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Langzeitfolgen und Lebensqualität bei ehemaligen Patienten mit Kopf- Halstumoren
Eine multinationale Querschnittsstudie

(Late Toxicity and Long-Term Quality of Life in Head and Neck Cancer Survivors

A Cross-sectional, Multi-national Study)

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1. Summaries

1.1. German abstract

Hintergrund

Patienten mit Kopf- und Halskrebs (HNC) sind aufgrund ihrer Erkrankung und der Behandlung mit einer Vielzahl von nachteiligen gesundheitsbezogenen Lebensqualitätsergebnissen (HRQoL) und Toxizitäten konfrontiert, darunter Gesichtsentstellung, Stimmveränderungen, Schluck- und Sprechschwierigkeiten sowie Probleme durch Mundtrockenheit und sensorischen Funktionen. Obwohl das Überleben zweifellos ein entscheidendes Ergebnis der Behandlung ist, ist es auch wichtig zu verstehen, wie die Behandlungen die HRQoL und das Auftreten von Toxizitäten im Laufe der Zeit nach der Diagnose an beeinflussen. Obwohl in den Jahren unmittelbar nach der Diagnose und Behandlung erhebliche Forschungsarbeit zu diesem Thema geleistet wurde, ist sehr wenig über die langfristige HRQoL und das Auftreten von Toxizitäten bei HNC-Überlebenden bekannt. Um diese Wissenslücke zu schließen, wurde ein Projekt mit dem Titel „Langzeitfolgen und Lebensqualität bei ehemaligen Patienten mit Kopf- Halstumoren“ wurde ins Leben gerufen. Die primären Forschungsfragen waren:

1. Gibt es klinisch relevante Unterschiede bei der HRQoL der Überlebenden in Abhängigkeit der Behandlung, die die Überlebenden erhalten haben?
2. Gibt es Unterschiede im Auftreten von langfristiger, ärztlich bewerteter Dysphagie, Mundtrockenheit, Trismus und Mundschmerzen in Abhängigkeit von der Behandlung, die die Überlebenden erhalten haben?

Methoden

In einem Querschnittsdesign kontaktierten die teilnehmenden Kliniker HNC-Überlebende, die mindestens fünf Jahre nach der Diagnose lebten, und luden sie ein, an der Studie teilzunehmen. Die Überlebenden füllten den Fragebogen zur gesundheitsbezogenen Lebensqualität (HRQoL) der European Organisation for Research and Treatment of Cancer (EORTC) (den EORTC QLQ-C30) sowie das Modul für Kopf- und Halskrebs (EORTC QLQ-H&N35) aus und wurden klinisch auf vier Toxizitäten untersucht: Dysphagie, Mundtrockenheit, Trismus und Mundschmerzen. Der Kliniker füllte ein Case Report Form aus und dokumentierte die Ergebnisse der Toxizitätsuntersuchung unter Verwendung der Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0). Die Überlebenden wurden in folgende Behandlungsgruppen eingeteilt:

1) nur Chirurgie (Surgery only)
2) nur Strahlentherapie (RT only)
3) Chemoradiotherapie (CRT)
4) RT +/- Chemotherapie (CT) und Neck dissection (ND)
5) Chirurgie und RT +/- CT (Surgery und RT +/-CT)

Deskriptive Statistiken zu den demografischen und klinischen Daten der Überlebenden in jeder Behandlungsgruppe wurden als absolute und relative Häufigkeiten berichtet, mit Ausnahme des Alters, das als Mittelwert und Spanne in Jahren berichtet wurde. Die HRQoL-Werte für jede Skala in den HRQoL-Fragebögen wurden für jede Behandlungsgruppe als Rohmittelwerte mit Standardabweichungen berichtet. Um die erste Forschungsfrage zu beantworten, wurden mittels Kovarianzanalyse adjustierte Mittelwerte und 95% Konfidenzintervalle (CI) für jede HRQoL-Skala nach Behandlungsgruppe berechnet (adjustiert für Geschlecht, Alter, Tumorstadium und Sublokalisation). Tukey-Post-hoc-Tests wurden verwendet, um die statistische Evidenz für klinisch relevante Unterschiede in den adjustierten Mittelwerten zwischen den Behandlungsgruppen zu bewerten. Für jede der vier ärztlich beurteilten Toxizitäten wurden die Daten als absolute und relative Häufigkeiten nach CTCAE-Schweregrad für jede Behandlungsgruppe berichtet. Um die zweite Forschungsfrage zu beantworten, wurden logistische Regressionen durchgeführt, um die Odds Ratio zu bestimmen, die eine Behandlungsgruppe „frei von Toxizität“ oder mit „Schweregrad 1“ im Vergleich zu „Schweregrad 2 oder höher“ aufweist. Als Referenz diente die Behandlungsgruppe „Surgery und RT + /- CT'. Geschlecht, Alter, Tumorstadium und Sublokalisationen wurden als Kovariablen einbezogen.

Ergebnisse

Insgesamt wurden 1113 Überlebende aus 26 Standorten in 11 Ländern eingeschlossen, wobei die Mehrheit aus Nordeuropa (23%), Mittel-/Westeuropa (43%) und Südeuropa (21%) stammte und die übrigen aus Brasilien (10%), Japan (3 %) und Israel (1%). Die meisten Studienteilnehmer waren Männer (71%), das Durchschnittsalter betrug 66 Jahre (Spanne: 23–93 Jahre) und die drei größten Diagnosegruppen waren Oropharynxkrebs (34%), Mundhöhlenkrebs (22%) und Kehlkopfkrebs (19%). Die meisten Überlebenden waren ehemalige Raucher (57%), wurden in einem hohen Tumorstadium diagnostiziert (UICC III: 22 %; UICC IV: 39 %) und hatten einen guten Karnofsky-Score (90 oder 100: 66%). Die mittlere Zeit seit der Diagnose betrug acht Jahre und 97% hatten keine aktuellen Anzeichen einer Krebserkrankung. Die größte Behandlungsgruppe war „Surgery und RT +/- CT“ mit 424 Überlebenden (38 %), gefolgt von der CRT-Gruppe mit 315 (28 %) und nur RT mit 134 (12 %). Die beiden kleinsten Gruppen waren „Surgery only“ (n = 129; 12 %) und „RT +/- CT und ND“ (n = 111; 12 %).

In adjustierten Modellen gab es starke Evidenz für klinisch bedeutsame Unterschiede in der HRQoL zwischen den Behandlungsgruppen bei *Müdigkeit, Mundschmerzen, Schlucken, Sinneswahrnehmungen, Mundöffnung, Mundtrockenheit* und *klebrigem Speichel*, wobei die größten Unterschiede bei *Mundtrockenheit* und *klebrigem Speichel* auftraten. Überlebende, die mit CRT behandelt wurden, hatten die höchste Symptomlast in Bezug auf *Mundtrockenheit* (Mittelwert: 37,2; 95%-KI: 21,0–53,3), klebrigen Speichel (Mittelwert: 20,9; 95%-KI: 5,2–36,7) und *Schlucken* (Mittelwert: 13,8; 95%-KI: 3,8–23,9) im Vergleich zu den niedrigsten Werten für

„Surgery only“ (jeweils Werte von 6,2 (95%-KI: 0,0–23,0); 0,0 (95%-KI: 0,0–15,3); und 0,0 (95%-KI: 0,0–8.0)). Bei *Müdigkeit, Schmerzen im Mund* und *Sinneswahrnehmungen* hatten „Surgery und RT +/-CT“ die höchste Symptomlast (jeweiliger Mittelwert und 95%-KI: 29,9 (17,7–42,1); 20,5 (12,1–28,9); 12,1 (0,0–25,0)), und die niedrigsten Werte wurden in der Gruppe „Surgery only“ für *Mundschmerzen* (Mittelwert: 10,3; 95%-KI: 1,5–19,1) und *Sinneswahrnehmungen* (Mittelwert: 0,0; 95%-KI: 0,0–11,5) sowie in der „RT only“-Gruppe für *Müdigkeit* (Mittelwert: 18,5; 95%-KI: 5,4–31,5) beobachtet. Insgesamt hatten Langzeitüberlebende, die mit nur einer Modalität behandelt wurden, in allen Bereichen eine bessere oder gleiche HRQoL im Vergleich zu Überlebenden mit multimodaler Behandlung, nach Adjustierung für Geschlecht, Alter, UICC-Stadium und Tumorlokalisation.

Der höchste Anteil an ärztlich beurteilter Dysphagie, Trismus und oralen Schmerzen mit einem CTCAE-Grad 2 oder höher wurde in der „Surgery and RT +/-CT“-Gruppe beobachtet (29,9%; 8,0% bzw. 4,6%) und der niedrigste in der „Surgery only“-Gruppe für Dysphagie (9,7%) und in der „RT only“-Gruppe für Trismus und Mundschmerzen (0,0% und 0,7%). Bei der vom Arzt festgestellten Mundtrockenheit hatte die „RT +/- CT und ND“-Gruppe den höchsten Anteil an Grad 2 oder höher auf (34,9%) und „Surgery only“ den niedrigsten Anteil (2,4%). Die multivariate logistische Regression zeigte, dass die Odds, keine Dysphagie zu haben oder sie nur mit einem Schweregrad von 1 zu haben, in der Gruppe mit „Surgery only“ 3,7-mal höher war (Odds Ratio (OR): 3,7; 95%-KI: 1,8–7,4)) und 2,9-mal höher in der RT Gruppe (OR: 2,9; 95%-KI: 1,5–5,7) im Vergleich zur „Surgery and RT +/- CT“-Gruppe. Überlebende, die nur operiert wurden, hatten ein 15,4-mal höhere Chance, keinen trockenen Mund zu haben oder nur einen Schweregrad 1 zu haben (OR: 15,4; 95%-KI: 4,6–51,7).

Fazit

Diese Ergebnisse deuten darauf hin, dass HNC-Patienten, die mit einer multimodalen Therapie behandelt wurden, nach Adjustierung für Geschlecht, Alter, Tumor-Stadium und Sublokalisation, langfristig eine schlechtere HRQoL bezüglich der Symptome: *Müdigkeit, Mundschmerzen, Schlucken, Sinneswahrnehmungen, Mundöffnung, Mundtrockenheit* und *klebrigem Speichel* haben als Überlebenden, die mit einer Monotherapie behandelt wurden. Bei klinisch bewerteter Dysphagie und Mundtrockenheit gibt es Hinweise darauf, dass diese Toxizitäten bei Langzeitüberlebender, die eine Monotherapie hatten, langfristig seltener auftreten als bei denen, die eine multimodale Therapie erhielten. Das Verständnis der Probleme, die mit denen Langzeitüberlebende von HNC zu kämpfen haben, könnte dazu beitragen, geeignete unterstützende Therapien auszuwählen und neu diagnostizierte Patienten über die möglichen langfristigen Auswirkungen ihrer Behandlung zu informieren. Darüber hinaus könnten Kliniker Nachsorgeprogramme anpassen, um sicherzustellen, dass die wahrscheinlichen negativen Folgen systematisch bewertet werden. Obwohl es sich bei dieser

Studie möglicherweise um die bisher größte Untersuchung zur Lebensqualität und Toxizitäten in der Gruppe der Langzeitüberlebenden ist und gut etablierte, validierte HRQoL-Fragebögen und fachkundige klinische Beurteilungen durchgeführt wurden, leiden die Ergebnisse wahrscheinlich unter einem „Healthy Survivor Bias“. Daher werden die HRQoL möglicherweise überschätzt und die Häufigkeit von Toxizitäten wahrscheinlich unterschätzt. Zukünftige Studien in dieser Gruppe der Überlebenden sollten Möglichkeiten in Betracht ziehen, auch Überlebende zu erreichen, die möglicherweise nicht bereit oder fähig sind, an einer klinischen Untersuchung teilzunehmen. Eine Möglichkeit wäre, ihnen einen alternativen Weg ohne Toxizitätsbewertung oder eine Bewertung per Videokonferenz anzubieten.

1.2. English abstract

Background

Head and neck cancer (HNC) patients face a range of detrimental health-related quality of life (HRQoL) outcomes and toxicities as a result of their disease and treatment, including facial disfiguration, voice alteration, difficulty swallowing and speaking as well as problems with dry mouth and sensory functions. While survival is clearly a critical outcome of treatment, understanding how the treatments affect HRQoL and toxicity occurrence over time from diagnosis onwards is also important. While considerable research has been done on this topic in the years immediately following diagnosis and treatment, there is very little known about the long-term HRQoL and toxicity occurrence in HNC survivors. A project entitled “Late Toxicity and Long-term Quality of Life in Head and Neck Cancer Survivors” was initiated to address this lack of knowledge. The primary research questions were

1. Are there clinically meaningful differences in long-term HRQoL outcomes in light of the treatment the survivors received?
2. Are there differences in the occurrence of long-term physician-rated dysphagia, dry mouth, trismus, and oral pain in light of the treatment the survivors received?

Methods

In a cross-sectional design, participating clinicians contacted HNC survivors who were at least five years post-diagnosis and invited them to participate in the study. Participating survivors completed the European Organisation for Research and Treatment of Cancer (EORTC) core HRQoL questionnaire (the EORTC QLQ-C30) and the HNC module (EORTC QLQ-H&N35) and underwent a clinical examination for four toxicities: dysphagia, dry mouth, trimus and oral pain. The clinician completed a case report form and documented the results of the toxicity examination using the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

The survivors were sorted into treatment groups as follows:

1) surgery only
2) radiotherapy (RT) only
3) chemo-radiotherapy (CRT)
4) RT +/- chemotherapy (CT) and neck dissection (ND)
5) any other surgery and RT +/- CT

Descriptive statistics for demographic and clinical data of the survivors in each treatment group were reported as absolute and relative frequencies, except age which was reported as the mean and range in years. The HRQoL scores for each scale in the HRQoL questionnaires were reported for each treatment group as raw means with standard deviations. To answer the first research question, analysis of covariance was used to determine adjusted means and 95% confidence intervals (CI) for each HRQoL scale by treatment group (adjusted for sex, age, and tumor stage and sub-site). A difference in mean of ten points or more was considered clinically relevant. Tukey post-hoc tests were used to assess the statistical evidence for clinically relevant differences in the adjusted means between the treatment groups. For each of the four physician-assessed toxicities, the data were reported as absolute and relative frequencies by CTCAE severity for each treatment group. To answer the second research question, logistic regressions were run to determine the odds of a treatment group being free of the toxicity or only having it at a grade 1 severity versus grad 2 or higher, with the 'surgery and RT +/- CT' group as the reference. Sex, age, tumor stage and sub-site were included as covariables.

Results

A total of 1113 survivors from 11 countries were enrolled, with the majority coming from Northern Europe (23%), Central/Western Europe (43%) and Southern Europe (21%), and the reminder from Brazil (10%), Japan (3%), and Israel (1%). Most were men (71%), the average age was 66 years (range: 23-93), and the three largest diagnosis groups were oropharynx cancer (34%), oral cavity cancer (22%), and larynx (19%). Most survivors were former smokers (57%), were diagnosed at a high tumor stage (UICC III: 22%; UICC IV: 39%), and had a good Karnofsky Performance Status (90 or 100: 66%). The median time since diagnosis was eight years and 97% had no current evidence of disease. The largest treatment group was 'surgery and RT +/- CT' with 424 survivors (38%), followed by the CRT group with 315 (28%) and RT only with 134 (12%). The two smallest groups were surgery only (n=129; 12%) and 'RT +/- CT and ND' (n=111; 10%).

In adjusted models, there was strong evidence for clinically meaningful differences in HRQoL between treatment groups for *fatigue, mouth pain, swallowing, senses, opening mouth, dry mouth,* and *sticky saliva*, with the largest differences for *dry mouth* and *sticky saliva*. Survivors treated with CRT had the highest symptom burden for *dry mouth* (mean: 37.2; 95%CI: 21.0-

53.3) and *sticky saliva* (mean: 20.9; 95% CI: 5.2-36.7)) and *swallowing* (mean: 13.8; 95%CI: 3.8-23.9) compared to the lowest scores for surgery only (respective scores of 6.2 (95%CI: 0.0- 23.0), 0.0 (95%CI: 0.0-15.3), and 0.0 (95%CI: 0.0-8.0)). For *fatigue, mouth pain* and *senses*, 'surgery and RT +/- CT' had the highest symptom burden (respective means and 95%CI: 29.9 (17.7-42.1); 20.5 (12.1-28.9); and 12.1 (0.0-25.0)), and the lowest scores were in the 'surgery' only group for *mouth pain* (mean: 10.3; 95%CI: 1.5-19.1) and *senses* (mean: 0.0; 95%CI: 0.0- 11.5) and in the RT only group for *fatigue* (mean: 18.5; 95%CI: 5.4-31.5). Overall, long-term survivors who had single modality treatment had better or equal HRQoL in every domain compared to survivors with multi-modal treatment after adjusting for sex, age, UICC stage and tumor sub-site.

The highest proportion of physician-assessed dysphagia, trismus and oral pain at CTCAE grade 2 or higher was in the 'surgery and RT +/-CT' group (29.9%, 8.0%, and 4.6% respectively). The lowest proportion of dysphagia at a grade 2 or higher was among the survivors who had been treated with surgery only (9.7%) and for trimus and oral pain it was among the survivors treated with RT (0.0%, and 0.7%, respectively). For physician-assessed dry mouth, the 'RT +/- CT and ND' group had the highest proportion of grade 2 or higher (34.9%) and surgery only the lowest (2.4%). Multivariate logistic regression showed that the odds of being free of dysphagia or only having it at a severity grade of 1 were 3.7 times higher among the surgery only group (odds ratio (OR): 3.7, 95%CI: 1.8-7.4) and 2.9 times higher among the RT only group (OR: 2.9, 95%CI: 1.5-5.7) compared to the 'surgery and RT +/-CT' group. Survivors with surgery only were 15.4 times more likely to be free of dry mouth or only have it at a severity grade of 1 (OR: 15.4, 95%CI: 4.6-51.7).

Conclusion

These results suggest that, even after adjustment for sex, age, tumor stage and sub-site, HNC patients treated with multi-modal treatment have worse HRQoL in *fatigue, mouth pain, swallowing, senses, opening mouth, dry mouth,* and *sticky saliva* in the long term compared to survivors who were treated with monotherapy. For clinically assessed dysphagia and dry mouth, there is evidence that these toxicities are present less often in the long-term among survivors who had monotherapy compared to multi-modal therapy. Understanding the problems experienced in long-term HNC survivors could help direct appropriate supportive therapies and inform newly diagnosed patients about the potential long-term implications of their treatment. As well, clinicians could adapt follow-up programs to ensure the negative consequences more likely to occur are systematical assessed. Although this study is possibly the largest ever examination of quality of life and toxicities in this survivor group and used well-established validated HRQoL questionnaires and expert clinical assessments, the results likely suffer from healthy survivor basis. Therefore poor HRQoL and toxicity frequency may be under reported. Future studies in this survivor group should consider ways to reach survivors who may not be willing to attend a clinical visit, perhaps by offering an alternative stream with no toxicity assessment or assessment via video conference.

