**	**12%**	**134**	**12%**	**310**	**28%**	**111**	**10%**	**422**	**38%**	**1105**	**100%**
90 or 100	89	70%	93	69%	216	70%	83	75%	257	61%	738	67%
Missing	7	5%	0	0%	5	2%	1	1%	11	3%	24	2%
Charlson comorbidity index												
0	83	65%	77	57%	213	69%	73	66%	258	61%	704	64%
1	23	18%	26	19%	58	19%	16	14%	83	20%	206	19%
2	9	7%	14	10%	19	6%	14	13%	35	8%	91	8%
≥3	13	10%	17	13%	20	6%	8	7%	46	11%	104	9%
Current evidence of disease												
Yes	5	4%	4	3%	5	2%	1	1%	17	4%	32	3%
No	120	94%	130	97%	305	98%	110	99%	403	95%	1068	97%
Missing/unknown	3	2%	0	0%	0	0%	0	0%	2	0%	5	0%
Second primary												
Yes	22	17%	22	16%	31	10%	12	11%	76	18%	163	15%
No	100	78%	112	84%	276	89%	97	87%	342	81%	927	84%
Missing/unknown	6	5%	0	0%	3	1%	2	2%	4	1%	15	1%
Time since diagnosis (years)												
5–6	25	20%	32	24%	82	26%	13	12%	90	21%	242	22%
7–8	44	34%	48	36%	112	36%	36	32%	139	33%	379	34%
9–10	28	22%	26	19%	60	19%	27	24%	80	19%	221	20%
>10	31	24%	28	21%	56	18%	35	32%	113	27%	263	24%

Note: Percentages are column percentages except for the Totals row. *Oropharynx* includes base of tongue and tonsil. *Salivary gland* includes parotid gland and other salivary gland.

Abbreviations: CRT, chemo-radiotherapy; CT, chemotherapy; ND, neck dissection; RT, radiotherapy.

[a]The order of the treatments is not known.

[b]ANOVA model $P < .001$.

[c]Chi2 test for independence $P < .005$.

[d]Fisher $P < .001$.

results from the ANCOVA changed if these survivors were removed from the analyses.

This study did not have a specific hypothesis and was aimed at exploring HRQoL difference between the treatment groups. A sample size of 1045 survivors would be necessary to assess differences across five groups in 10 HRQoL domains with 90% power and an alpha of 0.01 assuming a standard deviation of 25 points in each scale.

3 | RESULTS

3.1 | Enrolment

The first survivor was enrolled in October 2018 and the last in October 2021, with start of the COVID-19 pandemic slowing enrolment considerably in 2020. Twenty-six sites in 11 countries enrolled survivors, with the highest enrolment in Italy, Belgium, Germany, Norway and Brazil. Figure 1 shows the breakdown of enrolled survivors and the final number that could be included for analysis. Of the 1113 survivors with treatment information, eight did not complete the questionnaires, meaning that 1105 survivors are included in the analysis. The reasons for not completing the HRQoL questionnaires included that the participant did not wish to and in one case the person died before completing them.

3.2 | Survivor characteristics

The characteristics of the 1105 survivors broken down by treatment group are shown in Table 1. The treatment groups were populated as follows: 128 (12%) 'surgery only', 134 (12%) 'RT', 310 (28%) 'CRT', 111 (10%) 'RT ± CT and ND' and 422 (38%) 'surgery and RT ± CT'. The average age was 66 years (range 23–93), most were male (71%) and former smokers (57%). The most frequent tumour sub-sites were oropharynx (34%), oral cavity (22%) and larynx (19%), and the majority were diagnosed at an advanced stage (22% stage III and 39% stage IV). The median time since diagnosis was 8 years for all treatment

TABLE 2 Health-related quality of life measured with the EORTC QLQ-C30 and EORTC QLQ-H&N35 according to the type of treatment received reported as *unadjusted means* with 95% CI and standard deviation (SD).