2. A brief introduction to head and neck cancer

Head and neck cancers (HNC) are a diverse set of neoplasms encompassing the oral cavity, lips, pharynx, larynx, para and nasal sinuses, and salivary glands (Figure 1). Because these structures play a vital role in a person's visual presentation to the world, as well as their necessity in speaking, eating and even breathing, a head and neck cancer diagnosis and subsequent treatment can have debilitating consequences.[1,2] In addition to problems with oral health, disfigurement, an inability to speak clearly, the discomfort of persistent dry mouth, and difficulty eating are a few of the long-term sequalae that patients may experience.[3–5] Stemming from these issues, patients may avoid social situations, which can lead to isolation and other psychosocial consequences.[1,6]

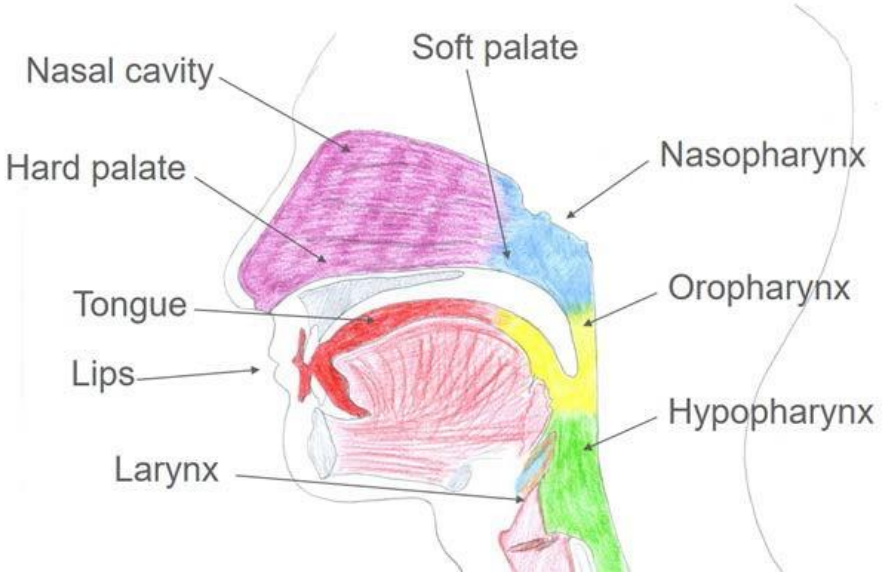

Figure 1 – Anatomical sites of head and neck cancer

Source: Created by the author

HNC's main risk factors are smoked or chewed tobacco, betel nut chewing, alcohol consumption (particularly in connection with smoking), and infection with human papilloma virus (HPV) or Epstein–Barr virus.[7–10] HPV plays a known role in oropharynx cancer development and is associated with diagnosis at a younger age and a better prognosis.[11] Epstein-Barr virus is known to have a principle role in the development of nasopharynx cancer.[12]

Symptoms such as persistent throat pain and voice alteration, red or white discolored areas in the mouth, lumps in the neck or problems swallowing are potential signs of head and neck

cancer.[13] Unfortunately, most HNC patients are diagnosed at an advanced stage of disease, at which point treatment may be less effective and have harsher side effects.[14] Regardless of the stage at diagnosis, the delicate anatomical structures involved and the range of functions implicated in head and neck cancer require a team of professionals to manage the disease and consequences of treatment, and can include general practitioners, medical and radio-oncologists, head and neck surgeons, surgeons with expertise in plastic surgery, and dentists as well as speech and swallowing therapists, dieticians, and physiotherapists.[13,15] Psycho-oncologists, other mental health specialists, and patient-support groups also have an important role in helping patients manage their expectations, feelings, and consequences connected to the diagnosis and treatment.[15]

Treatment recommendations vary in accordance with the specific sub-site, stage and involvement of lymph nodes but can include surgery, radiotherapy (RT), and chemotherapy (CRT), either as monotherapies or in combination.[13] Early stage tumors can be treated with conservative surgery or RT, while advance disease likely requires CRT or surgery followed by RT and chemotherapy (CT).

Upwards of 90% of all head and neck cancers are squamous cell carcinomas, with the remaining 10% comprising adenocarcinoma, adenoid cystic carcinoma, lymphoma, melanoma, and basal cell carcinoma.[16] The risk of a recurrence is particularly high among patients who were diagnosed at a high tumor stage, with estimated recurrences of between 40% and 60% of these patients; there is evidence that the rate of second primaries is consistent at about 3.5% per year.[17] Patients who experience a recurrence or a metastasis have an extremely poor prognosis, as demonstrated by a recent study investigating survival among 186 patients with metastatic HNC in which the median overall survival was 12.5 months.[18]

For this reason, as well as to watch for the development of late toxicities, patients should be followed up closely after successful treatment. Examples of recommended follow-up schedules include a European Clinical Practice Guideline[13] recommending follow-up appointments every two to three months after treatment for two years and then twice a year thereafter until five years post treatment. The European Head and Neck Society[15] recommends a slightly more intensive follow-up schedule, with follow-up every one to three months for one year after treatment, then every two to six months for the second year, and then every four to eight months for years three to five.[15] Both sources recommend yearly follow-up after five years.

3. Head and neck cancer epidemiology

Head and neck cancer as a diagnosis group is comprised of sub-groups that may vary, meaning one should consider the diagnoses included within a group when comparing incidence rates across populations. As an example, a 2018 publication by Conway et al. looked at differences in definitions in publications about oral cavity cancers and oropharyngeal cancers across the

four countries in the UK and found inconsistencies.[19] For example, the authors noted that the Office for National Statistics in England and the Northern Ireland Cancer Registry report oral cancers in a single combined group of lip, oral cavity, oropharynx, nasopharynx and hypopharynx cancers, whereas the Welsh Cancer Intelligence and Surveillance Unit combines oral cavity cancers and oropharynx cancers together as oral cancers.

The estimated incidence of HNC in 2020 worldwide was 932,000 and was the sixth most common newly diagnosed cancer that year (excluding non-melanoma skin cancer) (Table 1). Using the World Standard Population originally proposed by Segi et al., the world-wide age-standardized incidence (ASI) for HNC in 2020 per 100,000 was approximately 8.7. For context, the five most frequent cancers and their estimated age-standardized incidences in 2020 in increasing order were stomach cancer (1,089,100 cases; ASI: 11.1 per 100,000), colon cancer (1,148,500 cases; ASI: 11.4 per 100,000), prostate cancer (1,414,300 cases; ASI men only: 30.7 per 100,000), lung (2,206,800 cases; overall ASI: 22.4 per 100,000), and breast cancer (2,261,400 cases; ASI women only: 47.8 per 100,000).

Table 1 – World-wide incidence and mortality of head and neck cancers in 2020‡

	Estimated Incidence World-wide					**Estimated Deaths World-wide**				
Diagnosis	Ranking*	Incidence	Per 100,000†			Ranking*	Deaths	Per 100,000†		
			M&F	F	M			M&F	F	M
Lip and oral cavity	17	377,700	4.1	2.3	6.0	17	177,800	1.9	1.0	2.8
Larynx	21	184,600	2.0	0.5	3.6	19	99,800	1.0	0.3	1.9
Nasopharynx	23	133,400	1.5	0.8	2.2	22	80,000	0.8	0.5	1.3
Oropharynx	25	98,400	1.1	0.4	1.8	24	48,100	0.6	0.2	0.9
Hypopharynx	26	84,300	0.9	0.3	1.6	26	38,600	0.4	0.1	0.7
Salivary glands	29	53,600	0.6	0.5	0.7	29	22,800	0.2	0.2	0.3
	Total	932,000	8.7	4.8	15.9		467,100	4.9	2.3	7.9

‡ Data from Ferlay et al. 2021[20]
* Ranked from highest frequency to lowest among 35 specified cancers (non-melanoma skin cancer not included)
†Age standardized to the World Standard Population
M: male; F: female

The frequency of cancer diagnoses among the HNC sub-sites ranges. The most common HNC sub-sites in 2020 world-wide were the lip and oral cavity, with an estimated incidence of 377,700 (ASI: 4.1 per 100,000). In contrast, salivary gland cancers were the rarest HNC site, with an estimated 53,600 cases in 2020, followed by hypopharynx with 84,300 cases and oropharynx with 98,400. Largely due to the increasing prevalence of HPV, the incidence of oropharynx cancer in particular is expected to rise in the coming years.[12,21] Together, cancers of the lip and

oral cavity, the larynx, and the nasopharynx represented about 75% of all HNC cases world-wide in 2020, with a combined estimated incidence of 695,700.[20]

The relative magnitude of deaths for each HNC tumor sub-site closely follows the incidence ranking (Table 1). The largest number of HNC deaths in 2020 were attributed to cancers of the lip and oral cavity (ASI: 1.9/100,000), and the least to salivary gland cancers (ASI: 4.9/100,000). Of note are the number of deaths attributed to nasopharynx cancer. The ASI for nasopharynx indicate that for every 133 new diagnoses for this disease in 2020, there were about 80 deaths. This is the highest ASI diagnoses to death ratio among the HNC sub-sites worldwide in 2022.

The world-wide ASI for HNC per 100,000 individuals in 2020 varied considerably between the sexes: 4.8 for women and 15.9 for men. (Table 1). Data from Germany from 2017 and 2018 show a larger gap between the sexes; age standardized to the Old European Standard Population, the incidence for women was 7.6 per 100,000 and for men 21.8 per 100,000.[22] Data from 2018 in Norway shows ASIs of 5.2 per 100,000 for women and 11.8 per 100,000 for men.[23] In Southern Europe in 2014, the difference between men and women was even larger, with 17.2 cases per 100,000 for men and 3.5 per 100,000 for women.[24] Although some of this difference can be explained by variations of risk factors, there is some evidence that the range in incidence does not disappear when only never drinkers/never smokers are considered. A recent study in South Korea found that males still have 2.9 fold risk of developing head and neck cancer over females even when smoking and alcohol were removed as risk factors.[25] The precision of this study is questionable however, as it was a retrospective study and it is likely to have misclassification in the risk factor assessments.

Across Europe, the occurrence of HNC is slightly higher to what was previously described world-wide. The age-standardized incidence (World Standard Population) of HNC in Europe in 2020 was 12.1 per 100,000 overall.[26] When looking at Western Europe alone in 2020, it was the seventh most commonly diagnosed cancer.[26] Data from Norway for 2018 report 820 HNC cases*, accounting for 2.4% of all cancer cases there that year.[23] In Germany in 2018, 17,620 cases† were diagnosed, which was the ninth most common cancer and about 2.5% of all cancers diagnosed there that year.[22] Also from Germany, data from the Rhineland Palatinate Cancer Registry showed an ASI (European Standard Population) of 23.8 per 100,000 for HNC in 2009.[27] This higher ASI compared to Europe as a whole in 2020 could be due to the different standard population used for age standardization. However, it could also be in part due to decreasing incidence in the decade after 2009, as Bayer at al. reported a decrease in ASI of 0.9 per 100,000 per year between 2000 and 2009 in the same publication.

* Included ICD codes C00-C14, C30-C31, C32

† Included ICD codes C00-C14 and C32

Chronic infection with human papilloma virus has been recognized in recent years as an important risk factor for HNC, particularly for oropharyngeal cancers; in particular, HPV16 is present in approximately 85% of HPV+ oropharynx cancer cases. [28,29] An increasing trend in HPV-associated oropharyngeal cancers has been identified in high income nations such as the United States (US), Canada, Japan, Norway, and Australia.[30] The patients with an HPV-associated HNC diagnosis tend to be younger, have a range of smoking histories, have tumors that are identified at an earlier stage, and have a better prognosis than the non-HPV-related diagnoses.[31–33] While the proportion of HNC diagnoses assumed to be induced by smoking and alcohol use has declined in recent years, in parallel to the reduction in smoking, the proportion of HPV-induced HNC cancers has increased. Since 2005, the HPV vaccine has been available, but not enough time has passed to examine what impact such a vaccine could have on the occurrence of HNC.[14]

The five-year and ten-year survival proportions for HNC range depending on the specific sub-site. For example, a study on data from the US published in 2023 found a five-year relative survival of 68% for oral cavity and pharynx cancer.[34] Older data for the years 2002-2006 from the US show a high five-year relative survival proportion for lip cancer (97.4%), moderate five-year survival for cancer of the nasopharynx, oral cavity, larynx, and tonsil (62.3% to 69.8%), and low five-year survival for hypopharyngeal cancer (33.8%).[35] The authors of that study also concluded that survival for HNC as a group improved by more than 10% between 1982 and 2006. In Germany between 2017 and 2018, the relative five-year survival for oral cavity and pharynx cancer was 52% for men and 62% for women, and for larynx cancer it was 64% for men and 63% for women.[22] A study in Thuringia, Germany found lower five-year overall survival, with 48.5% of 8288 HNC patients diagnosed between 1996 and 2016 surviving to five years.[36] This is likely lower in part because of the older data from years when expected survival was less, as well as the fact that 11.4% of this study population had hypopharynx cancer, which has a poor prognosis. Data from Rhineland-Palatinate from 2000 to 2009 showed that overall mortality from HNC had decreased in this time frame (with possible exceptions for male salivary gland cancer patients and female oral cavity and oropharynx cancer patients).[27] Considering the placement of HNC as the sixth most frequently diagnosed cancer world-wide coupled with a broad expectation that at least half of patients will survive to five years, there is a necessity to ensure medical professionals understand the problems these survivors experience, how the patients cope, and what support services could be improved to assist them.[37]

The majority of tumor recurrences occur within the second and third years after diagnosis, and by five years post-diagnosis, cancer-free patients are usually considered cured.[38] However, the definition of a “survivor” is not definitive, with example definitions including having five years elapse without experiencing a recurrence, completing treatment, or even from the first day of

diagnosis.[37,39] Indeed, the term "cancer survivor" has also been viewed as including the family members, friends, and care givers that move through the experience of cancer with the patient as being survivors, as was done by the US National Coalition for Cancer Survivorship in 1986.[40]

In this thesis, however, survivors was defined as former HNC patients who have reached five years post diagnosis.

4. Instruments to assess health-related quality of life

A number of instruments to assess HRQoL specific to HNC have been well established. An important feature of HRQoL assessments is that they are patient-report outcomes (PROs), meaning that the results reflect the patient's or survivor's own perception of their symptom burden and quality of life. Usually this information is collected via questionnaires.

The University of Washington Quality of Life Questionnaire

Originally published in a smaller form in 1993, the University of Washington Quality of Life Questionnaire (UW-QoL) was developed for use in populations with head and neck cancer. Version 4 of the questionnaire comprises six questions covering physical functioning (chewing, swallowing, speech, taste, saliva and appearance), six questions on social/emotional functioning (anxiety, mood, pain, activity, recreation, and shoulder function), three questions on overall quality of life, and one question asking the patient to select the top three most important problems they experienced in the past seven days.[41–43] The number of answer options for the functional and global HRQoL questions range from three to six, and each question can be scored on a scale of 0 to 100, with 100 being the best possible score. An average value for physical functioning, social/emotional functioning, and overall quality of life can be determined by averaging the scores for the questions in those domains.

MD Anderson Questionnaires

The MD Anderson Symptom Index (MDASI) is a generic cancer questionnaire composed of 13 questions on symptoms (pain, fatigue, disturbed sleep, emotional distress, shortness of breath, drowsiness, dry mouth, sadness, difficulty remembering, numbness or tingling, lack of appetite, and nausea/vomiting) and six questions about interference with daily life activities (relations with others, enjoyment of life, mood, walking, general activities, and working) due to symptoms over the previous 24 hours.[44] Each question is answer on a numerical rating scale from zero to ten, with ten being the worst symptom burden or interference imaginable and zero being no problems.[45] A mean score for symptoms can be created by averaging the response numbers, and the interference questions can be averaged to determine the extent of symptom distress.

The MD Anderson Symptom Inventory Head and Neck Module (MDASI-HN) was developed to address symptoms specific to head and neck cancer patients. This module is used in

combination with the generic questionnaire and adds nine additional symptom questions concerning mouth sores, tasting food, constipation, teeth and gums, skin pain, voice and speech, choking and coughing, chewing and swallowing, and mucus. [46]

Also created by researchers at the MD Anderson Center Center is the MD Anderson Dysphagia Index.[47] This questionnaire contains 20 statements focusing solely on swallowing difficulties and are answered by patients on a five-point Likert scale ranging from "strongly agree" to "strongly disagree", each of which correspond to one to five points. Four scales can be determined: global QoL and the emotional, functioning, and physical scales by calculating the average of the statements in each scale and the multiplying the average by 20. Higher scores correspond to a better outcome (better functioning).

The European Organization for Research and Treatment of Cancer Core Questionnaire and Head and Neck Module

The Quality of Life Group (QLG) of the European Organization for Research and Treatment of Cancer (EORTC) is a key, international player in establishing HRQoL questionnaires. The EORTC QLQ-C30 is the QLG's core HRQoL questionnaire and assesses symptoms that are common across different cancer entities.[48] Twenty-eight of the 30 items are framed as questions that require a response on a Likert scale with four options: has the patient experienced the specific problem mentioned in the past week "not at all", "a little", "quite a bit", or "very much". Two more questions ask the patients to rate their overall health and their overall quality of life on a number line from one to seven, with seven being excellent. Most of the 30 questions concern the patient's experience with the specified problem over the previous week. The thirty questions can be converted into scores ranging from 0-100 for five functional scales (*physical, role, emotional, cognitive* and *social functioning*), and nine symptom scales (f*atigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea,* and *financial difficulties*) and one *global quality of life* scale.[48] High scores for the functional scales and global quality of life scale indicate good functioning while high scores in the symptom scales indicate a high symptom burden.

The EORTC QLQ-H&N35 is a HNC-specific module that covers symptoms specific to HNC. The 35 questions are answered on the same four-point Likert scale as in the QLQ-C30, and these questions can be converted into scores for 18 difference scales: *pain in the mouth, swallowing, senses problems, speech problems, trouble with social eating, trouble with social contact, sexuality, teeth, opening mouth, dry mouth, sticky saliva, coughing, feeling ill, use of pain killers, use of nutritional supplements, use of a feeding tube*, *weight gain* and *weight loss*.[49] The scores for scales again range from 0 to 100, with high scores indicating a high symptom burden.

The EORTC QLQ-HN43 is the relatively recently updated version of the EORTC QLQ-H&N35 and has completed final development steps in the form of a validation study published in 2019.[50] In addition to modifications to the questions comprising some of the scales, this updated version has new scales concerning *shoulder function, fear of progression (anxiety), swelling in the neck, problems with wound healing, skin problems,* and *neurological problems*.