	Surgery		RT		CRT		RT ± CT and ND		Surgery and RT ± CT	
QoL scale	Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD
EORTC QLQ-C30 domains										
Global QoL	74.5 (71.1–78.0)	19.9	75.0 (71.8–78.2)	18.5	73.8 (71.3–76.3)	22.5	76.4 (72.4–80.4)	21.2	69.0 (66.9–71.2)	22.8
Physical functioning	84.6 (81.5–87.8)	18.0	83.7 (80.3–87.1)	20.1	83.4 (81.0–85.8)	21.5	84.8 (81.4–88.2)	18.2	81.3 (79.4–83.2)	19.8
Role functioning	86.3 (82.1–90.6)	24.4	84.6 (80.2–89.0)	25.6	81.5 (78.2–84.7)	28.8	81.1 (76.0–86.2)	27.1	78.4 (75.6–81.2)	29.3
Emotional functioning	79.3 (75.4–83.3)	22.5	85.4 (81.9–88.9)	20.1	79.8 (77.3–82.4)	23.0	80.7 (75.7–85.6)	26.3	78.6 (76.3–80.9)	23.9
Cognitive functioning	83.7 (79.9–87.6)	22.0	88.6 (85.5–91.6)	17.6	81.5 (78.8–84.2)	24.2	82.0 (77.1–86.8)	25.7	81.4 (79.3–83.5)	22.0
Social functioning	89.1 (85.3–92.9)	21.7	90.2 (17.4–22.2)	19.5	83.9 (80.8–86.9)	27.5	80.6 (75.2–86.0)	28.7	80.9 (78.3–83.5)	27.1
Fatigue	**19.3 (15.7–23.0)**	**20.8**	**17.3 (13.2–21.3)**	**23.4**	**26.4 (23.4–29.3)**	**26.7**	**27.0 (21.3–32.7)**	**30.4**	**29.3 (26.7–31.9)**	**27.4**
Nausea and vomiting	3.3 (0.6–5.9)	15.1	2.9 (1.2–4.6)	9.9	4.6 (3.1–6.2)	14.1	4.4 (2.4–6.3)	10.5	3.9 (2.8–5.1)	11.9
Pain	16.0 (11.7–20.3)	24.3	12.9 (9.1–16.8)	22.6	16.9 (14.0–19.8)	26.1	22.4 (16.6–28.1)	30.5	22.2 (19.4–24.9)	28.4
Dyspnoea	16.4 (12.0–20.9)	25.4	19.3 (14.3–24.3)	29.4	18.7 (15.8–21.6)	26.1	20.7 (15.5–25.9)	27.7	21.3 (18.6–24.1)	28.6
Insomnia	**20.6 (15.6–25.5)**	**28.4**	**20.4 (15.5–25.3)**	**28.9**	**24.6 (21.2–27.9)**	**29.7**	**30.9 (24.3–37.6)**	**35.3**	**27.0 (23.9–30.1)**	**32.5**
Appetite loss	7.1 (3.9–10.3)	18.1	9.0 (5.3–12.6)	21.3	12.0 (9.2–14.8)	25.2	13.8 (9.0–18.6)	25.6	12.1 (9.7–14.5)	25.1
Constipation	9.9 (5.9–13.9)	22.7	8.7 (4.9–12.5)	22.0	14.2 (11.4–17.1)	25.3	15.3 (9.9–20.8)	29.1	13.2 (10.8–15.5)	24.6
Diarrhoea	5.2 (2.3–7.6)	13.6	4.0 (1.7–6.3)	13.6	7.3 (5.2–9.5)	19.1	8.1 (4.4–11.8)	19.7	6.9 (5.2–8.6)	17.6
Financial difficulties	8.4 (4.4–12.4)	22.6	8.3 (4.5–12.1)	22.2	15.8 (12.5–19.1)	29.3	15.3 (9.9–20.8)	29.1	15.7 (12.9–18.4)	28.7
EORTC QLQ-HN35 domains										
Pain in the mouth	**6.8 (4.8–8.9)**	**11.6**	**9.5 (6.6–12.3)**	**16.7**	**13.2 (11.1–15.2)**	**18.3**	**15.1 (11.3–18.9)**	**20.2**	**17.1 (15.2–19.1)**	**20.1**
Swallowing	**5.1 (3.3–6.9)**	**10.3**	**13.6 (10.2–17.0)**	**19.8**	**21.7 (19.1–24.3)**	**23.1**	**19.9 (15.4–24.5)**	**24.3**	**20.6 (18.4–22.8)**	**22.7**
Senses problems	**8.5 (5.2–11.7)**	**18.5**	**13.8 (9.8–17.8)**	**23.2**	**20.5 (17.2–23.8)**	**29.7**	**18.0 (13.2–22.8)**	**25.6**	**23.7 (20.9–26.6)**	**29.8**
Speech problems	12.2 (8.8–15.5)	19.4	13.0 (9.6–16.4)	19.7	15.7 (13.1–18.4)	23.5	13.1 (9.2–17.1)	21.0	20.7 (18.4–23.1)	24.5
Trouble with social eating	**6.9 (4.2–9.5)**	**15.3**	**10.1 (6.6–13.5)**	**20.2**	**16.3 (13.6–18.9)**	**23.7**	**15.5 (10.7–20.2)**	**25.2**	**19.6 (17.2–22.0)**	**25.4**
Trouble with social contact	7.2 (4.5–9.9)	15.3	5.3 (3.1–7.4)	12.7	8.8 (6.9–10.7)	16.8	9.4 (6.0–12.9)	18.5	11.3 (9.6–13.1)	18.3
Less sexuality	22.5 (16.8–28.1)	30.6	23.8 (17.9–29.8)	33.7	26.1 (22.2–30.0)	34.3	30.7 (23.6–37.7)	36.5	29.2 (25.9–32.6)	33.9
Teeth	**15.3 (10.7–20.0)**	**26.6**	**21.2 (15.5–27.0)**	**33.3**	**24.4 (20.5–28.2)**	**34.2**	**26.7 (20.2–33.2)**	**34.3**	**25.2 (21.8–28.5)**	**34.3**
Opening mouth	**8.7 (5.1–12.4)**	**20.7**	**11.0 (6.9–15.2)**	**24.2**	**22.3 (18.7–25.8)**	**31.8**	**21.0 (14.9–27.2)**	**32.7**	**26.8 (23.4–30.2)**	**35.3**
Dry mouth	**20.5 (15.6–25.4)**	**27.9**	**36.6 (30.7–42.5)**	**34.4**	**50.4 (46.4–54.4)**	**35.8**	**48.2 (41.0–55.4)**	**38.2**	**47.6 (44.1–51.2)**	**37.0**
Sticky saliva	**14.4 (10.2–18.7)**	**24.3**	**25.8 (20.0–31.6)**	**33.7**	**37.1 (33.1–41.2)**	**36.1**	**31.5 (25.0–38.0)**	**34.2**	**35.7 (32.4–39.1)**	**34.9**
Coughing	20.5 (16.0–28.8)	25.2	18.4 (13.9–22.9)	26.4	19.9 (16.8–23.0)	28.0	20.9 (15.7–26.1)	27.4	24.0 (21.2–26.8)	29.6
Felt ill	7.9 (4.6–11.3)	19.1	6.5 (3.4–9.6)	18.0	12.6 (9.9–15.3)	24.3	13.2 (8.3–18.2)	26.3	15.6 (13.1–18.1)	26.0
Pain killers	32.0 (23.8–40.2)	46.8	30.1 (22.2–38.0)	46.0	30.6 (25.5–35.8)	46.2	28.8 (20.3–37.4)	45.5	33.1 (28.6–37.7)	47.1

(Continues)

TABLE 2 (Continued)