In general, a difference of ten points for EORTC questionnaire scales is considered to be a clinically relevant difference.[51]

5. State of the research

Unless otherwise stated in the following section, the time point noted as "baseline" means after diagnosis but before beginning treatment. Where available in the literature, standard deviations (SDs) are reported to describe the distribution of the specified outcome. If SD was not available, 95% confidence intervals (CIs) are reported, and if no indication of the data's distribution is reported in this thesis, it means it was not available in the publication. While some results from other questionnaires are included in this research overview, the main focus concerns studies that have used the EORTC questionnaire for HRQoL assessment. This makes comparisons between studies more direct despite the considerable variation that can arise from different constellations of tumor sub-types, treatment groups, and assessment time points.

5.1. Health-related quality of life during the first five years after diagnosis

Examples from qualitative research give a specific glimpse into the struggles HNC patients may face during treatment and the immediate time afterwards. Patients may have a radically altered facial appearance and a combination of symptoms that make eating and speaking difficult.[1] One patient in the United States expressed one aspect of her experience as:

> *I just didn't feel like going out. I just felt like everybody would be looking at my face. I was also self-conscious about my speech. I can hide my back or my arm but you can't necessarily hide your mouth. If you talk, you feel like people notice your tongue or even my lip. So, I just wanted to avoid it all.*[52(page 6)]

Quantitative research has shown that some aspects of patients' HRQoL may return to levels present at diagnosis after about one year post treatment depending on the specific area of QoL considered. In particular, symptoms specific to HNC may persist in the long-term while more generic cancer symptoms and treatment side-effects are more likely to improve. A 2012 systematic review of HRQoL in HNC patients by So et al. identified 37 relevant articles that used a mix of validated questionnaires and concluded that global QoL had a pattern of worsening between diagnosis and approximately six months after treatment, followed by a gradual

improvement thereafter to 12 months.[53] However, problems with *dry mouth, sticky saliva*, and *fatigue* were significantly worse at 12 months post-treatment compared to baseline assessments. In So et al.'s review, *emotional functioning* was found to have the largest improvement at 12 months over baseline, and *social, role* and *cognitive functioning* were also largely fully recovered by 12 months. The authors found conflicting results for problems with *appearance*, *speech*, *sense of taste/smell*, and *swallowing*, with at least one study showing worse HRQoL at 12 months over baseline but also at least one study showing recovery to baseline levels.

Physical Functioning

Physical functioning as assessed by the EORTC QLQ-C30 addresses difficulties with strenuous activities, sustained walking, being sedentary, and whether assistance is required with eating and personal care. An example from a study on general (non-cancer) populations across 15 countries reported a mean score of 85 (SD:19), which provides some context for published data on HNC patients.[54] Prospective studies have shown an average decline in *physical functioning* between time of diagnosis and six to 12 weeks after diagnosis or treatment, but this was not always a clinically relevant decline (Figure 2A). For example, in a study including patients with a range of HNC diagnoses with a mix of treatments, Roick et al. found a difference in mean scores of only six points between baseline and three months post-diagnosis (from a mean score of 80 (standard deviation (SD): 22) to 74 (SD: 24), and Tribius et al. reported a difference of 5 points in the same time frame (from a mean score of 77 (SD: 23) to 72 (SD: 22)).[55,56] In Roick et al.'s study, the patients were largely unchanged in this regard at 6 months. Tribius et al. followed the patients until 12 months and reported that *physical functioning* had largely returned to baseline functioning. However, two studies that focus on one type of treatment showed clinically relevant declines between time of diagnosis and approximately six to 12 weeks post-diagnosis. Among patients with mixed HNC diagnoses who received chemo-radiation, Verdonck-de Leeuw et al. found significantly reduced *physical functioning* at six weeks post treatment compared to baseline (from a mean score of 87 (SD: 17) to 72 (SD: 22)). Patients in Singer et al.'s 2014 study, all of whom underwent total laryngectomy, had clinically meaningfully reduced *physical functioning* upon discharge from inpatient rehabilitation, approximately 6 weeks after treatment (from a mean functioning score of 83 at diagnosis to 70).[57] In both studies, on average patients had not quite fully recovered in this regard by 12 months but had nonetheless improved.

Studies show that *physical functioning* by 12 months has largely returned to baseline assessment levels, if not fully recovered. In Figure 2A, seven of the studies displayed did not have an assessment point between baseline and one year, so any change in the months and weeks immediately following diagnosis or treatment are of course not visible, and the trend line

between baseline and 12 months is more gradual. In general, *physical functioning* by 12 months is quite good, particularly in light of the mean general population score mentioned above.

Nordgren et al.'s examination of 122 patients with oral cavity cancer reported good *physical functioning* on average at 12 months (a mean score of 90 by 12 months)[58], as did the patients in their study with mixed HNC cancer published in 2006 (mean score of 83 at 12 months),[59] and their study on larynx cancer patients (mean score of 91 at 12 months).[60] For the larynx cancer patients, there was a notable increase in *physical functioning* over baseline that was not seen in Singer et al.'s 2014 study; this could be due to the fact that only 13% of the patients in Nordgren at al.'s study had a laryngectomy in contrast to 100% of the patients in Singer et al.'s study.[57] Patients who had lower grade stage tumors may have particularly high *physical functioning* at 12 months, as reported by Scott et al. with a mean score of 91 among patients who received RT (95% had T1 and T2 tumors).[4] This is in contrast to the much lower functioning at 12 months among the patients who received RT in Tribius et al.'s study (mean score of 78 (SD:23)), 46% of whom had T3 and T4 tumors.[55]

One study that used the University of Washington QoL questionnaire in a HNC population with mixed treatments showed considerably reduced *physical functioning* between baseline and six months.[61] However, this questionnaire groups symptom-specific aspects in the *physical functioning* domain (such as chewing, swallowing, and saliva problems) which is the likely reason for the notable different to the studies using the EORTC questionnaires. A second study by Pateman et al. did not combine the questions into a broad *physical functioning* score but instead reported the reported individual scores for each question.[62] If we look at only the "activity" score and the "recreation" score in this study (which removes the influence of symptom-specific responses), we see that functioning in these areas is still seen to decline between baseline and six months. These differences demonstrate the difficulties when comparing HRQoL results that have been assessed with different tools. The Pateman study comprised 63% patients with stage III and IV tumors, and it is not clear what percentage had monotherapy versus multiple treatments, which also could affect a patients' *physical functioning*. Or it could be that each questionnaires' mechanism to capture *physical functioning* is simply too different from each other to assess this in a similar way.

Overall, the literature shows that *physical functioning* tends to decline in the short term during treatment and then, mostly, gradually recovers in the first year. Longer-term, there is evidence that *physical functioning* remains quite good at two and three years post treatment, with respective reported mean functioning of 85 (SD:63)[5] and 85 (SD:20).[63] Six studies that reported physical function at around 60 months show that the results are all quite similar, ranging from a mean score of 80 to 85, indicating good *physical functioning* on average at this late time point (Figure 2A).

Figure 2 – Average functioning in four domains over time

Functioning assessed with the EORTC QLQ-C30 in eleven studies; B: baseline; M: months; x-axes show the approximate number of months after baseline; y-axes show mean scores; Study characteristics are reported in Table 2

Emotional Functioning

The trend for *emotional functioning* shows an overall gradual increase in functioning up to 12 months over baseline functioning (Figure 2B). *Emotional functioning* assessed by the EORTC QLQ-C30 is covered by four questions asking about feeling tense, irritable, worried and depressed. In a large general population, *emotional functioning* was estimated at 74 (SD: 25),[54] and most of the published data discussed here is similar to this at baseline. While analyses by Roick et al.[56] and Loorents et al.[3] showed no important change on average in *emotional functioning* between baseline and six months post-diagnosis, the patient collectives in Tribius et al.[55] and Oskam et al.[64] both showed clinically relevant improvements. This difference may be related to the differing distributions of tumor stage. Oskam's study population had 86% stage III and IV tumors and Tribuis' study population had 46% T3 and T4, while Loorents' study population was 21% T3 and T4 tumors. Perhaps patients with larger tumors had lower *emotional functioning* at baseline and so had more space to improve. However, Roick et al.'s patient collective also had a high percentage of large tumors (83% stage III and stage IV). The n values are small in these four studies (ranging from 26 to 111), which also make general extrapolation to large HNC populations unwise.

This trend of increasing functionality did not continue past six months, and by 12 months it was not notably changed on average. Studies that assessed patients beyond 12 months show that that it remained largely stable at a level indicating good functioning on average (Figure 2B).[58–60,63,65,66] One interesting difference found by Aghajanzadeh et al. found that HNC survivors at 60 months post-treatment differed on average in *emotional functioning* when grouped according to whether the survivor had clinically diagnosed trismus (average score with trismus at 60 months: 76 (95%CI: 67-85); without trismus: 87 (95%CI: 83-91)).[65] Although this is not a clinically meaningful different on average, it is in an indication that there are subgroups in the survivor studies who may by doing better or worse in light of specific symptoms. Treatment may also play a role here, as shown by Infante-Cossio et al. in 68 survivors of oral cavity or oropharynx cancer.[67] They found that the *emotional functioning* at three years of survivors who had had only surgery was better than survivors who had had CRT. This is likely related to the heavier symptom burden that can accompany more intensive treatment.

Table 2 – Studies reporting health-related quality of life up to five years post-diagnosis

First author, (year)	Study design	HRQoL assessment instrument	HNC subsites	Treatment groups	Assessment time point: n
Aghajanza-deh, (2023)[65]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	at baseline oral cavity: 16% oropharynx: 62% salivary gland: 4% nasopharynx/sinus: 8% unknown: 10%	at baseline RT: 21% surgery + [C]RT: 17% CRT: 62%	baseline: 211 12 months◊: 180 60 months◊: 129
Nallani, (2022)[61]	Ret.	UW-QoL	at baseline oral cavity: 54% oropharynx: 29% larynx: 12% hypopharynx: 2% other HNC: 5%	at baseline surgery= 36% surgery + adj. treatment: 46% CT, RT or CRT: 17%	baseline: 137 3 months◊: 139 6 months◊: 84
Roick, (2020)[56]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	at baseline larynx: 19% pharynx: 22% oral cavity: 16% tonsil: 16% tongue: 19% other: 8%	a mix of surgical, RT, and CT, either alone or in combination	baseline: 81 3 months*: 51 6 months*: 46
Scott, (2020)[4]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35 MDADI	at baseline tonsil: 68% base of tongue: 25% soft palate: 7%	a mix of trans oral surgery and RT with or without CT	baseline: 44 3 months◊: ns 12 months◊: ns
Singer, (2019)[50]	Pr.	EORTC QLQ-C30 EORTC QLQ-HN43	at baseline larynx: 16% hypoharynx: 9% oropharynx: 33% salivary glands: 4% nasal cavities/sinuses: 3% unknown: 3%	at baseline surgery: 20% RT: 16% CT: 2% CRT: 26% surgery + CRT: 16% surgery + CT: 1% surgery + RT: 15% Other/unknown: 5%	change between baseline and 3 months* 3 months*: 499 change between: 3 months* and 6 months*
Pateman. (2018)[62]	Pr.	UW-QoL	at baseline oral cavity: 34% oropharynx: 30% salivary gland: 13% other: 12% larynx: 8% nasopharynx, nasal cavity/sinuses: 4%	at baseline surgery: 21% surgery + [C]RT= 34% [C]RT: 40% CT: 1% Other: 4%	baseline: 95 1 month◊: 49 6 months◊: 41
Iryia,(2017)[68]	Cr.	EORTC QLQ-C30 EORTC QLQ-H&N35 UW-QoL	oral cavity: 56% pharynx: 26% larynx: 19%	a mix of surgical, RT, and CT, either alone or in combination	patients under treatment: 27
Loorents, (2016)[3]	RCT¤	EORTC QLQ-C30 EORTC QLQ-H&N35	No specific sub-sites stated ("head and neck cancer")	RT: 43% CRT: 57%	baseline: 47 3 months◊: 47 6 months◊: 47 12 months◊: 47
Tribius, (2015)[55]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	oral cavity: 32% oropharynx: 37% hypopharynx: 5% nasopharynx: 5% nasal: 4% unknown: 4%	RT: 5% CRT: 25% adj. RT: 42% adj. CRT: 28%	baseline: 111 6-8 weeks◊: 111 6 months◊: 111 12 months◊: 111
Verdonck-de Leeuw, (2014)[5]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	at baseline oropharynx: 46% larynx: 23% hypopharnyx: 19% oral cavity: 12%	CRT: 100%	baseline: 131 6 weeks◊: 122 6 months◊: 94 12 months◊: 92 24 months ◊: 62
Oskam, (2013)[64]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	oral cavity: 38% oropharynx: 62%	surgery only or surgery with adjuvant RT	baseline: 26 6 months*: 26 12 months*: 26

* post diagnosis; ◊ post treatment; ● post treatment start; ¤ secondary analysis
HRQoL: health-related quality of life; HNC: head and neck cancer; MDASI-HN: MD Anderson Symptom Inventory - Head and Neck Module; UW-QoL: University of Washington Quality of Life Questionnaire;
Pr.: prospective; Ret.: retrospective; Cr: cross-sectional; RCT: randomized control trial;
RT: radiotherapy; CT: chemotherapy; CRT: chemoradiotherapy

Table 2 Continued – Study characteristics

First author, (year)	Study design	HRQoL assessment instrument	HNC subsites	Treatment groups	Assessment time point: n
Singer, (2014)[57]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	at baseline larynx: 79% pharynx: 43% (some had 2 diagnoses)	laryngectomy: 100% 13% had adj. RT	baseline: 174 day before discharge:133 after inpatient rehab: 110 12 months: 86
Rathod, (2013)[69]	RCT	EORTC QLQ-C30 EORTC QLQ-H&N35	at baseline oropharynx: 53% hypopharynx: 29% larynx: 18%	RT: 100% (IMRT and 3D-conformal)	baseline: 50 3 months◊: 49 6 months◊: 48 12 months◊: 41 24 months◊: 36
Al-Mamgani, (2012)[70]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	parotid gland: 100%	a mix of surgery and RT and surgery and CRT	Multiple time points from baseline to 2 years for 39 patients.
Al-Mamgani, (2012)[71]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	hypopharynx: 100%	A mix of RT and CRT	Multiple time points from baseline to 2 years for 59 patients.
Infante-Cossio, (2009)[67]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	oral cavity or oropharynx: 100%	surgery: 60% surgery + RT: 40%	baseline: 68 12 months*: 68 36 months*: 68 Only 9 domains from EORTC QLQ-C30 reported.
Nordgren, (2008)[58]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	oral cavity: 100%	at baseline surgery only: 20% RT only: 25% Surgery + RT +/-CT: 55%	baseline: 122 12 months●: 47 60 months●: 59
Nordgren, (2006)[59]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	at baseline base of tongue: 15% oropharynx: 42% epipharynx: 12% hypopharynx: 31%	at baseline RT: 39% CRT: 38% surgery + RT: 23%	baseline: 89 12 months●: 31 60 months●: 36
Abendstein, (2005)[66]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	alive with HRQoL data at 5 years (n=167) oral cavity: 35% pharynx: 22% larynx: 28% other: 16%	alive with HRQoL data at 5 years (n=167) surgery: 11% RT: 44% CRT: 15% surgery + RT: 27% surgery + CRT: 3%	baseline: 167 12 months: 141 60 months: 167
Nordgren, (2003)[60]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	larynx: 100%	at baseline RT only: 75% RT +/-CT and ND: 9% laryngectomy +/- RT/CT: 13%	baseline: 86 12 months●: 40 60 months●: 46
Bjordal, (2000)[63]	Cr.	EORTC QLQ-C30 EORTC QLQ-H&N35	larynx: 47% oral cavity: 31% oropharynx: 13% hypopharynx: 5% nasopharynx: 3%	a mix of before treatment (n=204), surgery, RT and CT, alone and in combination.	newly diagnosed: 204 recurrent: 58 disease-free (1-3 years): 360

* post diagnosis; ◊ post treatment; ● post treatment start; ¤ secondary analysis
HRQoL: health-related quality of life; HNC: head and neck cancer; MDASI-HN: MD Anderson Symptom Inventory - Head and Neck Module; UW-QoL: University of Washington Quality of Life Questionnaire;
Pr.: prospective; Ret.: retrospective; Cr: cross-sectional; RCT: randomized control trial;
RT: radiotherapy; CT: chemotherapy; CRT: chemoradiotherapy

Social Functioning and Role Functioning

Social functioning assessed by the EORTC QLQ-C30 is covered by two questions asking about the extent to which a person's physical condition or medical treatment has impacted their family life or social activities. *Role functioning* is covered by two questions concerning limitations in work or daily activities and taking part in hobbies and leisure time activities. For context, the population mean norm results for these scales in a large international study were 86 (SD: 24) and 84 (SD: 25), respectively, which can be regarded as an example of typical functioning in a non-cancer population.[54]

Studies assessing these aspects prospectively show a similar pattern for both *social* and *role functioning* (Figures 2C and 2D), with functioning generally returning to baseline levels or better by 12 months post-treatment. While functioning for both scales can range notably at baseline, there is some evidence that this range narrows at longer term assessment points, although of course the number of studies assessing longer term points are fewer than at baseline. Low average baseline social and role function were reported by Tribius et al., with mean functioning of 60 (SD: 34) and 58 (SD: 37) respectively. After a small decrease in functioning noted at the end of treatment, these patients had on average improved notably in both areas by 12 months (mean functioning of 72 (SD: 27) and 68 (SD: 24)), but were still on average less functional in these areas compared to the general population. Five studies that had an assessment at approximately 1.5 to 3 months post diagnosis all noted a decrease in average functioning compared to baseline.[3,5,55–57] Roick et al. did not assess patients beyond six months post-diagnosis, but at six months there was evidence of improved functioning for both areas (mean six-month *social functioning* of 78 (SD:25) and *role functioning* of 66 (SD: 33)).

By twelve months, there is evidence that *social functioning* has returned to or exceeded functioning at baseline, with average 12-month functional scores ranging from a mean of 83 (SD: 21) in a Dutch population of HNC patients who received CRT to two studies that found particularly good functioning with means of 90 (SD: 3)[64] and 94 (Figure 2C).[60] Two examples where patients did not recover *social functioning* by 12 months are Singer et al.'s study on patients undergoing laryngectomy (mean *social functioning* at 12 months of 73 over 81 at baseline) and Aghajanzadeh et al.'s analysis of patients with trismus (mean *social functioning* at 12 months of 73 (SD: 63-83) over 83 (SD: 80-86) at baseline). This could be an indication that specific problems related to speech may impede the return to pre-treatment social activities. There is also evidence that *role functioning* largely maintains baseline levels or recovers to baseline levels by 12 months.[5,55,58,60,64] However, *role functioning* still may not be similar to the example of typical *role functioning* in a general population. For example, Aghajanzadeh et al.'s analysis of patients with trismus showed persistently low r*ole functioning* on average (mean functional score of 66 (95%CI: 56-75) compared to 74 (SD: 70-79) at baseline),[65] as did Singer

et al.'s analysis of patients with laryngectomy (mean functional score of 63 compared to 79 at baseline)[57], and Nordgren et al.' s analysis of pharyngeal cancer patients (mean functional score of 71 compared to 79 at baseline)[59]. This discrepancy is an indication of the difficulties in teasing out the mechanisms behind differences, as the variations between studies have multiple levels: they comprise different tumor sub-types in varying proportions and to varying degrees of severity and the treatments are not the same.