QoL scale	Surgery		RT		CRT		RT ± CT and ND		Surgery and RT ± CT	
	Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD	Mean (95% CI)	SD
Nutritional supplements	16.4 (9.9–22.9)	37.2	12.7 (7.0–18.4)	33.4	14.3 (10.4–18.2)	35.0	9.9 (4.3–15.6)	30.0	17.6 (14.0–21.3)	38.1
Feeding tube	0.8 (0.0–2.3)	8.8	1.5 (0.0–3.6)	12.2	4.2 (2.0–6.5)	20.1	2.7 (0.0–5.8)	16.3	5.0 (2.9–7.1)	21.8
Weight loss	14.2 (8.0–20.3)	35.0	12.8 (7.0–18.5)	33.5	11.7 (8.1–15.3)	32.2	10.0 (4.3–15.7)	30.1	16.2 (12.6–19.7)	36.8
Weight gain	19.0 (12.1–26.0)	39.4	17.4 (10.8–24.0)	38.1	18.6 (14.2–23.0)	38.9	22.9 (14.9–31.0)	42.2	21.7 (17.8–25.7)	41.3

Note: **Bolded rows** contain at least one difference of 10 or more points between treatment groups. For the functional scales and the global quality of life scale, high scores indicate good functioning and good quality of life; for all other scales, high scores are an indication of high symptom burden/poor quality of life in that area.
Abbreviations: CRT, chemo-radiotherapy; CT, chemotherapy; ND, neck dissection; RT, radiotherapy.

groups except for 'RT ± CT and ND', which was 9 years. Three percent had current evidence of disease and 15% had had a second primary (not necessarily in the head and neck).

There was evidence for differences in patient characteristics among the treatment groups (age: $P < .0001$, sex: $P = .004$, tumour sub-site: $P < .0001$ and UICC stage $P < .001$), while performance status and comorbidity index were more evenly distributed (Karnofsky: $P = .05$, Carlson: $P = .2$). The characteristics with the largest differences among the treatment groups were the tumour sub-sites and the UICC stage.

3.3 | HRQoL results

The raw (*unadjusted*) data showed differences of 10 points or more between survivors in some of the treatment groups for *Fatigue*, *Insomnia*, *Pain in the Mouth*, *Swallowing*, *Senses Problems*, *Trouble with Social Eating*, *Teeth*, *Opening Mouth*, *Dry Mouth* and *Sticky Saliva* (Table 2). This changed slightly in the models where we adjusted for age, sex, UICC stage and tumour sub-site, where *Teeth* and *Trouble with Social Eating* no longer had a 10-point difference, but *Sexuality* did (Table 3 and Figure 3); in the adjusted model, *Sexuality* had a 10.3-point difference between 'surgery only' and 'RT ± CT and ND'. The adjusted means for *Trouble with Social Eating* all shifted down to zero or near zero. Among the domains with a difference 10 points or more in the adjusted model, survivors in the 'surgery only' and 'RT only' treatment groups continued to have the lowest scores, indicating the lowest symptom burden. The survivors in the 'surgery and RT ± CT' group had the highest symptom scores compared to the other treatment groups for *Fatigue*, *Pain in the Mouth*, *Senses Problems* and *Opening Mouth* (Figures 2 and 3); the 'RT ± CT and ND' group had the highest scores for *Insomnia* and *Sexuality* (Figures 2 and 3); and CRT had the highest symptom scores for *Swallowing*, *Dry Mouth* and *Sticky Saliva* (Figures 3 and 4).

All of the 10-point differences for *Fatigue*, *Pain in the Mouth*, *Swallowing*, *Sense Problems* and *Dry Mouth* had good evidence of statistically significant with post hoc Tukey–Kramer tests $P \leq .01$, with the exception of the 10.6-point difference for *Dry Mouth* between RT and CRT ($P = .05$). The 11.8-point difference between 'surgery only' and 'RT ± CT and ND' for *Insomnia* had a *P*-value of .04, and the 10.3-point difference found for *Sexuality* had $P = .2$. *Opening Mouth* had a statistically meaningful 10-point difference between 'surgery only' and 'surgery and RT ± CT' ($P < .0001$) and between 'RT only' and 'surgery and RT ± CT' ($P = .0012$), and between 'surgery only' and 'CRT' ($P = .0124$); all the 10-point differences in *Sticky Saliva* had *P* values <.01 except for 'surgery only' vs 'RT only' ($P = .03$).

The three domains with the largest adjusted mean difference among the treatment groups were *Dry Mouth* (largest difference [Δ] was 31.0 between 'surgery only' and 'CRT'), *Sticky Saliva* (Δ was 20.9 between 'surgery only' and 'CRT') and *Opening Mouth* (Δ was 16.5 between 'surgery only' and 'surgery and RT ± CT') (Figures 3 and 4). In the remaining groups with a clinically meaningful difference, the maximum differences in each domain were between 10.2 (*Pain in*

TABLE 3 Health-related quality of life measured with the EORTC QLQ-C30 and QLQ-H&N35 according to the type of treatment received: means are *adjusted* by age, gender, UICC stage and tumour sub-site.