Fatigue

Fatigue is a problem for all types of cancer, and has a known connection to treatment, including either directly related to the treatment itself or due to the logistics associated with managing on-going systemic treatment.[72,73] The EORTC QLQ-C30 assesses *fatigue* in three questions asking about the need to rest and feeling weak and tired. An example of average *fatigue* burden in a large general population in the literature is 30 (SD: 25).

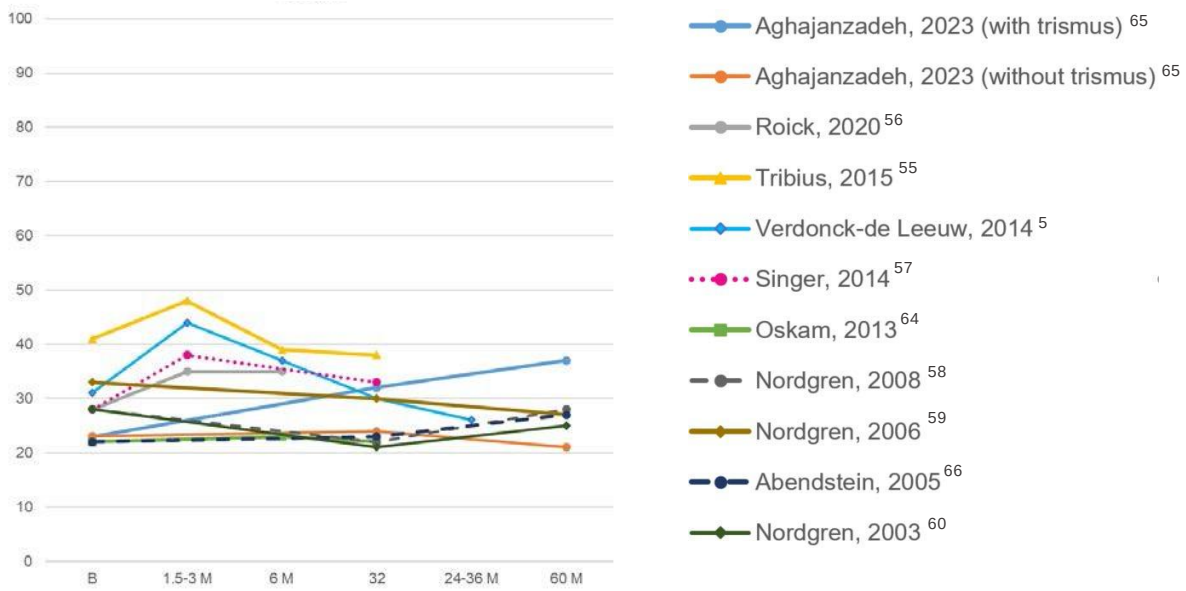

Figure 3 – Average fatigue burden over time

Fatigue assessed with the EORTC QLQ-C30 in eleven studies; B: baseline; M: months; x-axis shows the approximate number of months after baseline; y-axis shows mean scores; Study characteristics are reported in Table 2

The literature shows that on average patients experience an increase in *fatigue* after treatment begins compared to pre-treatment (baseline) *fatigue* levels (Figure 3). Verdonck-de Leeuw et al. reported a notable increase in *fatigue* at 6 weeks post treatment over baseline in a population of patients who had had CRT (Figure 3: baseline: 31 SD: 26; 6 weeks: 44 SD: 25).[5] Similar increases were also reported by Tribius et al., Loorents et al., Singer et al., and Roick et al.[3,55–57] By six months post-treatment, *fatigue* appears to have decreased over six month levels, and by 12 months there is evidence that *fatigue* returns to baseline (Figure 3). A notable exception to this again are the patients with trismus in the study by Aghajanzadeh et al., who had increased

fatigue at 12 months over baseline (baseline mean: 23 (95%CI:20-26); 12-month mean: 32 (95%CI:25-40). Scott et al.'s study on patients undergoing transoral surgery versus RT also found that patients' *fatigue* improved by 12 months but that there was a notable difference at 12 months between the treatment groups, with patients treated with RT having worse *fatigue* than the patient who had transoral surgery (mean score of 14 (SD:17)) versus 33 (SD: 23)).[4] A possible explanation for this could be the repetitive nature of RT treatment, requiring a multiple clinical visits in contract to a surgical intervention which is not intended to be repeated.

Symptoms Specific for Head and Neck Cancer

Oral Pain

The EORTC QLQ-H&N35 assesses oral pain through four questions asking about pain or soreness experienced in the mouth, jaw and throat. Using this questionnaire, a survey of a general Swedish population reported very low problems with oral pain (average oral pain score of 3 (SD: 9).[74] Not surprisingly in a population with a HNC diagnosis, pain is increased at baseline compared what is typically experience by the general population. Examples of notably higher baseline pain among patients with a mix of HNC diagnosis include a Dutch study (mean: 34 (SD: 27))[5], two German studies (mean: 38 (SD: 34)[55]; mean: 23 (SD: 28)[56]), and two Swedish studies (mean: 18[66];mean: 22 (95%CI: 19-25)[65]). It is possible that patients with specific cancer subtypes experience more pain at diagnosis, such as reported by Nordgren et al.'s collective of 89 pharynx cancer patients (mean: 32)[59] and 122 oral cavity cancer patients (mean: 29)[58] as well as Oskam et al.'s study including 26 oral cavity and oropharynx cancer patients (mean: 26 (SD: 4))[64]. Scott et al. found notable difference in baseline oral pain between patients who were planning on undergoing RT versus trans-oral surgery, with pre-treatment RT patients reporting higher pain (mean: 30 (SD: 20) versus mean: 9 (SD: 12))[4], but this is likely related to the higher proportion of advanced tumors in the RT group.

Following baseline assessments, oral pain decreased on average in most studies with some identified exceptions (Figure 4A). Singer et al.'s study on patients undergoing laryngectomy reported a notable increase in pain upon discharge from inpatient rehabilitation, but this then declined to below baseline by 12 months post-diagnosis.[57] The patients studied by Roick et al. also reported increased oral pain on average over baseline, and this remained increased by six months post-diagnosis.[56] Although this increase was not clinically relevant on average, the direction of the trend was in contrast to a number of other studies, as can be seen in Figure 4A. This could be due to a difference in treatment group distribution or perhaps it is related to the patients being questioned about their QoL while still in hospital for inpatient rehabilitation treatment.

Figure 4 – Average oral pain, sensory problems and speech burden over time
Burden assessed with the EORTC QLQ-C30 in eleven studies; B: baseline; M: months; x-axes show the approximate number of months after baseline; y-axes show mean scores; Study characteristics are reported in Table 2

Studies reporting on pain in the mouth at 12 months show declining problems over baseline (Figure 4A). Loorents et al.'s study on HNC patients who had received RT or CRT also reported an increase in oral pain from baseline to the completion of RT followed by a decline to near baseline levels at 12 months.[3] As well, the patients scheduled for RT treatment in Scott et al.'s study who had notably increased pain at base line also had decreasing pain to levels comparable to the other patients in that study who received transoral surgery.[4] An exception to

this trend of decreasing pain is a group of Swedish patients who were known to have trismus at 12 months; they reported notably higher oral pain compared to the patients without trismus (mean with trismus: 28 (95%CI: 19-38); mean without trismus: 13 (95%CI: 9-17)).[65] After 12 months, overall pain remains reduced over baseline assessments, for example as reported by 360 HNC survivors who had been disease-free for one to three years (mean: 13; SD: 18)[63], by 62 survivors at 24 months post treatment (mean: 15; SD: 19)[5], and by 167 survivors at the 60th month mark (mean 13).[66]

Senses

The EORTC QLQ-H&N35 assess QoL related to the *senses* by asking two questions about problems with the sense of smell and taste. The general public has few problems with *senses*, as indicated by the low burden reported by a general population study (mean: 5; SD: 14).[74] Similar to the problems with *swallowing*, *problems with senses* tend to increase after treatment begins, possibly improve somewhat between the end of treatment and 12 months post-treatment, and then largely maintain the functioning achieved at that point into the long-term (Figure 4B). Examples of four studies that report large increases in *problems with senses* are Singer et al.'s study on patients who had laryngectomies (baseline mean: 16; mean at discharge from inpatient rehabilitation: 76),[57] Tribius et al. (baseline mean: 21 (SD: 28); mean at 6-8 weeks post-treatment 45 (SD: 30)),[55] Roick et al. (baseline mean: 19 (SD: 39); mean at three months: 38 (SD: 34)),[56] Verdonck-de Leeuw et al. (baseline mean: 11 (SD. 20); mean at six weeks post-treatment: 37 (SD: 28)),[5] and a study by Al-Mamgani et al. including 186 parotid gland cancer patients.[70] The other studies in Figure 4B may also have had a spike immediately following treatment had they assessed that time point; for example, Loorent et al. also noted a sharp increase in *problems with senses* immediately following treatment in the 47 HNC patients investigated.[3] However, overall there is evidence that the level of sensory functioning as perceived by the patient at 12 months is the level that is maintained in the years following.

Speech

Difficulties with *speech* are covered by three items in the EORTC QLQ-H&N35 asking about being hoarse and whether talking has been difficult in general and on the telephone. Patients who require a total laryngectomy struggle with this aspect in particular, as they learn to communicate without a larynx or vocal cords.[75] For example, a considerable spike in *speech* burden can be seen in Singer et al.'s examination of patients who received a total laryngectomy (Figure 4C), going from a mean baseline assessment of 30 to 65 upon discharge from inpatient rehabilitation.[57] Nordgren et al.'s 2003 study also included laryngeal cancer patients, but these patients noted a higher burden of *speech* difficulties at baseline than the patients in Singer et al.'s study, and then the burden appears to reduce drastically over the following year.[60]

However, but it should be noted that the averages reported by Nordgren et al. at one year include only the patients who also completed the five year assessment; this brings a considerable bias, as the survivors at five years may be healthier at one year than the patients who do not survivor to five years and so the burden at five years may be underestimated. As well, the lack of an assessment point for Nordgren's patients in the 2003 study immediately following treatment may have omitted an increase before a decline. The baseline *speech* impairment of the laryngeal patients in both studies is markedly different compared to an example of a mean general population estimate of 4 (SD: 12), indicating very little difficulty with *speech*.[74] However, difficultly speaking is not only limited to patients with a laryngeal diagnosis. Even before any treatment is initiated, there is evidence that newly diagnosed HNC patients already perceive difficulties communicating orally, with examples of moderate symptom burdens on average in HNC patients with varying diagnoses at baseline of 22,[69] 29 (SD: 27),[5] 30 (SD: 32),[56] and 33 (SD: 30).[55]

Over the first 12 months, studies show that patients who already have considerable problems with *speech* at baseline and/or experience a notable increase in problems after treatment begins do improve on average by 12 months;[5,55,57,60] however, the improved level by 12 months may still indicate a substantial burden for speaking (Figure 4C). Patients who have relatively good speaking ability (in particular relative to the average baseline speaking ability reported by the laryngeal cancer patients above) tend to report a similar level at 12 months and beyond up to 60 months. An exception to this includes the group of patients examined by Aghajanzadeh et al. who were known to have trismus; these patients' problems with *speech* did not improve on average over the 60 months following diagnosis.[65] Differences according to the type of treatment received have also been reported, with patients receiving multi-modal treatment having worse outcomes than patients with monotherapy.[50]

Social Eating and Social Contact

Social eating is a specific type of *social contact* that may be particularly difficult for HNC patients and survivors because of the central role food plays at social gatherings and the impairments with trismus, chewing, teeth and swallowing that patients may experience. Examples of patient statements from qualitative research indicate how debilitating this can be:

> *"I am not attending the [family] functions, there were a few functions and I was invited, but I did not go. I can't eat anything. Then why to go? I am not comfortable to go there and return without eating anything. I can't sit there for a long time, if I don't eat I feel dizzy and tired."* [76] (page 183)

When discussing avoiding social functions, another HNC patient noted:

> *"I can't eat anything. I eat only porridge. They feel sad if I come without eating anything. They feel that they are eating and I am not eating. So, I feel bad."* [76] (page 183)

The *social eating* scale in the EORTC QLQ-H&N35 questionnaire comprises four questions asking about trouble eating and enjoying meals in general and trouble eating in the company of family and other people. An example from the general population shows very few problems with this (mean: 3 (SD: 9).[74] There is evidence that the baseline *social eating* ability on average of cancer patients is already considerably worse than the general public, with examples ranging from a mean of 10 in larynx cancer patients[60] to 33 (SD: 31) in a group of patients with mixed cancer diagnoses (Figure 5A).[55] On average, patients report that their *social eating* improves by 12 months post-treatment, but the level at 12 months may still be considerably impaired.

For example, in two studies with mixed diagnoses, average *social eating* was 23 (SD: 30)[5] and 33 (SD: 30),[55] both of which were similar to baseline assessments although improved compared to assessments soon after treatment. A notably good score for *social eating* was reported for laryngeal patients at 12 months after the start of treatment, with a mean of 2, mirroring the low burden present in a general population[60]. This, is again likely due to the mean value only including patients who went on to complete the five-year assessment. Therefore, it is possible that these patients were doing particularly well, although by 60 months these patient again had increased symptom burden.

In general, the burden in *social eating* at 12 months is not substantially different to that at baseline with some exceptions. The collection of HNC patients with diagnosed trismus had a notable increase in problems (baseline mean: 13 (95%CI: 10-16); 12-month mean: 34 (95%CI: 27-42).[65] This suggests that it is important to identify subgroups of patients who may need specialized support. The evidence in the long term up to 60 months shows a general increasing trend in burden, with an exception seen for the patients without trismus in the study by Aghajanzadeh et al., who tended to have decreasing burden for *social eating* on average (Figure 5A). When comparing the *social eating* outcomes with social contact outcomes, there is evidence that patients with considerable *social eating* problems may have few problems with *social contact* (Figure 5B). For example, the patients in Tribius et al.,[55] Roick et la.,[56] Verdonck-de Leeuw et al.,[5] Singer et al.,[57] Oskam et al.,[64] Nordgren et al. (2008)[58] and Loorents et al.[3] all reported lower average problems with *social contact* than *social eating*. In general *social contact* problems are low, with a spike at around the end of treatment, for example up to a mean of 18 (SD: 25)[5] or 20 (SD: 21).[55] Between 12 and 60 months post-treatment, not much change is reported.[58–60,65,66]

Figure 5 – Average social eating, social contact, opening mouth, and sexuality burden over time
Burden assessed with the EORTC QLQ-C30 in eleven studies; B: baseline; M: months; x-axes show the approximate number of months after baseline; y-axes show mean scores; Study characteristics are reported in Table 2

Opening Mouth

The extent of problems *opening one's mouth wide* is assessed in the EORTC QLQ-H&N35 in a single question. In average, the general population is not likely to be significantly burdened by this (mean burden of 2 (SD: 11).[74] The literature shows a wide range of problems with this before treatment start (Figure 5C). Some of the variability may be explainable by the size of the tumor. For example, lower average problems with *opening mouth* were reported among a larynx cancer population with 36% stage III/IV tumors (mean: 2)[60] and a population of mixed HNC tumors with 40% stage III/IV tumors (mean 8).[66] This is in contrast to the average symptom burden of 33 (SD: 38) reported in a mixed HNC population with 46% T3/T4 tumors with only 22% N0 and the mean of 20 (SD: 31) among HNC patients with 83% stage III/IV tumors. However, this reasoning does not cleanly explain the range entirely. For example, among 186 parotid gland cancer patients, 24% had stage III/IV tumors, and the average baseline burden for *opening mouth* was about 35.[70]

Studies where an assessment was made around the end of treatment consistently show an increase in problems with *opening mouth* over baseline ability followed by a slight improvement by 12 months. But even at 12 months, the range of abilities is considerable. If the studies are considered in terms of the treatment received, some differences may be explained. Tribius et al.'s study with mixed HNC diagnoses and mixed treatments had 25% of patients treated with CRT and 5% RT only and had a high symptom burden at 12 months (mean: 35, SD: 36).[55] Oskam et al. had a similarly high burden (mean: 33), and 92% of those patients had received surgery and RT. This is in contrast to the 22% of patients who received surgery and RT among 89 pharyngeal patients who had a lower symptoms burden (mean: 17). Again, however, this theory does not always hold, as for example shown by a collective of mixed HNC patients, 46% of whom were treated with multi-modal therapy, who reported similar difficulties *opening mouth* as the 89 pharyngeal patients mentioned previously (mean: 15).[66] Again this demonstrates the difficulty in combining results from studies that contain a different combinations of tumor sub-types and different treatment distributions.

In the years past 12 months up to 60 months, some studies show a trend for increasing problems with *opening the mouth*, but the range is smaller than what can be seen at baseline. The line showing the trismus patients in the study by Aghajanzadeh et al. in Figure 5C is not an example of a typical HNC population, because these patients were of course known to have trismus and therefore it is not surprising the patients report a high perceived symptom burden.

Sexuality

A 2016 literature review specifically looking at head and neck cancer and sexual function identified nine relevant articles.[77] Across these studies, the authors concluded that between

24% and 100% of the patients reported a negative impact on sexuality stemming from their disease and treatment. A prospective Dutch study using detailed patient questionnaires specifically for sexual function in both men and women also included that patients' sexuality and sexual functioning deteriorated between baseline and three months post-treatment, in particular for patients treated with CRT.[78] A 2023 Australian study also identified a decline in sexual satisfaction among HPV positive oropharynx cancer patients treated with CRT but found that this decline had improved to baseline levels by 12 months.[79] The authors also noted that approximately 25% of patients indicated that maintaining their sexual functioning was a top priority. In contract to the associations with treatment found by the Dutch and Australian colleagues cited above, Singer et al. found no association between treatment and *sexual* difficulties in patients treated with partial or total laryngectomy, but instead reported that these difficulties were associated with higher distress levels and advanced tumor size.[80]

In the EORTC QLQ-H&N25, QoL related to *sexuality* is assessed using two questions asking about reduced interest and enjoyment in sex. Other studies with an assessment time point at around the end of treatment also show that sex can be negatively affected (Figure 5D). Similar to the findings of the Australian study mentioned above, Figure 5D also indicates that *sexuality problems* can improve to approximately baseline assessment levels by about 12 months post-treatment. As well, by 12 months, variation in the extent of *sexuality problems* between the studies examined here has narrowed. However, there are indications that *sexuality problems* may increase in the years following the one-year assessment time point. Compared to a general population assessment of *sexuality problems* that found a mean burden of 19 (SD: 30), four studies reported greater *sexuality problems* at 60 months post-diagnosis on average. This suggests that HNC patients continue to deal with *sexuality problems* in the long term on average at a greater level than that experienced by a population that has not had cancer.