QoL scale	Surgery	RT	CRT	RT ± CT and ND	Surgery and RT ± CT
EORTC QLQ-C30 domains					
Global QoL	78.3 (67.7–89.0)	78.6 (67.7–89.6)	78.2 (67.9–88.4)	80.9 (69.8–92.0)	73.2 (63.0–83.4)
Physical functioning	100.0 (97.1–100)	100.0 (95.5–100.0)	100.0 (93.5–100.0)	100.0 (95.1–100.0)	100.0 (92.4–100.0)
Role functioning	88.5 (74.9–100.0)	85.3 (71.3–99.2)	81.7 (68.7–94.8)	81.6 (67.6–95.7)	79.1 (66.1–92.2)
Emotional functioning	67.1 (55.8–78.3)	71.0 (59.5–82.5)	66.5 (55.7–77.3)	67.1 (55.5–78.7)	65.4 (54.7–76.2)
Cognitive functioning	82.3 (71.3–93.2)	85.9 (74.7–97.1)	77.5 (67.0–88.0)	78.3 (67.0–89.6)	78.0 (67.6–88.5)
Social functioning	78.0 (65.3–90.7)	77.8 (64.8–90.8)	72.4 (60.3–84.6)	68.8 (55.7–81.9)	69.6 (57.5–81.7)
Fatigue[a]	***18.7 (5.9–31.4)***	***18.5 (5.4–31.5)***	***27.5 (15.3–39.7)***	***28.0 (14.8–41.2)***	***29.9 (17.7–42.1)***
Nausea and vomiting	4.9 (0.0–11.1)	4.9 (0.0–11.3)	6.6 (0.6–12.5)	6.3 (0.0–12.7)	5.8 (0.0–11.7)
Pain	22.7 (9.8–35.7)	21.3 (8.0–34.6)	24.0 (11.5–36.4)	29.6 (16.2–43.0)	28.9 (16.5–41.3)
Dyspnoea	3.2 (0.0–16.7)	5.7 (0.0–19.5)	5.8 (0.0–18.7)	7.4 (0.0–21.3)	8.3 (0.0–21.2)
Insomnia	**21.4 (6.4–36.5)**	**23.9 (8.5–39.2)**	**27.3 (12.9–41.7)**	**33.2 (17.7–48.7)**	**28.8 (14.4–43.2)**
Appetite loss	0.1 (0.0–11.9)	2.7 (0.0–14.6)	6.2 (0.0–17.5)	7.8 (0.0–19.9)	5.8 (0.0–17.0)
Constipation	0.0 (<0.0)	0.0 (<0.0)	0.0 (0.0–2.6)	0.0 (0.0–3.3)	0.0 (0.0–0.7)
Diarrhoea	6.0 (0.0–14.5)	4.3 (0.0–13.0)	7.9 (0.0–16.0)	9.0 (0.2–17.8)	7.6 (0.0–15.7)
Financial difficulties	36.8 (23.4–50.1)	37.5 (23.8–51.2)	40.9 (28.1–53.8)	41.1 (27.3–54.9)	42.1 (29.3–54.9)
EORTC QLQ-HN35 domains					
Mouth pain[a]	***10.3 (1.5–19.1)***	***14.6 (5.6–23.6)***	***16.8 (8.4–25.2)***	***18.7 (9.6–27.7)***	***20.5 (12.1–28.9)***
Swallowing[a]	***0.0 (0.0–8.0)***	***6.4 (0.0–17.1)***	***13.8 (3.8–23.9)***	***12.0 (1.2–22.8)***	***12.1 (2.1–22.1)***
Senses problems[a]	***0.0 (0.0–11.5)***	***2.7 (0.0–16.5)***	***8.0 (0.0–21.0)***	***5.5 (0.0–19.4)***	***12.1 (0.0–25.0)***
Speech problems	0.7 (0.0–11.8)	1.0 (0.0–12.4)	5.3 (0.0–15.9)	2.2 (0.0–13.7)	10.1 (0.0–20.7)
Trouble with social eating	0.0 (0.0–1.3)	0.0 (0.0–5.5)	0.0 (0.0–10.3)	0.0 (0.0–10.0)	2.4 (0.0–13.1)
Trouble with social contact	8.5 (0.2–16.7)	7.4 (0.0–15.9)	10.8 (2.9–18.7)	11.3 (2.7–19.8)	13.2 (5.3–21.1)
Sexuality	**0.9 (0.0–18.0)**	**2.7 (0.0–20.2)**	**7.3 (0.0–23.7)**	**11.2 (0.0–29.0)**	**9.3 (0.0–25.7)**
Teeth	11.5 (0.0–27.9)	17.4 (0.7–34.2)	18.5 (2.8–34.2)	20.5 (3.6–37.4)	19.6 (3.9–35.2)
Opening mouth[b]	***8.4 (0.0–23.5)***	***12.6 (0.0–28.1)***	***20.0 (5.4–34.4)***	***18.8 (3.1–34.4)***	***24.9 (10.4–39.4)***
Dry mouth[b]	***6.2 (0.0–23.0)***	***26.6 (9.3–43.8)***	***37.2 (21.0–53.3)***	***34.6 (17.2–52.0)***	***33.0 (16.8–49.1)***
Sticky saliva[b]	***0.0 (0.0–15.3)***	**11.2 (0.0–28.1)**	***20.9 (5.2–36.7)***	***15.0 (0.0–32.1)***	***18.8 (3.1–34.5)***
Coughing	8.3 (0.0–22.1)	6.5 (0.0–20.5)	8.1 (0.0–21.3)	8.7 (0.0–22.8)	12.1 (0.0–25.2)
Felt ill	12.5 (0.8–24.2)	11.5 (0.0–23.4)	16.5 (5.2–27.7)	17.2 (5.1–29.3)	19.9 (8.7–31.1)
Pain killers	40.8 (18.2–63.3)	42.3 (19.2–65.4)	41.5 (19.9–63.1)	38.7 (15.4–61.9)	43.0 (21.5–64.6)
Nutritional supplements	0.4 (0.0–17.7)	0.0 (0.0–16.5)	0.9 (0.0–17.6)	0.0 (0.0–13.8)	3.3 (0.0–19.9)
Feeding tube	0.0 (0.0–3.9)	0.0 (0.0–4.5)	0.0 (0.0–6.1)	0.0 (0.0–5.1)	0.0 (0.0–7.0)
Weight loss	12.9 (0.0–29.8)	10.4 (0.0–27.6)	9.3 (0.0–25.4)	7.8 (0.0–25.2)	14.0 (0.0–30.1)
Weight gain	21.3 (1.7–40.9)	22.3 (2.2–42.3)	22.7 (3.9–41.4)	26.2 (6.0–46.4)	25.7 (6.9–44.4)

Note: Means with 95% CI are reported. For the functional scales and the global quality of life scale, high scores indicate good functioning and good quality of life; for all other scales, high scores are an indication of high symptom burden/poor quality of life in that area. Results are adjusted for age, gender, UICC stage and tumour subsite. **Bolded rows** contain at least one difference of 10 or more points between treatment groups but the difference is not statistically significant (Tukey post-hoc test >0.01). ***Bolded and italics*** contain at least one 10-point difference with evidence of a statistical difference (Tukey post-hoc test ≤0.01).