Dry Mouth, Sticky Saliva and Swallowing

The *swallowing* scale in the EORTC QLQHH&N35 is covered by four questions asking about difficulties swallowing liquids, pureed and solid food and problems with choking, while *dry mouth* and *sticky saliva* are single item scales. In the updated version of the EORTC HNC module (the EORTC QLQ-HN43), the *dry mouth* and *sticky saliva* items were merged into a single scale.[50]

Difficulties with these issues are not pronounced in the general population as reported by a Swedish general population (*dry mouth* mean: 12, SD: 23; *sticky saliva* mean: 6, SD: 17; *swallowing* mean: 2, SD: 7). Problems with *dry mouth* and *sticky saliva* can increase dramatically between baseline and the end of treatment and does not tend to improve much from there (Figure 6), and in fact *sticky saliva* appears to generally increase after 12 months.

Differences can be seen in this pattern when looking at *dry mouth* outcomes according to treatment. For example, Al-Mamgani et al. reported stark differences between hypopharynx

patients treated with RT versus CRT at 12 months (mean *dry mouth* for RT= 44 versus CRT=83; mean *sticky saliva* for RT=40 versus CRT=83).[71] Singer et al. also reported better outcomes at three months after treatment start for monotherapy patients versus CRT patients for combined *dry mouth/sticky saliva* as assessed by the updated EORTC HNC module (mean of 42 versus 64 respectively).[50] Similarly, surgery only patients were found to fare better than multi-modal patients among 122 oral cancer patients for *dry mouth* burden;[58] at both three months and one year after diagnosis, the surgery only patients had fewer problems with *dry mouth* than the RT only and multi-modal treatment groups. As well, the authors note that "patients treated with surgery as the only mode of treatment had a stable and high [HRQoL] at all assessment points…". [58 (page 464)] Of interest here is that the oral cancer patients treated only with RT questioned by Nordgren et al. had a notably higher symptom burden for *dry mouth* at three months post-baseline compared to the monotherapy treatment group reported by Singer et al. at three months (mean values of 65 versus 42).[50,58] This discrepancy is likely due at least in part to the inclusion of surgery only patients in Singer's monotherapy group. In a study comparing patients who underwent transoral surgery versus RT for oropharynx cancer, a dramatic difference in increasing symptom burden for *dry mouth* was reported.[4] The surgery patients reported a mean score of 9.7 at baseline and then 18.3 at one year, whereas the RT patients went from 11.1 to 58.3.

Of particular note is the evidence that the patients' perception of *sticky saliva* burden largely continues to worsen in the long term, with average burdens at 60 months reflected by high symptom scores ranging from 33 [58] to 63.[65] Improved or at least not worsened *dry mouth* burden at 60 months over assessments at 12 months were reported for four studies,[58,59,65,66] but one study on laryngeal cancer patients showed a steady increase in burden over three assessments from baseline to 12 months and then at 60 months.[60] Regardless of any improvement in the first year after treatment for *dry mouth* and *sticky saliva*, these symptoms continue to cause problems for survivors of HNC in the long term.

Problems with *swallowing* can be relatively minor at baseline, such as described by 167 mixed HNC patients in Abendstein et al.'s study (mean: 9)[66], 26 oral cancer cavity and oropharynx cancer patients in Oskam et al.'s study (mean: 9),[64] and Nordgren et al.'s study on oral cavity patients (mean:11) (Figure 6C).[58] However, some patients are already experiencing drastic *swallowing* problems at diagnosis, such as for example reported by Verdonck-de Leeuw et al. (mean. 35 ; SD: 30),[5] Tribius et al. (mean: 33; SD: 32),[55] Singer et al. (mean: 26),[57] Nordgren et al.'s study on pharyngeal cancer patients (mean: 25),[59] 59 hypopharyngeal cancer patients investigated by Al-Mamgani et al. (mean: 24),[71] and 50 oropharynx, hypopharynx and larynx cancer patients (mean: 27).[69] One could suspect that the patients with a high *swallowing* burden at diagnosis have a higher tumor stage, but this is not always the case. While the patient

collectives in Tribius et al.[55], Singer et al.[57], and Roick et al.[56] do report large proportions of higher stage tumors, this is also true for Oskam et al.[64] and Abendstein et al., who had much lower symptom burden.[66]

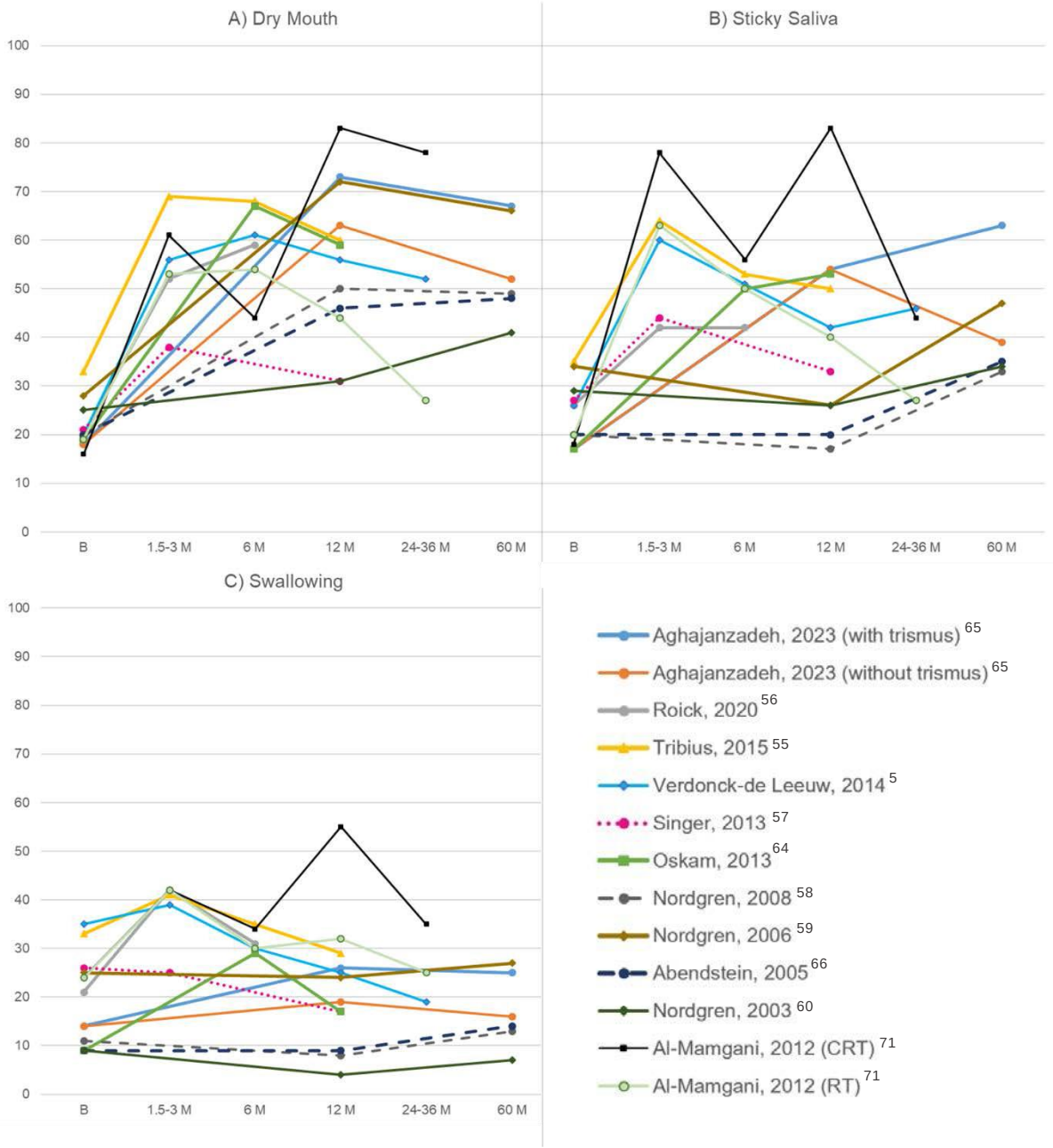

Figure 6 – Average dry mouth, sticky saliva and swallowing burden over time
Burden assessed with the EORTC QLQ-C30 in eleven studies; B: baseline; M: months; x-axes show the approximate number of months after baseline; y-axes show mean scores; Study characteristics are reported in Table 2

The proportion of tumor stages in the study by Verdonck-de Leeuw et al.[5] is not reported, but is presumably mostly higher tumors stages because of the need for CRT treatment. Treatment has also been shown to be associated with *swallowing* outcomes, for example by Singer et al. who showed that *swallowing* was better among monotherapy patients than patients who received multi-modal treatment at 3 months post-treatment.[50] Al-Mamgani et al. also reported

notable difference in *swallowing* between patients treated with RT or CRT at 1 year, with RT patients having fewer problems than the CRT (CRT: 55, RT: 32). Of course there is also a connection between tumor size and treatment, with advanced tumors being more likely to need aggressive treatment than smaller tumors.

Overtime, the literature shows that difficulties with *swallowing* are likely to worsen after treatment, improve somewhat to by 12 months post-treatment, but then stabilize at that level for the time following 12 months (Figure 4C). Examples of the extent of *swallowing* problems at 12 months included a remarkably high burden among a small group of CRT patients (mean: 55)[71] as well as lesser but still notable burdens reported by Tribius et al. (mean: 29; SD: 29),[55] Verdonck-de Leeuw et al. (mean: 25; SD: 29),[5] and the Swedish study on patients with and without trismus (mean with trismus: 26 (95%CI: 19-32); mean without trismus: 19 (95%CI: 15-23)).[65] As seen in Figure 4C, there is evidence that swallowing function achieved by 12 months does not improve in the years afterwards (but also does not necessarily worsen).

The MD Anderson Dysphagia Index is a widely used questionnaire explicitly assessing dysphagia in HNC patients.[47,81,82] Examples from the literature using this instrument also show a reduction in the swallowing function after baseline,[83,84] but differences have been reported depending on the baseline swallowing ability; patients who start off with poorer swallowing may notice an improvement by six months post-treatment, whereas patients who had good functioning at baseline main report reduced swallowing by six months.[85]

Conclusion regarding health-related quality of life from baseline to 60 months post-treatment

The literature shows that HNC patients are likely to experience increases in difficulties for functional aspects (*physical, emotional, social* and *role functioning*) and symptom burden in the short term up to around the end of treatment. Exceptions to this appear to be *emotional function*, which tends to increase or remain stable over baseline assessments, and to some extent problems with *oral pain* and *speech problems*, for which evidence shows some patient groups are stable in the short term.

By 12 months post-treatment, functioning and some symptoms such as *fatigue, pain, speech, sexuality problems, opening mouth* and to a lesser extent *problems with senses* have largely improved on average (and in some cases may return to baseline levels or better), but there are notable exceptions for this depending on diagnosis and treatment (in particular for *speech* and *senses*). Improved HRQoL at 12 months does not necessarily equate to good HRQoL, as baseline HRQoL may already be quite poor.

At 12 months post diagnosis, problems *opening the mouth wide, dry mouth, sticky saliva*, and *swallowing* still pose a considerable problems for many HNC patients, which are all factors that

contribute to problems with social eating. While swallowing problems and social eating seem to increase only a little or moderately between 12 months and 60 months, the literature shows that problems with *dry mouth, sticky saliva* and *opening mouth* continue to increase on average in a manner that reflects clinically relevant increasing symptom burdens.

5.2. Health-related quality of life more than five years after treatment

Moving past the five-year milestone and into the years of survival beyond, very little is known about how HNC patients fare in terms of HRQoL, and even less about what, if any, the differences might be depending on the treatment received. A systematic review of studies assessing HRQoL at time points greater than five years after diagnosis identified only eight studies using a total of four different questionnaires.[86] In addition to the lack of research in this area, the studies that have been published mostly included only a low number of patients, ranging from 26 to 60[64,87–90] plus two larger studies with 204 and 242 each,[91,92] and one notably large study with 640 patients (Table 3).[93]

Table 3 – Studies reporting health-related quality of life in the long-term

First author, (year)	Study design	HRQoL assessment instrument	HNC sub-sites	Treatment groups	Long-term assessment time point after diagnosis*: n
Dohopolski (2023)[94]	Cr.	MDASI-HN	oropharynx: 100%	RT +/- CT: 68% Surgery +/- RT/CT: 32%	5-15 years: 396
Yan, (2017)[87]	Pr.	UW-QoL	gingival: 43% oral cavity: 33% tongue: 23%	surgery: 70% surgery + RT: 30%	8 years: 30
Tsai, (2014)[91]	Cr.	EORTC QLQ-C30	nasopharynx: 100%	RT: 34% CRT: 66%	5-13 years: 242
Oskam, (2013)[64]	Pr.	EORTC QLQ-C30 EORTC QLQ-H&N35	oral cavity: 38% oropharynx: 62%	surgery only or surgery with adjuvant RT	8-11 years: 26
Wan Leung, (2011)[93]	Cr.	EORTC QLQ-C30 EORTC QLQ-H&N35	nasopharynx: 49% oral cavity: 20% oropharynx: 12% hypopharynx: 12% larynx: 7%	RT or adj. RT: 100%	minimum 2 years after treatment (median: 4.3 years): 640
Wijers, (2002)[89]	Cr.	Questionnaire created for the study	nasopharynx: 36% oropharynx: 38% larynx: 23% hypopharynx: 3%	RT: 100%	3-22 years (mean: 9.6 years): 39
Rogers, (1999)[90]	Cr.	EORTC QLQ-C30 EORTC QLQ-H&N35 UW-QoL	oral cavity and oropharynx	surgery and surgery + RT	5-10 years: 38
Bjordal, (1994)[92]	RCT♦	EORTC QLQ-C30	oral cavity: 22% pharynx: 7% larynx: 50% nose/sinus: 6% other: 16%	RT alone: 48% surgery + RT: 51% CRT: 1%	7-11 years: 204

* Prospective studies had more than one assessment time point, but only the time point past five years post-diagnosis is noted here.
♦ Long-term follow-up of an RCT.
HRQoL: health-related quality of life; HNC: head and neck cancer; MDASI-HN: MD Anderson Symptom Inventory - Head and Neck Module; UW-QoL: University of Washington Quality of Life Questionnaire;
Pr.: prospective; Ret.: retrospective; Cr: cross-sectional; RCT: randomized control trial;
RT: radiotherapy; CT: chemotherapy; CRT: chemoradiotherapy

Possibly the first ever study on long-term survivors of HNC was published by Bjordal et al. in 1994, at which point the HNC-specific module to accompany the EORTC QLQ-C30 had not yet been developed.[92] This was a follow-up analysis of a randomized study that assigned HNC patients to one of two groups: conventional fractionated RT or hypofractionated RT. Two-hundred and four survivors participated in the follow-up at seven to 11 years after RT, and the authors reported better average functioning for *role, social*, and *emotional functioning* and less *fatigue* among patients receiving hypo-fractionated RT versus convention RT. Rogers et al. looked at 38 oral cancer and oropharynx cancer survivors at five to ten years after surgery and determined that HRQoL was similar at five years post treatment to that at one year post-treatment, with exceptions for *emotional functioning* and *cognitive functioning* both of which showed clinically relevant improvements.[90] However, the small number of patients make it difficult to rely on the results.

Oskam et al. published a prospective study on oral cavity and oropharynx cancer survivors and included a late assessment point at eight to 11 years after diagnosis.[64] Results showed that in comparison to baseline values, *swallowing* was still an increased problem (baseline mean: 8.8 [SD:3.3] versus 23.2 [SD:4.8]), as were *problems with senses* (baseline mean: 4.8 [SD:2.6] versus 15.1 [SD:5.7]), *sexuality* (baseline mean: 20.0 [SD:7.5] versus 37.8 [SD:11.6]), *opening mouth* (baseline mean: 14.3 [SD:6.7] versus 41.3 [SD:7.9]), *dry mouth* (baseline mean: 19.0 [SD:7.1] versus 46.0 [SD:8.1]), and *sticky saliva* (baseline mean:16.7 [SD:7.1] versus 41.7 SD:[7.2]). These results are interesting, but again they cannot be considered robust, because the number of survivors assessed was so low (n=26). A larger more recent study on 242 nasopharynx cancer survivors (five to 13 years of survival) reported mean HRQoL results for the EORTC QLQ-C30 but did not use the QLQ-H&N35, so this study did not capture the symptoms most likely to be bothering the survivors.[91] Dohopolski et al. published a relatively large cross-sectional study on long-term outcomes among oropharynx cancer survivors.[94] The authors assessed QoL with MDASI-HN among 396 survivors who had primary surgery versus primary RT and concluded that no differences were evident. However, both treatment arms were a mix of monotherapy and multi-modal therapy, which may have made differences difficult to identify.

In a considerably larger study, Wan Leung et al. assessed 640 HNC survivors. The inclusion criteria were that survivors were at least two years past their treatment, but the study's median survival length of 4.3 years warrants its inclusion here.[93] Considerable problems with *dry mouth* (mean: 48; SD: 31), *sticky saliva* (mean: 41; SD: 31), *swallowing* (mean: 30; SD: 24), *social eating* (mean: 29; SD: 27), and *speech* (mean: 28; SD: 26) were reported by these survivors. Clinically relevant better outcomes in problems with *dry mouth* and *sticky saliva* were reported for survivors who had received 3D-conformal RT versus 2D-conformal RT, and there were no

clinically relevant differences for HRQoL outcomes between survivors who had received intensity-modulated RT (IMRT) versus three-dimensional RT (3DRT). This group was nearly half comprised of nasopharynx cancer patients, which makes it difficult to extrapolate to other HNC survivor populations despite its high number of participants.

6. Physician-assessed dysphagia, dry mouth, trismus and oral pain

In contrast to patient-reported outcomes, physician-assessed toxicities rely on a clinical examination by a physician as well as good input from the patient.[95] Advantages include that the physician can often deduce whether a particular symptom was likely caused by an intervention or disease process or by something unrelated. When using PROs, patients may for example report having had diarrhea in the past week, but whether the problem was related to the patient's diagnosis or treatment cannot be known to the same extent as with a physician assessment. A disadvantage of physician-assessed toxicity is a documented tendency for physicians to miss some toxicities or to grade their severities as more or less severe than the patients would.[95] The most common tool to quantify the severity of a toxicity is the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).[96] This tool describes a spectrum of severities for a wide range of adverse events (toxicities) using numbered grades, with the higher grades indicating more severity up to 5, which is death. Grade 1 toxicities may be only mildly noticeable to the patient, but severities of grade 2 and higher mean some altered behavior or an intervention is necessary.

6.1. Dysphagia

The CTCAE has five grades for dysphagia, and severity is based on how much trouble the patient has eating or whether a feeding tube is necessary. Up to two thirds of HNC patients may present with clinical dysphagia symptoms even before treatment starts, but the treatment itself can induce the problem as well.[97] Research has shown some differences in dysphagia frequency between treatment modalities. For example, among 212 HNC patients in Australia undergoing RT or CRT who were prospectively assessed for dysphagia at week one or two of treatment, approximately 26% of CRT patients had dysphagia ≥ CTCAE grade 2 compared to the RT patients with approximately 15%.[98] This peaked for both groups during the last week of treatment, with about 80% of CRT patients at CTCEA ≥ 2 compared to about 57% of RT patients, and by 12 weeks post-treatment both groups had a smaller proportion of dysphagia CTCAE ≥ 2 than at the start of treatment. Among 60 HNC patients in Germany treated with either CRT or RT and immunotherapy examined retrospectively, 83% were found to have dysphagia at CTCEA ≥ 2 at the end of treatment.[99] This had fallen to less than 2% by about 4.5 months post treatment. It is known that increased radiation doses lead to more frequent

dysphagia (as well as decreased salivary functioning and increased pain).[100] Among 238 HNC patients treated in the Netherlands, researchers identified five patterns of dysphagia over a span from diagnosis to 24 months after RT (this study used the Radiation Therapy Oncology Group/EORTC Late Radiation Morbidity Scoring Criteria).[101]

1. 53% consistently had no or only minor dysphagia over the follow-up time (low persistent pattern)
2. 16% had grade 1 dysphagia at six months that continued over the follow-up (intermediate persistent pattern)
3. 8% had grade 2 or worse at six months that continued over the follow-up (severe persistent pattern)
4. 15% had grade 2 or worse at six months, but recovered over the follow-up (transient pattern)
5. 8% had less than grade 2 at six months and become worse over the follow-up (progressive pattern)

Hence, there is evidence that this problem can persist even after the treatment has concluded. Indeed, an analysis using data from three trials run by the Radiation Therapy Oncology Group on HNC patients receiving concurrent CT with RT found that the number of toxicities did not plateau until about 36 months post randomization.[102] Reducing or managing dysphagia is important not only because it is associated with a reduction in QoL: it also can lead to immediate life-threatening consequences, for example in the form of aspiration.[103]

6.2. Dry mouth

Permanent salivary gland hypo-function can occur after HNC treatment through radiation damage to the glands or surgical intervention on salivary glands.[99,104] Other non-disease related factors that can contribute to reduced saliva production are increased age and smoking, both of which are risk factors for HNC.[105,106] The CTCEA has three grades for dry mouth and are assigned according to whether (or the extent to which) the patient's dry mouth is affecting their ability to eat. Grades 4 and 5 do not exist.[96] Among 60 HNC patients treated with CRT or RT with immunotherapy, there were no dry mouth events at CTCEA grade 2 or higher at any time point in the study (up to 4.5 months post-treatment).[99] However, at the end of treatment and at six weeks post-treatment, respectively 7% and 30% had CTCAE grade 1 dry mouth. This is in contrast to an article on 149 HNC patients treated with RT in Italy between 2004 and 2006; 66% had CTCEA grade 2 dry mouth, but it is not clear at which time point this assessment was done.[100]

A meta-analysis comparing intermediate to severe dry mouth occurrence (CTCAE grades 2 to 4) between two types of RT treatment IMRT and two dimensional RT (2DRT)) identified four

studies with follow-up ranging from six months up to five years.[107] Pooled findings showed that patients with IMRT consistently had better clinical dry mouth outcomes compared to the patients receiving 2DRT at six months, one year, two years, three years, and five years post-treatment. Respectively at each time point, 28%, 25%, 30%, 0%, and 9% of IMRT patients had dry mouth CTCAE grade 2 to 4. For 2DRT, these proportions were 57%, 77%, 77%, 64%, and 30%, notably higher. This meta-analysis shows the benefit of improved RT technique in this regards, but also shows that this symptom continues to be seen long-term in some patients even among the IMRT group.

6.3. Trismus

The CTCAE does not define an objective measurement as a cut off for clinical trismus, but a maximal inter-incisor distance of less than 35 millimeters (mm) is often used as such.[105] In the CTCAE, the grades are determined by having a decreased range of motion (with no specific measurement stated) without impaired eating ability (grade 1), decreased range of motion necessitating small bites, soft foods or purées (grade 2), and decreased range of motion to the point that adequate intake of food orally is not possible (grade 3). There are no grades 4 or 5 for this toxicity. Increased probability of having clinical problems with trismus are associated with increased RT dose, with an estimated 24% increased chance for each additional 10 grays absorbed by the muscles that move the mandible.[108] Scarring from surgical treatment can also be a contributing factor.[109]

A meta-analysis examined the occurrence of late trismus (defined by the authors as being present 12 months or more after RT) between nasopharyngeal patients treated with IMRT and those treated with 2DRT or 3DRT.[110] Three articles were identified and the pooled results show that patients treated with IMRT are less likely to have trismus at this late time point: 6% of IMRT patients compared to 21% of 2D/3DRT patients. However, the analysis did not consider the severity of the trismus. Among a collective of 45 primarily oropharynx cancer patients treated with CRT (33% of whom also had surgery), 24% were found to have trismus before treatment, 45% at the end of CRT, 27% ten weeks after CRT, and 37% six months after CRT.[111] Trismus was assessed by objective measurements between the upper and lower left median incisors, but a clear statement as to the severity of trismus in each treatment group is not given.

Tumor site is an important risk factor for trismus, as tumors closer to the mastication muscles (e.g., nasopharynx and oropharynx) can result in trismus more often than those further away (e.g., larynx and hypopharynx).[111] Trismus was among the top three most burdensome symptoms experienced by 89 oral cavity and oropharyngeal cancer patients treated in the Netherlands and assessed between 0.9 and 4.1 years post-treatment (median: 1.7 years; lack

of saliva was the most burdensome and the second was reduced tongue movement).[112] This shows that trismus can be a persistent, burdensome problem long after treatment is over.

6.4. Pain

Pain is a unique symptom in that it is not objectively measurable, but is known to be a problem in up to 70% of HNC cases.[113] Orofacial pain can be a direct result of the treatment itself, or it can be due to secondary problems such as mucositis and osteomyelitis.[114] For HNC patients, pain can be particularly debilitating due to the extensive innervation of the anatomical area.[114] The CTCAE has three grades for oral pain, with descriptions that rely on the impact of the pain for the patient.[96] Grade 1 is described as “mild pain”, grade 2 as “moderate pain” that limits key activities of daily living, and grade 3 as “severe pain” that limits self-care activities of daily living. One common cause of oral pain in HNC patient is mucositis.[115] An older systematic review of mucositis among HNC published in 2003 found that only three of 33 identified studies reported oral pain. Among the three studies, 69% of patients had oral pain.[116] Other estimates suggest that between 55% to 86% of oropharyngeal cancer patients develop severe mucositis, and therefore experience the accompanying pain, after RT or CRT therapy.[114] Among 149 HNC patients treated with RT or CRT in Italy, 50% were determined to have oral pain at CTCAE grade 2 or 3 at about two months after the start of therapy.[100] After being unable to find any reviews or studies specifically on oral pain in head and neck cancer patients, I contacted members of the International Society of Oral Oncology to ask for advice on articles I should consider. The response back indicated that oral pain is an area not well researched, and that a recent attempt to do a systematic review had failed because of insufficient published data (Dr. D Saunders at Health Sciences North Hospital, Canada, Dr. A Villa at Miami Cancer Institute Baptist Health, USA, and Dr. Yarom Noam at Sheba Medical Center, Tel Aviv, Israel; personal communication, June 20, 2023).

6.5. Long-term toxicities

After survivors are beyond five years post diagnosis or post treatment, there are very few studies that have assessed toxicities using the CTCAE. A literature review published in 2021 looking for such articles identified only three, all of which included only nasopharynx cancer survivors.[117] Among the three articles, one reported that 49% of the survivors with an assessment at five years post-diagnosis suffered from at least one toxicity at a grade 3 severity.[118] A Taiwanese study on 242 nasopharyngeal cancer survivors at five to 13 years after diagnosis found that 41% had dysphagia at grade 2 or 3 and 56% had dry mouth at grade 2 or 3.[91] The third study was from China and included 789 nasopharyngeal cancer survivors.[119] Among the survivors treated with IMRT, 1% had trismus, and among the survivors who had IMRT plus CT, 3% had

trismus. Nasopharynx cancer is a special entity among HNC, and the extrapolation possibilities of these studies are especially limited. Large-scale, long-term studies specifically assessing toxicities as rated by a physician as well as asking the survivors about their quality of life across the range of HNC sites are needed.

7. Research questions

The paucity of evidence concerning late toxicities and the status of HRQoL among long-term survivors of HNC led to a study funded by the EORTC Quality of Life Group (QLG) to address these issues. The study was called "Late Toxicity and Long-Term Quality of Life in Head and Neck Cancer Survivors" ("Late Tox Study"). This dissertation investigates two primary research questions that were part of that study. Specifically, among long-term survivors of HNC:

- Are there clinically meaningful differences in long-term HRQoL outcomes in light of the treatment the survivors received?
- Are there differences in the occurrence of long-term physician-rated dysphagia, dry mouth, trismus and oral pain in light of the treatment the survivors received?

8. Methods

8.1. Study design and study population

The Late Tox Study was an international cross-sectional study initiated jointly by the EORTC QLG and HNC Group.[120]

Project collaborators at participating sites were asked to review their medical records for eligible survivors and then contact them to ask if they would be willing to participate (see inclusion criteria below). Potential collaborators were primarily made aware of the opportunity to enroll survivors in the study during project planning discussions and project update meetings at the spring and fall meetings of both the QLG and the HNC Group of the EORTC. No restrictions were placed on which countries could participate or the type of medical facility, other than that the collaborator needed to be confident that he/she could enroll at least ten survivors.
The inclusion criteria for the study population were as follows:

- A verified head and neck cancer diagnosis with at least one of the following ICD-10 codes:
  - C32 (larynx)
  - C01-06 (oral cavity)
  - C09-10 (oropharynx)
  - C11 (nasopharynx)
  - C31 (nasal sinuses)
  - C00 (lip)
  - C07-08 (salivary glands)
  - C12-14 (hypopharynx)
  - C30 (nasal cavity)
  - C77 and C80.0 (lymph node metastases from unknown primary in the head and neck area)

- First HNC diagnosis occurred five years or more in the past
- Ability to understand and complete the questionnaires in the local language
- Ability to attend the clinic where the clinical exam for the toxicities was carried out
- Age 18 years or older
- Written informed consent provided

Explicit exclusion criteria were cancers of the eye, thyroid, or orbit tumors, skin cancer in the head and neck region, and lymphoma of the head and neck region.

Patients who agreed to participate were invited to attend an appointment for a clinical toxicity examination with a physician and to fill out HRQoL questionnaires.

8.2. Data collection

The HRQoL were collected from the survivors directly and the physicians provided the clinical and demographic data and performed the toxicity assessments. Data collection was possible in a paper-and-pen format or as direct digital data entry using an instance of the Computer Health Evaluation System (CHES), an online web-based platform.[121] Collaborators also had the option to send their completed forms and questionnaires to the study coordinator in Mainz, where the data were then entered into CHES. Most collaborators preferred the latter option.

8.2.1. Sociodemographic and clinical data

On a case report form, the physician documented the survivors' diagnosis, treatment history and sociodemographic characteristics. The sociodemographic details included the patient's:

- sex
- age
- total years of education: less than ten years, ten years, more than ten years
- living situation: lives alone, with a partner (with or without children), with no partner but with children, or with other people
- smoking habits: never, former, or current smoker
- alcohol consumption: never, monthly or less, two to four times a month, two to three time a week, or four to five times a week

Clinical data included:

- ICD code and date of diagnosis
- T (tumor), N (nodes), and M (metastasis) values and TNM version
- UICC (Union for International Cancer Control) stage
- tumor histology: squamous cell, sarcoma, or other
- second primary: yes/no and date/location if occurred

- current evidence of disease: yes/no
- the type of treatment: surgery, RT, CT, CRT, CRT and surgery, CT and surgery, RT and surgery, or other
- type of surgery: none, transoral/transnasal/ endoscopic without neck dissection, transoral/transnasal/ endoscopic with neck dissection, transcervical (with or without neck dissection), neck dissection only, any intervention with regional flap reconstruction, any intervention with free flap reconstruction
- Charlson Comorbidity Index[122]
- Karnofsky Performance Status[123]

The case report form is available in full in Appendix 1.

8.2.2. Health-related quality of life data

HRQoL were collected using the EORTC QLQ-C30 and EORTC QLQ-H&N35.

The details about the composition and scoring of these questionnaires have already been described in Chapter 3, but for completeness are briefly repeated here. The EORTC QLQ-C30 is a 30-item generic cancer questionnaire that assesses HRQoL using five functional scales (*physical functioning, role functioning, emotional functioning, cognitive functioning,* and *social functioning*), nine symptom scales (*fatigue, nausea and vomiting, pain*, *dyspnea, insomnia, loss of appetite, constipation, diarrhea* and *financial difficulties*), and one *global quality of life* scale.[48] Each functional and symptom scale was converted to a score ranging from 0-100 as described in the questionnaire manual. For functional scales, high values indicate high functioning, while for symptom scales, high values indicate high symptom burden. A copy of the questionnaire is available in Appendix 2.

The EORTC QLQ-H&N35 is the HNC-specific module. It comprises seven multi-item scales, covering *pain in the mouth, problems with swallowing, senses, speech, social eating, social contact,* and *sexuality*; and there are ten single items scales covering *problems with teeth, dry mouth, sticky saliva, coughing, trismus, changes in weight,* and *use of nutritional supplements feeding tubes, and analgesics*. The scales and items in the QLQ-H&N35 are also converted to scores ranging from 0-100, with higher values indicating higher problems. Both questionnaires are well-established, validated instruments.[49,55,63,64,74,124] A copy of the questionnaire is available in Appendix 3.

For all scales, a difference of at least ten points was considered the cut off for a minimal clinically relevant difference.[51]

8.2.3. Toxicity data

The physician assessed the survivors for four toxicities: dysphagia, dry mouth, trismus, and oral pain. Version 5 of the CTCAE was used to rate each toxicity's severity when present. The physicians documented their opinions on a paper form where the full descriptions of each CTCEA grade were listed for each toxicity (Table 4). Obviously a grade 5 for dysphagia is not possible in this study as it means death, but it was included so that the complete range of grades were presented. The option 'na' for not assessed was provided to differentiate between whether a physician consciously did not assess a toxicity versus forgetting to document a grade. This way I could follow up with any missings that had not been intentionally left blank. A rating of '0' indicated that the survivor did not have the toxicity.

Table 4 – Description of the CTCAE grades for dysphagia, dry mouth, trismus and oral pain

Toxicity	Grade	Description
Dysphagia	na	This toxicity was not assessed
	0	This toxicity is not present.
	1	Symptomatic, able to eat regular diet
	2	Symptomatic and altered eating/swallowing
	3	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated
	4	Life-threatening consequences; urgent intervention indicated
	5	Death
Dry mouth	na	This toxicity was not assessed
	0	This toxicity is not present.
	1	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min
	2	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min
	3	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min
Trismus	na	This toxicity was not assessed
	0	This toxicity is not present.
	1	Decreased ROM (range of motion) without impaired eating
	2	Decreased ROM requiring small bites, soft foods or purees
	3	Decreased ROM with inability to adequately aliment or hydrate orally
Oral pain	na	This toxicity was not assessed
	0	This toxicity is not present.
	1	Mild pain
	2	Moderate pain; limiting instrumental ADL
	3	Severe pain; limiting self care ADL

na: not assessed, ADL: activities of daily living

8.3. Analyses

8.3.1. Descriptive statistics

The Late Tox Study survivor collective was described for the entire study population as well across treatment groups by reporting the distribution (absolute and relative frequencies) of the sex, geographical area, smoking status, years of education, tumor sub-site, histology, UICC stage, Karnofsky Performance score, Charlson Comorbidity Index, current evidence of disease, second primary occurrence, and number of years since diagnosis. Age was reported for the group as a whole as well as for each treatment group as the mean and range in years.

For the geographical areas, the countries involved were grouped as Northern Europe (Norway and Sweden), Central/Western Europe (Germany, the Netherlands, Belgium), Southern Europe (Greece, Italy, Portugal), and Israel, Japan, and Brazil. The Karnofsky Performance scores were grouped into four categories: less than 50, 50 or 60, 70 or 80, 90 or 100, and the Charlson Comorbidity Index results were reported as the frequency of scoring 0, 1, 2 and ≥3. Time since diagnosis was determined by subtracting the date of the survivor's diagnosis from the date of enrolment in the study and rounding to the nearest complete year. These values were grouped into four categories: 5 or 6 years, 7 or 8 years, 9 or 10 years and >10 years. The number of years of education was the total number of all educational years, including grade school and any post-secondary education. The number of missing values for each variable were reported.

8.3.2. Analytical statistics

To identify differences in the distribution of demographic and clinical characteristics across the treatment groups, Chi-square test for independence or Fisher's test were used for count data, and an analysis of variance was done for the age distribution.

Each of the HRQoL domain scores were calculated for each treatment group as the mean score with 95% CI and SDs for the raw data. Differences of ten points or more in the mean raw data were noted. Then, analysis of covariance (ANCOVA) was used to calculate adjusted means with 95% CI for all HRQoL scales and to assess evidence for differences between treatment groups. Tukey-Kramer post hoc tests were used to determine where the differences were. Age, sex, UICC stage, and tumor sub-site were included as covariables. Wherever adjusted means or CI resulted in numbers below 0 or greater than 100, these were recorded as '0' and '100' respectively, as these are the limits of the HRQoL scores.

The results of the physician assessments for dysphagia, dry mouth, trismus, and oral pain were reported as the absolute and relative frequencies of each possible grade as well as how many patients were missing an assessment for each toxicity. Logistic regression models with sex, age, UICC stage, and tumor sub-site as covariables were run for each toxicity, with the outcome being a dichotomized grade: either the toxicity was not present/grade 1 or the toxicity was

present at a grade 2 or higher. This dichotomization was chosen because at a grade 1 according to the CTCAE, the toxicities in this analysis are only mildly evident to the patient and do not require much accommodation, but grades 2 and higher mean a considerable burden to the individual. The logistic regression models were created to produce the odds of a survivor being free of the toxicity or only having it at a severity of 1, and the reference category was the 'surgery and RT +/- CT' group. All statistical work was completed using Statistical Analysis Software (SAS, version 9.4).

8.3.2.1. Determination of the UICC stage

A mix of TNM versions seven and eight were expected in the data, and, after consultation with the collaborators, a decision was made to ensure that the final data set contained a UICC stage according to version seven.[125,126] Version seven was chosen because it was expected that the majority of patients would have this in their patient files anyway given that these diagnoses were not recent. As well, this study did not collect information on HPV status, which is necessary for some staging decisions in TNM version eight for HNC.

To harmonize all tumor stages to version seven, I noted all combinations of TNM values for each of the diagnoses possible in the project and their corresponding version seven UICC stage. Then I created a program in SAS that determined the UICC stage for each combination. Then a comparison was done between the UICC stage noted by the physician in the case report form and the calculated UICC stage determined by the program. If discrepancies were found, first a check for data entry errors was done. If this did not explain the discrepancy, the following rules were applied:

- **If the TNM version indicated in the case report form was version eight**, then the calculated UICC stage was regarded as final.
    - The reasoning being that the difference is likely due to the version difference.