Abbreviations: CI, confidence interval; CRT, chemo-radiotherapy; CT, chemotherapy; ND, neck dissection; RT, radiotherapy.

[a]Indicates *all the 10-point differences* between treatment groups were statistically significant (Tukey post-hoc *P* value ≤.01).

[b]Indicates *at least one (but not all)* of the 10-point differences between treatment groups was statistically significant (Tukey post-hoc *P* value ≤.01).

the Mouth) and 13.8 (*Swallowing*). Where notable differences between the treatment groups were present, the predominance of problems experienced by survivors treated with multimodal therapies could be seen.

There were 909 survivors (89.5% of the study population) who had neither current evidence of disease nor had had a second primary. When the adjusted models were rerun to include only these 909 patients, the means and CI did not change in clinically

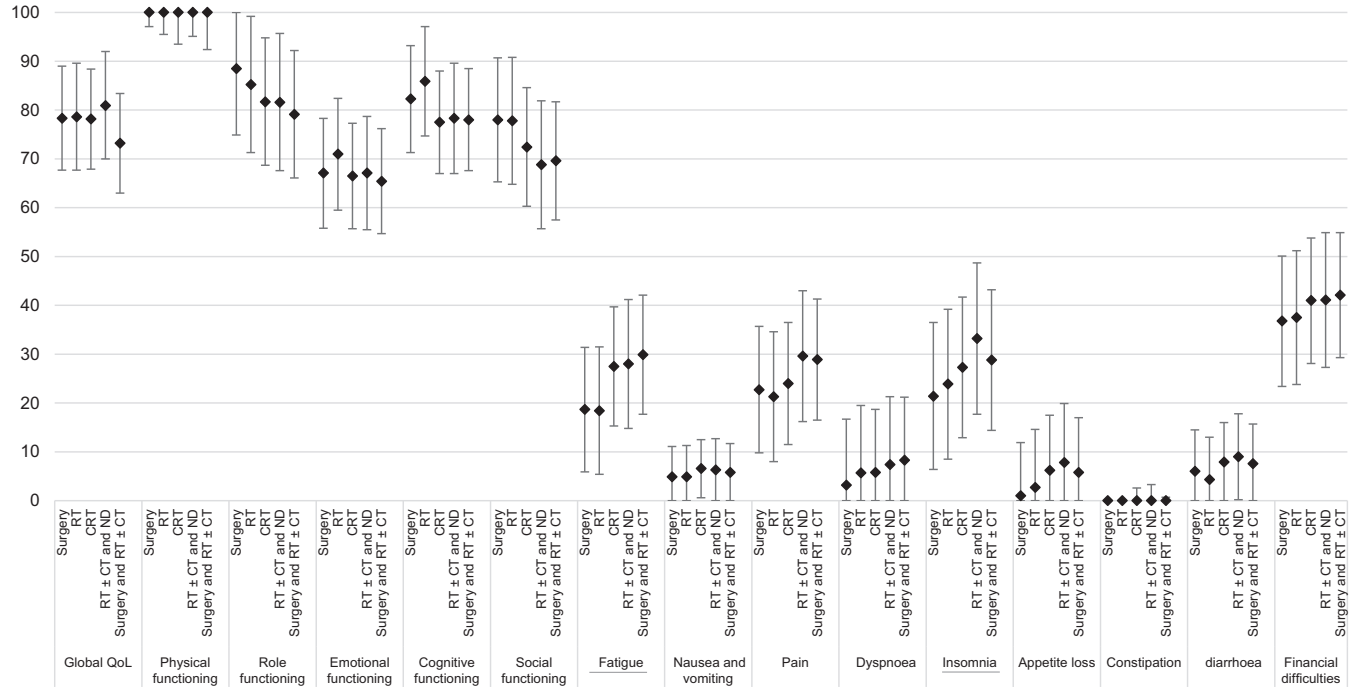

FIGURE 2 Adjusted means and 95% confidence intervals for the health-related quality of life domains within the EORTC QLQ-C30 by treatment group. CRT, chemo-radiotherapy; CT, chemotherapy; ND, neck dissection; RT, radiotherapy. Underlined scales contain at least one difference of 10 points or more between the treatment groups; For the functioning scales, high scores indicate high functioning; for symptom scales, low scores indicate low symptom burden.

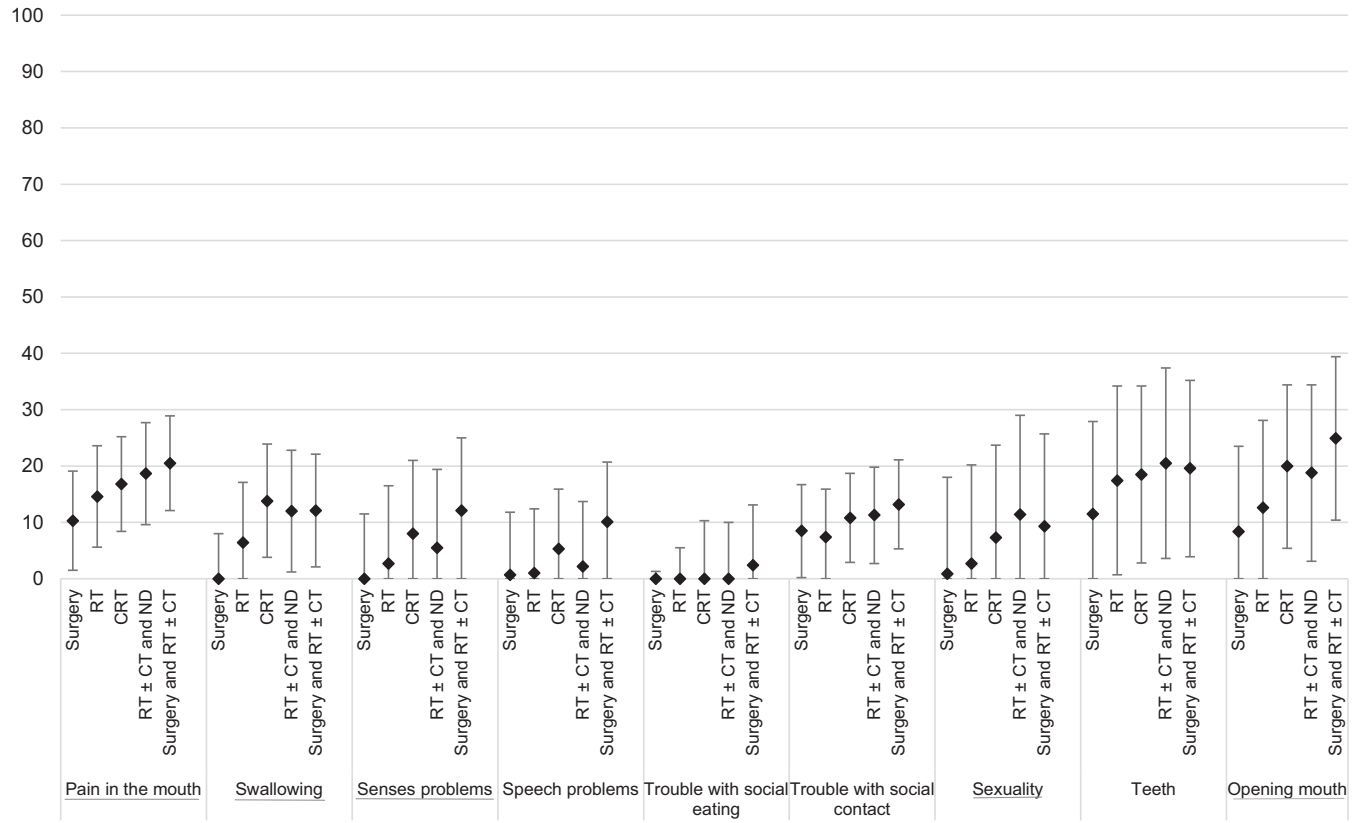

FIGURE 3 Adjusted means and 95% confidence intervals for the health-related quality of life domains within the EORTC QLQ-H&N35 by treatment group (Part 1). CRT, chemo-radiotherapy; CT, chemotherapy; ND, neck dissection; RT, radiotherapy. Underlined scales contain at least one difference of 10 points or more between the treatment groups; Low scores represent a low symptom burden.