- **If the TNM version indicated in the case report form was version seven**, then the calculated UICC stage was regarded as final.
    - The decision assumed the discrepancy was due to physician error in determining the UICC stage but that the TNM values could be regarded as correct.
        - **An exception to this rule** was made for oropharynx diagnoses.
            - For oropharynx patients, the UICC stage indicated by the physician in the case report form was used because it was felt to be even less certain as to whether the error was from the

physician determining the UICC stage or recording the TNM values.

- If no TNM values were indicated, but a UICC stage was recorded by the physician, then the UICC stage indicated by the physician was regarded as final.

These rules were determined in conjunction with and agreed to by the project physicians.

8.3.2.2. Determination of treatment groups

The exposure of interest was 'treatment'. Treatment information was captured in the case report form across several questions concerning the general treatment regime followed by details on the type of surgery when present. Using this information, five treatment groups were defined:

1) Surgery only
2) Radiotherapy only
3) Chemo-radiotherapy
4) Radiotherapy +/- chemotherapy and neck dissection ('RT +/- CT and ND')
5) Surgery and radiotherapy +/- chemotherapy ('surgery and RT +/- CT')

The 'surgery and RT +/- CT' group contains survivors who had radiotherapy and/or chemotherapy plus any kind of surgery other than a sole neck dissection, while the 'RT +/- CT and ND' group had survivors who had radiotherapy and/or chemotherapy plus a neck dissection. The reason for separating out the neck dissections from all other surgical interventions was the expected difference in outcomes; group five may have extensive anatomical and functional changes after radical surgery, while neck dissection is a considerably less radical intervention.

The types of surgery that could be represented in the 'surgery and RT +/- CT' treatment group are:

- transoral/transnasal/endoscopic without neck dissection
- transoral/transnasal/endoscopic with neck dissection
- transcervical (with or without neck dissection)
- any intervention with regional flap or free flap construction

9. Results

9.1. Enrolment

The first survivor was enrolled in October 2018 and the last in November 2021, with a total number of 1117 survivors. With the exception of the site in Athens, Greece, and Porto, Portugal, all sites sent their documents (either as scanned pdf files or mailed as paper copies) to Mainz for data entry. The collaborators in Athens and Porto opted to enter all their data directly into CHES themselves. All survivors used paper and pencil to complete their questionnaires.

Of the 1117 survivors enrolled, 11 were found to have a date of diagnosis that was less than five years in the past. These ranged from 3.9 years to just short of five years post-diagnosis. After discussions with collaborators, it was decided that for these few survivors, if the number of years was at least 4.5 (and therefore could be rounded up to five), the survivor would be included in the analysis, thereby excluding two survivors. The remaining nine were included in the analysis as being five years post diagnosis. An additional survivor had an ineligible diagnosis and another had no treatment information; both were excluded from the analyses. As well, eight survivors did not complete any HRQoL questionnaires and are therefore excluded from the HRQoL analysis, and 20 had no clinical examination for toxicities and are therefore excluded from the toxicity analysis (see Figure 7). Among the eight survivors who did not complete HRQoL questionnaire, six had been given the questionnaires to complete at home and did not return them and two refused to complete the questionnaires. Of the 20 survivors without a toxicity assessment, one died before his examination appointment and the other 15 are missing due to a misunderstanding about the study protocol, whereby one local collaborator thought the examination was optional. The remaining four missing examinations were for survivors from Mainz. These survivors submitted their questionnaires but were then unable to come to the toxicity assessment.

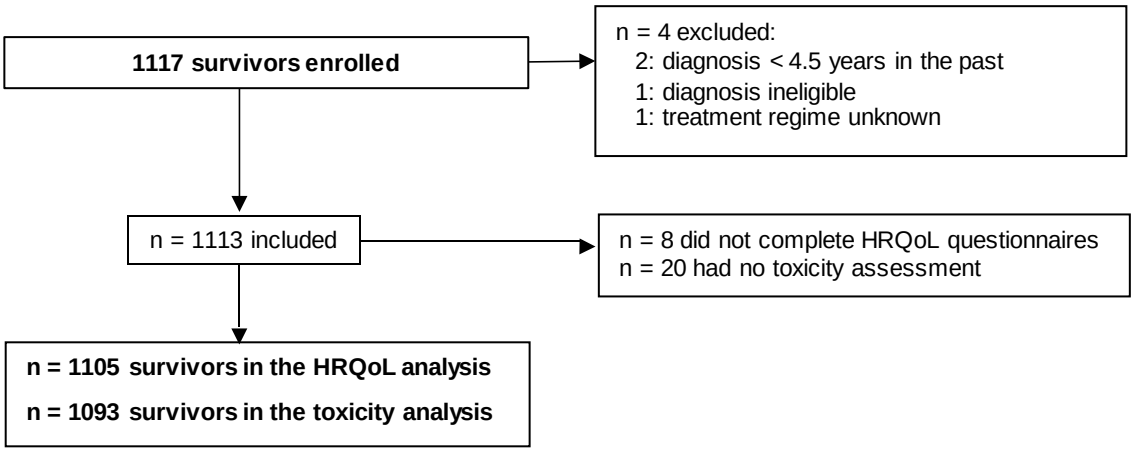

Figure 7 – Number of survivors included in the analysis

9.2. Survivor characteristics

The majority of the survivors were male (71%) and the average age was 66 years (range: 23-93) (Table 3). Most lived in Central Europe (43%) and Northern Europe (23%), but there was also representation from Brazil (10%), Japan (3%) and Israel (1%). The most common tumor sites were the oropharynx (34%), oral cavity (22%) and larynx (19%) and the dominant histology was squamous cell carcinoma (88%). The survivors' head and neck cancer had mostly been diagnosed at a higher tumor stage, with 39% stage IV and 22% stage III. Approximately three quarters of the study population was five to ten years post-diagnosis, and 3% had current evidence of disease. The majority of survivors (66%) had a Karnofsky Performance Status of 90 to 100, which means most survivors were able to carry on normal activities with no special care required. As well, the majority (64%) had none of the co-morbidities listed in the Charlson Comorbidity Index.

The treatment groups comprised unequal numbers of survivors, with 424 (38%) in the 'Surgery and RT +/- CT' group. The second largest was the CRT with 315 (28%) survivors, followed by the three remaining groups which were all similar in size: RT n=134 (12%), surgery n=129 (12%), and 'RT +/- CT and ND' n=111 (10%) (Table 3).

There was evidence of statistical differences in the distribution of sex, geographical area, education, tumor sub-site, histology, UICC stage, and a history of a second primary between the treatment groups. The survivors in each treatment group had overwhelmingly had squamous cell carcinoma, and very few survivors had had a second primary.

Table 5 – Characteristics of the 1113 survivors by type of treatment

	Surgery		RT		CRT		RT +/- CT and ND		Surgery and RT +/- CT		Totals	
Totals[+]	**129**	**12%**	**134**	**12%**	**315**	**28%**	**111**	**10%**	**424**	**38%**	**1113**	**100%**
Sex[a]												
Male	79	61%	107	80%	236	75%	76	68%	291	69%	789	71%
Female	50	39%	27	20%	79	25%	35	32%	133	31%	324	29%
Age (years)[b]												
Mean (range)	67 (23-93)		70 (43-92)		64 (27-88)		66 (47-86)		66 (23-90)		66 (23-93)	
Geographic area[a]												
Northern Europe	20	16%	22	16%	79	25%	45	41%	85	20%	251	23%
Central /Western Europe	67	52%	65	49%	99	31%	52	47%	193	46%	476	43%
Southern Europe	23	18%	39	29%	95	30%	6	5%	75	18%	238	21%
Israel	2	2%	0	0%	2	1%	1	1%	5	1%	10	1%
Japan	3	2%	0	0%	11	3%	1	1%	15	4%	30	3%
Brazil	14	11%	8	6%	29	9%	6	5%	51	12%	108	10%
Smoking status												
Never smoker	40	31%	28	21%	102	32%	33	30%	115	27%	318	29%
Former smoker	70	54%	91	68%	173	55%	64	58%	239	56%	637	57%
Current smoker	14	11%	15	11%	35	11%	13	12%	62	15%	139	12%
Missing	5	4%	0	0%	5	2%	1	1%	8	2%	19	2%
Total years of education[a]												
<10	48	37%	54	40%	110	35%	20	18%	146	34%	378	34%
10	14	11%	27	20%	44	14%	15	14%	64	15%	164	15%
>10	61	47%	52	39%	154	49%	73	66%	203	48%	543	49%
Missing	6	5%	1	1%	7	2%	3	3%	11	3%	28	3%
Tumor subsite[c]												
Oropharynx, base of tongue, tonsil	11	9%	39	29%	151	48%	63	57%	116	27%	380	34%
Oral cavity	67	52%	7	5%	15	5%	5	5%	147	35%	241	22%
Larynx	34	26%	68	51%	31	10%	5	5%	69	16%	207	19%
Nasopharynx	0	0%	6	4%	72	23%	4	4%	4	1%	86	8%
Parotid gland/other salivary gland	11	9%	0	0%	0	0%	1	1%	48	11%	60	5%
Unknown primary	0	0%	3	2%	11	3%	31	28%	7	2%	52	5%
Hypopharynx	2	2%	6	4%	24	8%	2	2%	16	4%	50	4%
Nasal cavity and sinuses	4	3%	5	4%	11	3%	0	0%	17	4%	37	3%
Histology[a]												
Squamous cell	111	86%	125	93%	282	90%	110	99%	349	82%	977	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[c]												
I	86	67%	59	44%	1	0%	4	4%	71	17%	221	20%
II	29	22%	37	28%	30	10%	11	10%	68	16%	175	16%
III	6	5%	19	14%	82	26%	50	45%	91	21%	248	22%
IV	4	3%	14	10%	197	63%	39	35%	179	42%	433	39%
Missing/Unknown	4	3%	5	4%	5	2%	7	6%	15	4%	36	3%

Table 5 – Characteristics of the 1113 survivors by type of treatment (continuation from previous page)

	Surgery		RT		CRT		RT +/- CT and ND		Surgery and RT +/- CT*		Totals	
Karnovsky performance status												
less than 50	0	0%	0	0%	1	0%	0	0%	2	0%	3	0%
50 or 60	4	3%	4	3%	13	4%	1	1%	13	3%	35	3%
70 or 80	29	22%	37	28%	78	25%	26	23%	141	33%	311	28%
90 or 100	89	69%	93	69%	218	69%	83	75%	257	61%	740	66%
Missing	7	5%	0	0%	5	2%	1	1%	11	3%	24	2%
Charlson comorbidity index												
0	83	64%	77	57%	217	69%	73	66%	260	61%	710	64%
1	23	18%	26	19%	59	19%	16	14%	83	20%	207	19%
2	10	8%	14	10%	19	6%	14	13%	35	8%	92	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	121	94%	130	97%	310	98%	110	99%	405	96%	1076	97%
Missing/Unknown	3	2%	0	0%	0	0%	0	0%	2	0%	5	0%
Second primary[a]												
Yes	23	18%	22	16%	33	10%	12	11%	76	18%	166	15%
No	100	78%	112	84%	279	89%	97	87%	344	81%	932	84%
Missing/Unknown	6	5%	0	0%	3	1%	2	2%	4	1%	15	1%
Time since diagnosis (years)												
5 to 6	25	19%	32	24%	83	26%	13	12%	90	21%	243	22%
7 to 8	44	34%	48	36%	114	36%	36	32%	139	33%	381	34%
9 to 10	28	22%	26	19%	61	19%	27	24%	81	19%	223	20%
> 10	32	25%	28	21%	57	18%	35	32%	114	27%	266	24%

Notes: Percentages are column percentages except for the Totals row.
+ Percentages in the Totals row are row-wise
RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection
a: Chi2 $p \leq 0.01$
b: ANOVA model $p \leq 0.01$
c: Fisher $p \leq 0.01$

9.3. Health-related quality of life by treatment group

The unadjusted means for the HRQoL scores in the EORTC QLQ-C30 and QLQ-H&N35 differed by ten or more points between at least one treatment comparison for ten scales: *fatigue, insomnia, pain in the mouth, swallowing, senses problems, trouble with social eating, teeth, opening mouth, dry mouth*, and *sticky saliva* (Table 6 and Table 7). For all differences of ten points or more, the monotherapy groups had better outcomes than the multi-modal treatment groups. The average functioning scores for all scales across treatment groups ranged from 78.4 to 90.2, with no clinically relevant differences between the treatment groups (Table 6). The average score for the symptom scale *nausea and vomiting* across all treatment groups was less than 5, and for *diarrhea* average scores were less than 9. Even among the domains with no difference of more than ten points between treatment groups, nearly all favored the mono-therapy treatment groups

Table 6 – **Unadjusted** cancer-specific health-related quality of life outcomes according to the type of treatment received

HRQoL 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
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 & 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
Dyspnea	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
Diarrhea	5.2 (2.9-7.6)	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

Notes: Data were collected using the EORTC QLQ-C30.
For shaded domains, high scores indicate good functioning; for the unshaded domains, high score indicate a high symptom burden.
HRQoL: health-related quality of life; CI: confidence interval; SD: standard deviation
RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection
Bold rows contain at least one difference of ten or more points between treatment groups.

Table 7 – **Unadjusted** head and neck cancer-specific health-related quality of life outcomes according to the type of treatment received

HRQoL 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
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
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 (16.0-24.9)	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
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

Notes: Data were collected using the EORTC QLQ-H&N35.
High score indicate a high symptom burden.
HRQoL: health-related quality of life; CI: confidence interval; SD: standard deviation
RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection
Bold rows contain at least one difference of ten or more points between treatment groups.

9.4. Quality of life results by treatment group in adjusted models

In models adjusted for sex, age, and tumor sub-site and stage, there were some changes to the group of scales with at least one ten-point difference between treatment groups (Tables 8 and 9 and Figures 8, 9, and 10). Eight remained as showing clinically relevant differences: *fatigue, insomnia, pain in the mouth, swallowing, senses problems, opening mouth, dry mouth,* and *sticky saliva.* The ten-point difference between the treatment groups seen for *teeth* and *trouble with social eating* in the unadjusted models disappeared in the adjusted models. For *teeth*, the adjusted means decreased and the largest difference was then 9.0 points between the surgery group and the 'RT +/- CT and ND' group. *Trouble with social eating* adjusted down to an average of 0 for all treatment groups except 'surgery and RT +/-CT', which was only 2.4; however, the confidence intervals show that for the multiple therapy groups, there could still be a ten-point difference. The adjusted mean burden for *sexuality* also showed a difference of 10.3 points between the surgery group (mean: 0.9, 95% CI: 0.0-18.0) and the 'RT +/- CT and ND' group (mean: 11.2; 95% CI: 0.0-29.0). Therefore, the adjusted models suggest a difference of ten points or more in at least one treatment group comparison for nine domains: *fatigue, insomnia, pain in the mouth, swallowing, senses problems, sexuality, opening mouth, dry mouth,* and *sticky saliva.* All differences of ten or more points favored one or both of the monotherapy groups over the multi-modal therapy groups.

Regardless of whether a ten-point difference was found or not, the monotherapy groups had equal or better mean adjusted scores than the multi-therapy groups for all scales except for *pain killers*, where the lowest score was found for 'RT +/- CT and ND' with 38.7 (95%CI: 15.4-61.9) (Figures 8, 9, and 10). Of note, however, are the confidence intervals, which are often wide. *Pain killers* is a good example of this with confidence intervals spanning more than 40 points for four of the five treatment groups. Despite some overlap of confidence intervals, the advantage of the surgery only group in domains such as *pain in the mouth, swallowing* and *dry mouth* are particularly noticeable in the graphical representations of these results (Figures 9 and 10).

Treatment seems to have little association with long-term *physical functioning*, with all treatment groups having adjusted means scores of 100 with tight confidence intervals. The survivors also had very few problems with *nausea and vomiting* (highest adjusted mean (HAM): 6.6; 95%CI: 0.6-12.5), *appetite loss* (HAM: 7.8; 95%CI: 0.0-19.9), *constipation* (HAM: 0.0; 95%CI: 0.0-3.3), *dyspnea* (HAM: 8.3; 95%CI: 0.0-21.2), and *diarrhea* (HAM: 9.0; 95%CI: 0.2-17.8), and did not seem to require *nutritional supplements* (HAM: 3.3; 95%CI: 0.0-19.9), or use a *feeding tube* (HAM: 0.0; 95%CI: 0.0-7.0).