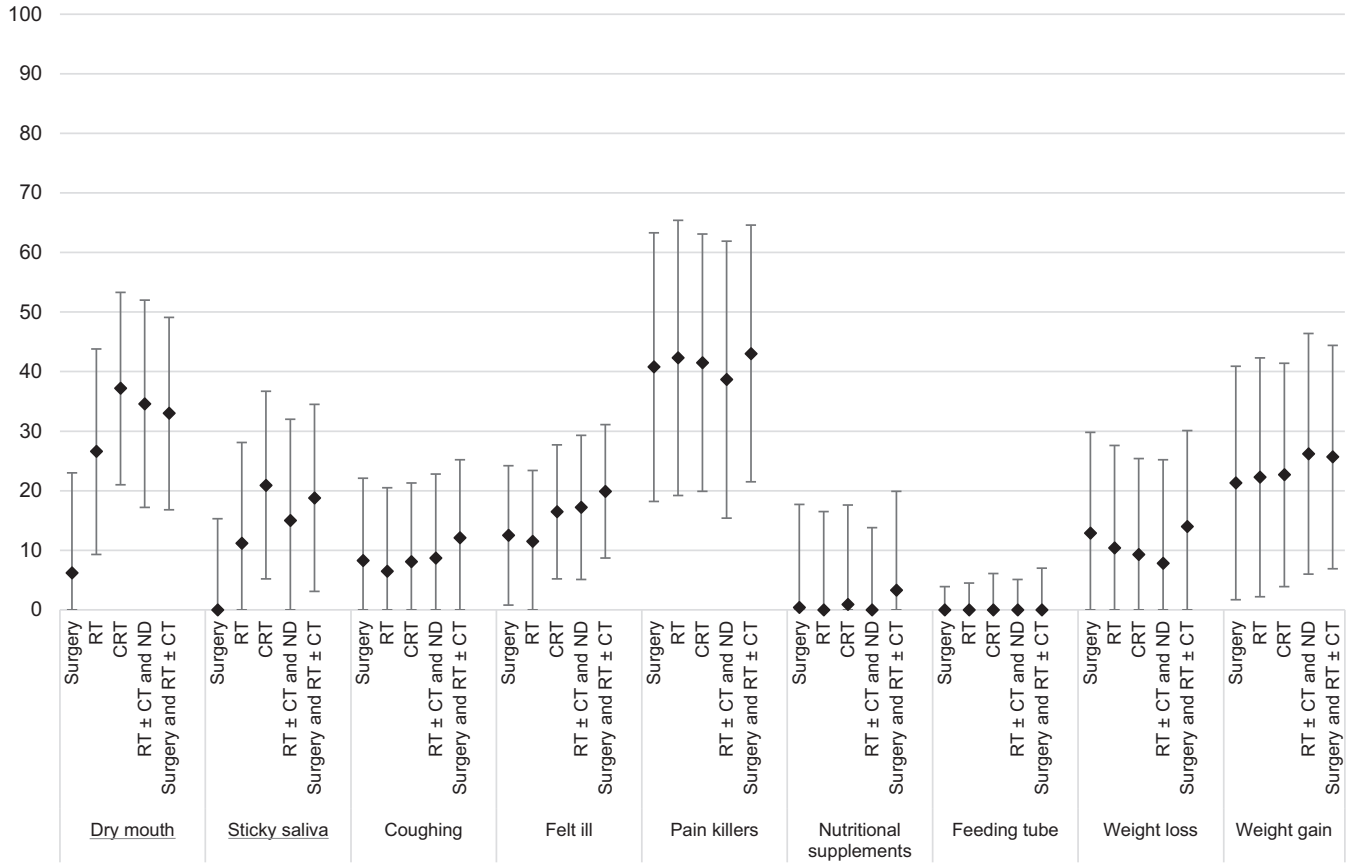

FIGURE 4 Adjusted means and 95% confidence intervals for the health-related quality of life domains within the EORTC QLQ-H&N35 by treatment group (Part 2). CRT, chemo-radiotherapy; CT, chemotherapy; ND, neck dissection; RT, radiotherapy. Underlined scales contain at least one difference of 10 points or more between the treatment groups; Low scores represent a low symptom burden.

meaningful way, with most domains moving 1–4 points (data not shown).

4 | DISCUSSION

To the best of our knowledge, this is the first international study investigating HRQoL at 5 years or more post-diagnosis enrolling more than 1000 survivors. We found notable differences in the long-term HRQoL of HNC survivors in light of treatment received for some domains, even when the effects of tumour stage, tumour location, age and sex of the patient were controlled for. To date, this has been an understudied cancer survivor group, as shown by a recent literature review that identified only eight studies examining long-term HRQoL in this cancer survivor group including 22–242 survivors each.[36]

Among some of the domains with a clinically relevant adjusted mean difference in scores between treatment groups, a considerable difference between the highest scores and published examples from the general population can be seen, indicating that even years after treatment, the effects of treatment may persist. For example, Hammerlid et al reported a mean score of 3.4 for *Pain in the Mouth* in a Swedish general population, while this was 20.5 and 18.7 in our two multimodal surgery groups and 10.3 in the 'surgery only' group.[37] Likewise, *Opening Mouth*, *Dry Mouth* and *Sticky Saliva* were considerable problems for the multimodal treatment groups, but less so for the 'surgery only' and 'RT only' groups. In the Swedish general population, means of 2.0, 12.0 and 5.9 were found for these three domains, respectively, showing that our 'surgery only' group had even fewer problems with *Dry Mouth* and *Sticky Saliva* than this general population.[37] One possible explanation for this difference with the general population could be a difference in expectations between a cancer survivor and person who has not had cancer, with the general population perhaps regarding any kind of dry mouth as a problem whereas the cancer survivor may not. This was also the case for *Swallowing* and *Senses Problems*, where the 'surgery only' group had adjusted estimated means of 0.0 and the general population 1.6 and 4.5. The CI for our estimates should also be considered, but nevertheless, the survivors who only had surgery were more similar to the general population sample than the 'RT only' or multimodality groups. The finding that patients undergoing surgery only have a lower symptom burden compared to 'RT only' and 'CRT' patients was also found in a Swedish/Norwegian population of oral cancer survivors 5 years after treatment.[24] Despite differences between treatment groups, *Sexuality* seemed to be a smaller problem for survivors in our study compared to the general Swedish population reported by Hammerlid et al (adjusted estimates from 0.9 to 11.4 vs 19.2), perhaps suggesting that

sexuality issues are related to some other aspect than HNC treatment.[37] Nolte et al reported *Fatigue* and *Insomnia* scores of 29.5 and 26.6, which are within range of our results as well, indicating that while our survivor population experiences these problems to some extent, it is not substantially different from a general international population.[38] There was little change in the *Insomnia* scores between the raw means and the adjusted means, suggesting that the age, sex, diagnosis group and UICC stage did not have much influence on insomnia.

Abendstein et al reported 5 year mean values of 48, 35, 20 and 19 for *Dry Mouth*, *Sticky Saliva*, *Opening Mouth* and *Senses Problems* among 167 survivors of oral cavity, pharynx, larynx and 'other' HNC carcinomas, indicating higher levels of symptoms than what was experienced by our study participants, with the exception of *Opening Mouth* for 'CRT' and 'surgery and RT ± CT'.[21] However, our study's CI consistently included these values; a direct comparison of our adjusted means with unadjusted published means may not be an accurate comparison, as we wanted to focus on the effect of the treatment itself. Published data on 360 disease-free HNC patients at 3 years' post-treatment also showed an elevated symptom burden for *Dry Mouth* (mean: 45), *Sticky Saliva* (37), *Opening Mouth* (14) and *Senses Problems* (19).[1]

The domains where no clinically meaningful differences between the treatment groups were found are of interest as well to gain a picture of how treatment may affect long-term HRQoL. For example, the adjusted mean *Physical Functioning* scores across our study's treatment groups were 100 (indicating the highest functioning possible), while Nolte at el. reported an average of 85.1 in an international general population.[38] This could be an indication of a selection of health survivors, whereby the survivors in our study were healthy enough to attend a clinical visit, while Nolte et al collected the HRQoL data through online surveys, which would have required less physical strength, or it could be that treatment has little to no effect on this domain in the long-term. Even in our unadjusted models, *Physical Functioning* was quite good, ranging from a mean of 81.3–84.6. Indeed, 67% of our survivor population had a Karnofsky score of 90 or higher, which corresponds to being able to carry out normal activities. Speech, too, in our study was not a notable problem for the survivors, but this could be because the survivors had adjusted to their voice limitations and may not regard it as a significant problem anymore. Dyspnoea is also interesting in that survivors across treatment groups had a low symptom burden (8.3 or less) but examples from a general population are 18.5 and 15.9.[37,38] Across all treatment groups, *Financial Difficulties* was also a considerable problem, with adjusted mean scores ranging from 36.9 to 42.5, whereas the general population measurement was considerably lower at 10.6.[38]

The strengths of this study included the large sample of over 1100 individuals from an international setting and the use of well-established, validated questionnaires to ascertain HRQoL. Our study has good statistical power and adds substantial HRQoL information for HNC survivors on what to expect in the long-term and an indication of where the differences may be expected depending on treatment. Limitations include that for multimodal treatment the order of the treatments was not recorded. This means we cannot be sure whether the patients received the radiotherapy as primary or adjuvant therapy and the surgery as primary treatment or in salvage, which could affect HRQoL. Originally, the two multimodal surgery groups were together, and we separated these into RT ± CT plus neck dissection and RT ± CT plus any other surgery on the assumption that in the latter groups the surgeries were more radical and would impact more on HRQoL than a neck dissection. Additional treatment information such as the type of chemotherapy agent and radiation dosage limit a more precise analysis. Treatments have evolved over the last decades, and, for example, the use of laser surgery, robotic surgery, intensity-modulated radiotherapy and proton therapy have meant evolving acute toxicities, which may in turn affect the long-term outcomes. Although we adjusted for stage of disease and tumour site, it remains possible that some of the differences we found are influenced by these important factors. We also do not have information on HPV status; adjusting for this factor would have been interesting as HPV-associated disease has a better prognosis than HPV-negative disease. It would have been preferable to also include the EORTC Survivorship questionnaire (SURV100) in this study, but it was not available at the time the study protocol was created and indeed is still in Phase IV testing.[39] It is possible that some issues specific to survivorship were missed or that comorbidities not assessed by the Charlson Comorbidity Index are present. Using a 10-point difference between the treatment groups based on the findings of Osoba et al is a reasonable choice, but we realize that while Osoba et al were looking for a minimally significant change, we have investigated a minimally significant difference. Moreover, the 10-point difference is only a rough estimate with studies suggesting more fine-tuned scores may be preferable.[40–43] It is likely that survivors who were not doing well were less likely to agree to participate than those who function well, particularly because physical attendance at the clinic was part of the study. The lack of information about those who declined to participate and those who did not respond at all prevents us from understanding the extent of differences between participants and non-participants. Ideally, long-term prospective studies would be preferable to assess HRQoL, but the trajectory would cover many years and, given the long-term prognosis of the disease, a considerable number of patients would need to be enrolled at diagnosis in order to gain robust results after 5 years. An alternative could be to implement routine assessments of HRQoL and then examine these retrospectively.

5 | CONCLUSIONS

This study of long-term HRQoL among HNC survivors provides one of the most comprehensive overviews on this topic to date. Clinically meaningful differences in HRQoL between treatment groups were found among long-term HNC survivors in nine HRQoL domains, seven of which had statistical significance. Survivors who have had only

surgery or RT had the smallest symptom burden compared to survivors with multimodality treatment even after taking site and stage into account. In some domains, survivors' HRQoL scores were better than examples from the general population. Our conclusions on the problems experienced by long-term HNC survivors provide a basis to educate patients on specific long-term quality of life issues related to their treatment and could contribute to clinicians tailoring specific follow-up regimes. As well, even before treatment begins, newly diagnosed patients can be informed about the possible long-term effects of treatment.

AUTHOR CONTRIBUTIONS

Katherine J. Taylor: Conceptualization and methodology; survivor enrolment; data curation and formal analysis; writing—original draft; writing—review and editing; project administration. **Cecilie D. Amdal:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Kristin Bjordal:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Guro L. Astrup:** Survivor enrolment; writing—review and editing. **Bente B. Herlofson:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Fréderic Duprez:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Ricardo R. Gama:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Alexandre Jacinto:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Eva Hammerlid:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Melissa Scricciolo:** Survivor enrolment; writing—review and editing. **Femke Jansen:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Irma M. Verdonck-de Leeuw:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Giuseppe Fanetti:** Survivor enrolment; writing—review and editing. **Orlando Guntinas-Lichius:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Johanna Inhestern:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Tatiana Dragan:** Survivor enrolment; writing—review and editing. **Alexander Fabian:** Survivor enrolment; writing—review and editing. **Andreas Boehm:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Ulrike Wöhner:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Naomi Kiyota:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Maximilian Krüger:** Survivor enrolment; writing—review and editing. **Pierluigi Bonomo:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Monica Pinto:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Sandra Nuyts:** Survivor enrolment; writing—review and editing. **Joaquim Castro Silva:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Carmen Stromberger:** Survivor enrolment; writing—review and editing. **Pol Specenier:** Survivor enrolment. **Francesco Tramacere:** Survivor enrolment; writing—review and editing. **Ayman Bushnak:** Survivor enrolment; writing—review and editing. **Pietro Perotti:** Survivor enrolment; writing—review and editing. **Michaela Plath:** Survivor enrolment; writing—review and editing. **Alberto Paderno:** Survivor enrolment; writing—review and editing. **Noa Stempler:** Survivor enrolment; writing—review and editing. **Maria Kouri:** Conceptualization and methodology; survivor enrolment; writing—review and editing. **Vincent Grégoire:** Supervision. **Susanne Singer:** Conceptualization and methodology; writing—review and editing; supervision; funding acquisition. All authors have read and agreed to the published version of the article. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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DATA AVAILABILITY STATEMENT

Data may be requested from the data repository of the EORTC (https://www.eortc.org/data-sharing/). Further information is available from the corresponding author upon request.

ETHICS STATEMENT

All participants gave written informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki. The ethical approval at the coordinating centre in Mainz, Germany, was granted by the Landesärztekammer (Medical Association) Rhineland-Palatinate (No. 2018-13579) and was obtained at each site in accordance with local regulations.

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