Table 8 – **Adjusted** cancer-specific health-related quality of life outcomes according to the type of treatment received

HRQoL Scale	Surgery Mean (95%CI)	RT Mean (95%CI)	CRT Mean (95%CI)	RT +/- CT and ND Mean (95%CI)	Surgery and RT +/- CT Mean (95%CI)
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*	***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 & 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)
Dyspnea	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)
Diarrhea	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)

Notes: Data were collected using the EORTC QLQ-C30
Results are adjusted for sex, age, UICC stage and tumor sub-site
HRQoL: health-related quality of life; CI: confidence interval; RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection;
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)
* indicates all differences of 10 points or more between treatment groups were statistically significant (Tukey post-hoc p value ≤ 0.01)
◊ indicates at least one (but not all) of the differences of 10 points or more between treatment groups was statistically significant (Tukey post-hoc p value ≤ 0.01)

Table 9 – **Adjusted** head and neck cancer-specific core quality of life outcomes according to the type of treatment received

HRQoL Scale	Surgery Mean (95%CI)	RT Mean (95%CI)	CRT Mean (95%CI)	RT +/- CT and ND Mean (95%CI)	Surgery and RT +/- CT Mean (95%CI)
Pain in the mouth*	**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*	**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*	**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◊	***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◊	***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◊	***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)

Notes: Data were collected using the EORTC QLQ-H&N35
Results are adjusted for sex, age, UICC stage and tumor sub-site
HRQoL: health-related quality of life; CI: confidence interval; RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection;
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)
* indicates all differences of 10 points or more between treatment groups were statistically significant (Tukey post-hoc p value ≤ 0.01)
◊ indicates at least one (but not all) of the differences of 10 points or more between treatment groups was statistically significant (Tukey post-hoc p value ≤ 0.01)

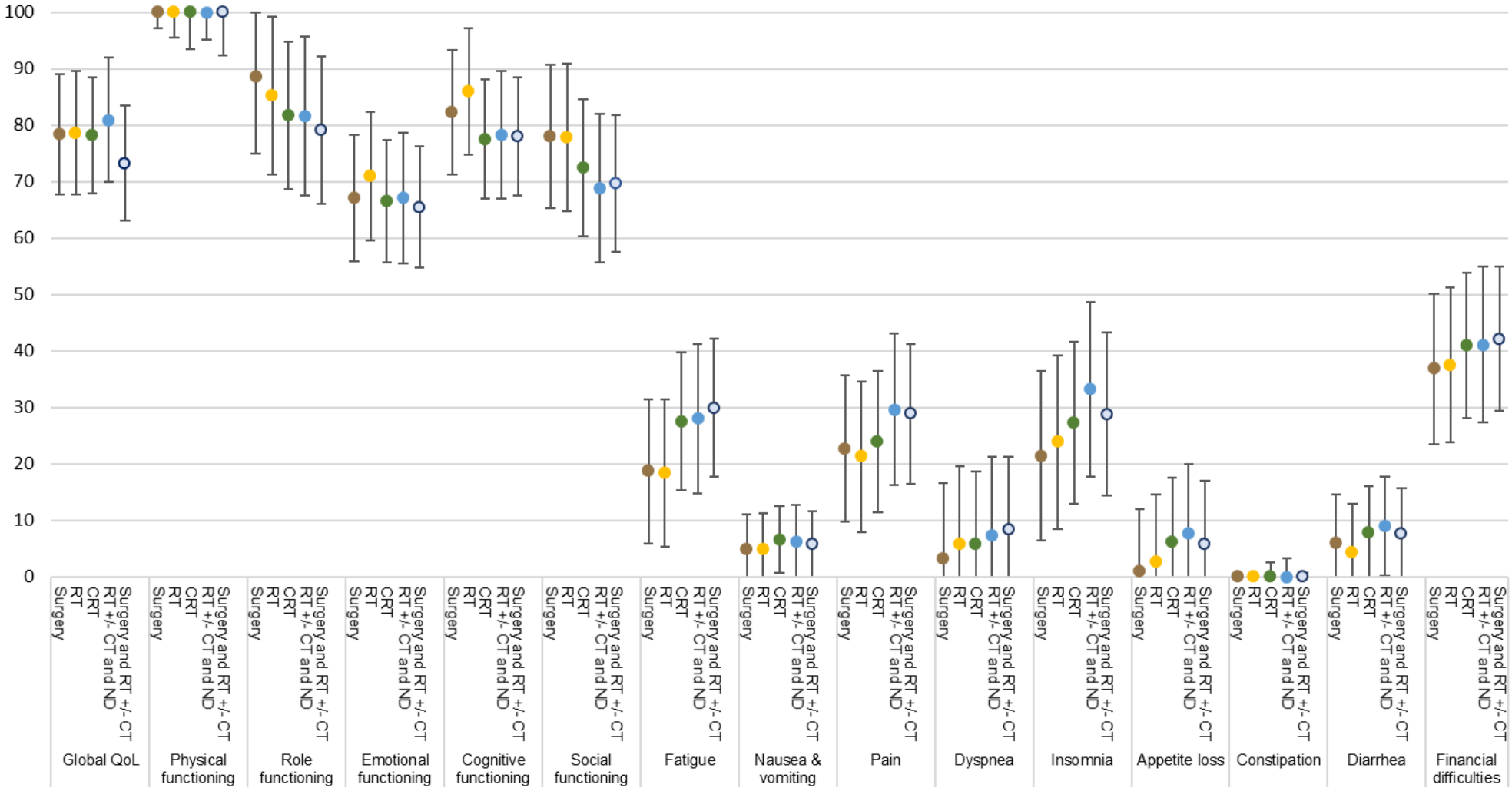

Figure 8 – Adjusted cancer-specific health-related quality of life outcomes according to the type of treatment received

Notes: Data were collected using the EORTC QLQ-C30; QoL: quality of life; RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection
Data points indicate the mean score adjusted for sex, age, UICC stage and tumor sub-site. Lines indicate the 95% confidence interval.

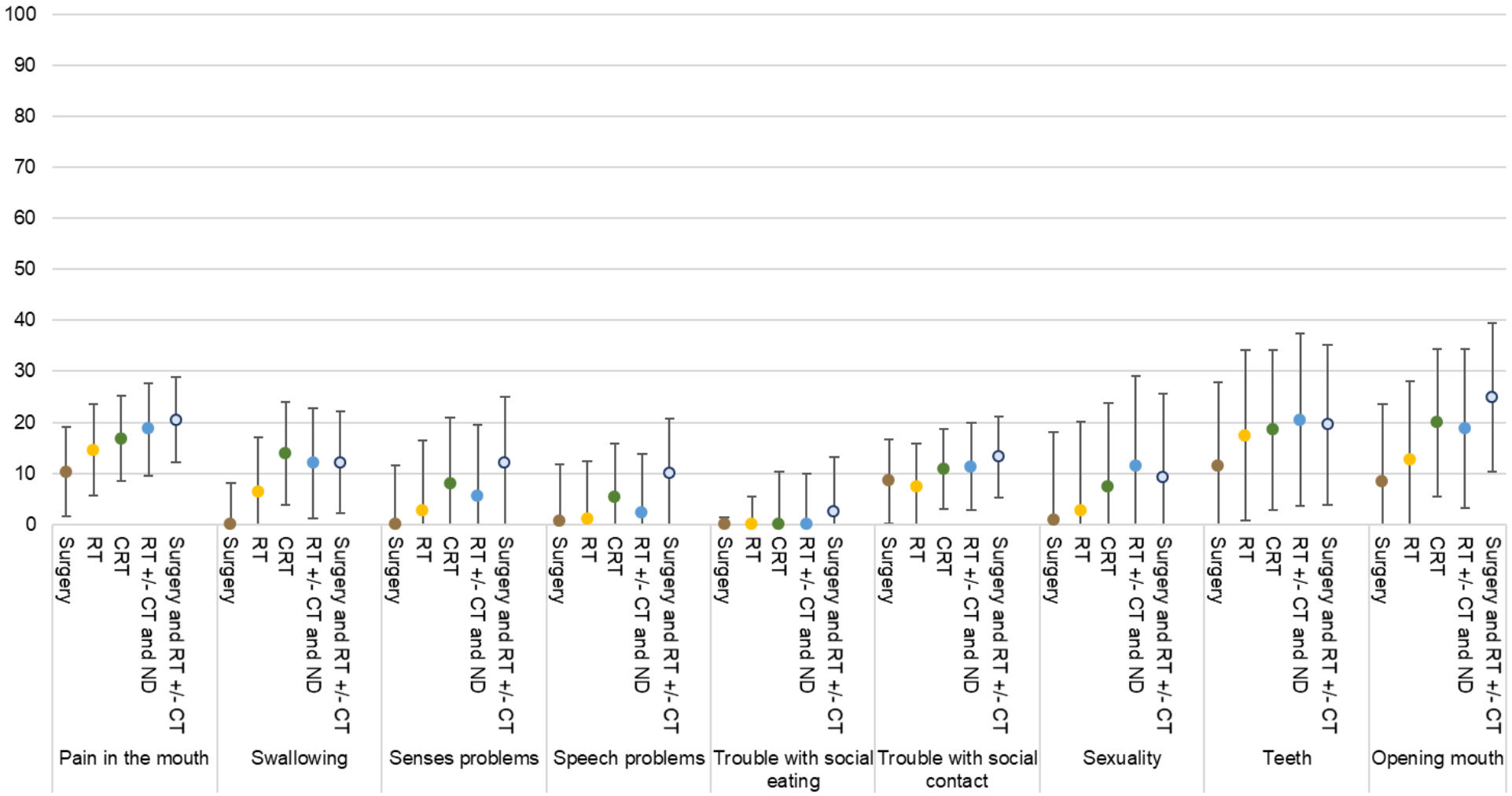

Figure 9 – Adjusted head and neck cancer-specific health-related quality of life outcomes according to the type of treatment received (part 1 of 2)

Notes: Data were collected using the EORTC QLQ-H&N35; QoL: quality of life; RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection
Data points indicate the mean score adjusted for sex, age, UICC stage and tumor sub-site. Lines indicate the 95% confidence interval.

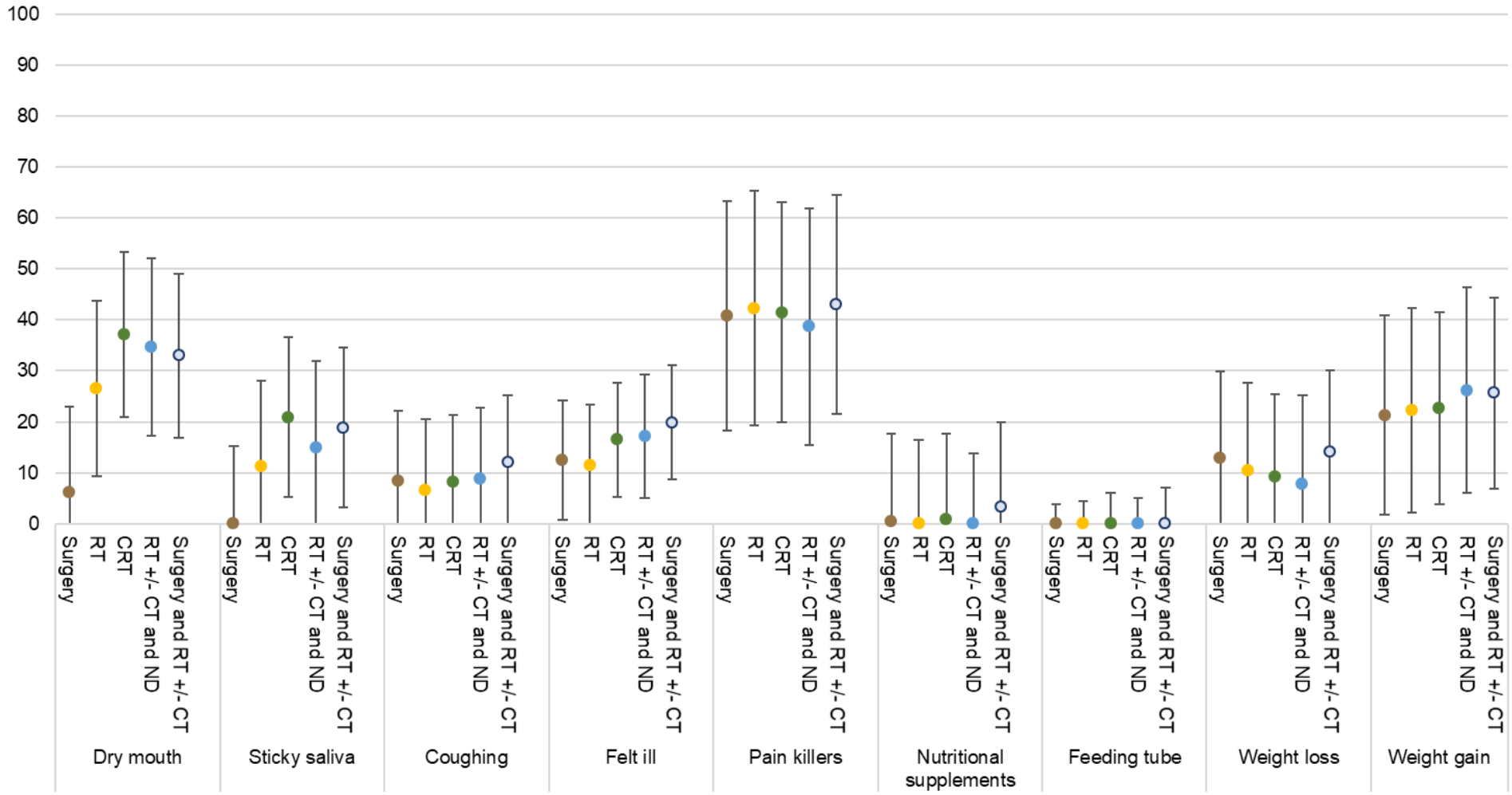

Figure 10 – Adjusted head and neck cancer-specific health-related quality of life outcomes according to the type of treatment received (part 2 of 2)

Notes: Data were collected using the EORTC QLQ-H&N35. QoL: quality of life; RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection
Data points indicate the mean score adjusted for sex, age, UICC stage and tumor sub-site. Lines indicate the 95% confidence interval.

Some of the adjusted mean differences between the treatment groups of ten or more points had weak evidence for statistical significance. For *insomnia* and *sexuality*, each domain had one difference of more than 10 points, but strong evidence that this was not due to chance was lacking (Table 10). The remaining seven domains each had at least one clinically relevant difference of ten points or more with an indication of strong statistical evidence.

There was strong evidence for clinically relevant differences for *fatigue, pain in the mouth, swallowing* and *senses problems* between the treatment groups (Table 10). For the *fatigue* scale, there was a clinically relevant difference for both surgery only and RT only versus 'surgery and RT +/- CT'. *Pain in the mouth* and *senses problems* each only had one clinically relevant difference, specifically between surgery and 'surgery and RT +/- CT' and surgery and 'RT +/- CT and ND', respectively. Differences in *swallowing* scores were found for surgery compared to RT only, 'RT +/- CT and ND', and 'surgery and RT +/- CT'.

Opening mouth, dry mouth and *sticky saliva* each had one clinically relevant difference lacking statistical evidence that the difference was not due to chance. For *opening mouth*, this difference was between surgery and 'RT +/- CT and ND' difference: 10.4, p=0.1), for *dry mouth* it was between RT and CRT (difference: 10.6, p=0.05), and for *sticky saliva* it was between surgery and RT (difference: 11.2, p=0.03) (Table 10). These three domains were also the domains with the largest number of differences.

Across all domains the largest differences were seen for *dry mouth*, with differences between 20.4 and 31.0 for comparisons between surgery only treatment and each of the other treatment groups. *Sticky saliva* had the second highest differences, again for multi-modal treatment groups compared to surgery only. The third largest symptom difference was seen for *opening mouth*, with clinically relevant differences with strong evidence of statistical significance ranging from 11.6 to 16.5.

Table 10 – Health-related quality of life scales with differences of ten points or more between treatment groups

HRQoL Scale	Treatment group comparison+	Difference in average scoreΔ	p-value (Tukey post-hoc test)
Fatigue	1 vs 5	11.2	<0.01
	2 vs 5	11.4	<0.01
Insomnia	1 vs 4	11.8	0.04
Pain in the mouth	1 vs 5	10.2	<0.01
Swallowing	1 vs 3	13.8	<0.01
	1 vs 4	12.0	<0.01
	1 vs 5	12.1	<0.01
Senses problems	1 vs 5	12.1	<0.01
Sexuality	1 vs 4	10.3	0.2
Opening mouth	1 vs 3	11.6	0.01
	1 vs 4	10.4	0.12
	1 vs 5	16.5	<0.01
	2 vs 5	12.3	<0.01
Dry mouth	1 vs 2	20.4	<0.01
	1 vs 3	31.0	<0.01
	1 vs 4	28.4	<0.01
	1 vs 5	26.8	<0.01
	2 vs 3	10.6	0.05
Sticky saliva	1 vs 2	11.2	0.03
	1 vs 3	20.9	<0.01
	1 vs 4	15.0	0.005
	1 vs 5	18.8	<0.01

+ Treatment group number explanations:
1: surgery only
2: radiotherapy only
3: chemo-radiotherapy
4: radiotherapy +/- chemotherapy and neck dissection
5: surgery and radiotherapy +/- chemotherapy

Δ The difference is between the adjusted means for the specified treatment group pair (adjusted for sex, age, UICC stage and tumor sub-site)

9.5. Toxicities by treatment group

For all survivors, dysphagia occurred the most frequently at a grade 2 or higher (24.2%), followed by dry mouth (23.9%), trismus (6.0%), and oral pain (3.4%) (Table 11). However, there were considerable differences in toxicity occurrence between the treatment groups (Table 11 and Figure 11). Among survivors who had been treated only surgically, 76.6% had no indications of dysphagia, whereas this was found for between 41.2% and 44.0% of survivors

who had had multi-therapy. Comparatively few of the survivors treated with surgery only and RT only had dysphagia at a grade 2 or higher, with respectively 9.7% and 11.9%.

Table 11 – Frequency of the severity of four toxicities by treatment group

		Surgery (n=124)		RT (n=134)		CRT (n=311)		RT +/- CT and ND (n=109)		Surgery and RT +/- CT (n=415)		Totals	
		n	%	n	%	n	%	n	%	n	%	n	%
Dysphagia	NP	95	76.6%	82	61.2%	128	41.2%	48	44.0%	177	42.7%	530	48.5%
	G1	17	13.7%	36	26.9%	91	29.3%	38	34.9%	109	26.3%	291	26.6%
	G2	12	9.7%	15	11.2%	80	25.7%	21	19.3%	106	25.5%	234	21.4%
	G3	0	0%	1	0.7%	10	3.2%	2	1.8%	18	4.3%	31	2.8%
	G4	0	0%	0	0%	0	0%	0	0%	0	0%	0	0.0%
	M	0	0%	0	0%	2	1%	0	0%	5	1.2%	7	0.6%
Dry Mouth	NP	78	62.9%	56	41.8%	72	23.2%	28	25.7%	125	30.1%	359	32.8%
	G1	43	34.7%	60	44.8%	153	49.2%	43	39.4%	171	41.2%	470	43.0%
	G2	3	2.4%	17	12.7%	80	25.7%	38	34.9%	110	26.5%	248	22.7%
	G3	0	0%	1	0.7%	4	1.3%	0	0%	8	1.9%	13	1.2%
	M	0	0%	0	0%	2	0.6%	0	0%	1	0.2%	3	0.3%
Trismus	NP	110	88.7%	124	92.5%	249	80.1%	92	84.4%	317	76.4%	892	81.6%
	G1	7	5.6%	8	6.0%	38	12.2%	10	9.2%	62	14.9%	125	11.4%
	G2	3	2.4%	0	0%	21	6.8%	6	5.5%	32	7.7%	62	5.7%
	G3	0	0%	0	0%	2	0.6%	0	0%	1	0.2%	3	0.3%
	M	4	3.2%	2	1.5%	1	0.3%	1	0.9%	3	0.7%	11	1.0%
Oral Pain	NP	106	85.5%	120	89.6%	274	88.1%	87	79.8%	327	78.8%	914	83.6%
	G1	12	9.7%	13	9.7%	25	8.0%	20	18.3%	67	16.1%	137	12.5%
	G2	4	3.2%	0	0%	12	3.9%	1	0.9%	18	4.3%	35	3.2%
	G3	0	0%	1	0.7%	0	0%	0	0%	1	0.2%	2	0.2%
	M	2	1.6%	0	0%	0	0%	1	0.9%	2	0.5%	5	0.5%

NP: Not present; G: Grade according to the CTCAE (version 5); M: Missing;
RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection

A similar relationship between the treatment modalities was found for dry mouth, with the multi-therapy treatments having between 27.0% and 34.9% grade 2 or worse dry mouth, compared to 2.4% among survivors treated only surgically and 13.4% among those who had received only RT. Respectively 62.9% and 41.8% of the survivors treated with surgery only and RT only had no indications of dry mouth, while this was true for between 23.2% and 30.1% of the multi-therapy groups (Table 11 and Figure 11).

The differences between the treatment groups are considerably less pronounced for trismus and oral pain. No indications of trismus were found for 76.4% to 92.5% of the survivors across all treatment modalities, and 0.0% to 7.9% had this problem at a grade 2 or higher. Oral pain severity levels were similarly distributed, with no indications of the problem for 79.8% to 89.6% of survivors across treatment modalities, while 0.7% to 4.5% had a severity of grade 2 or more.

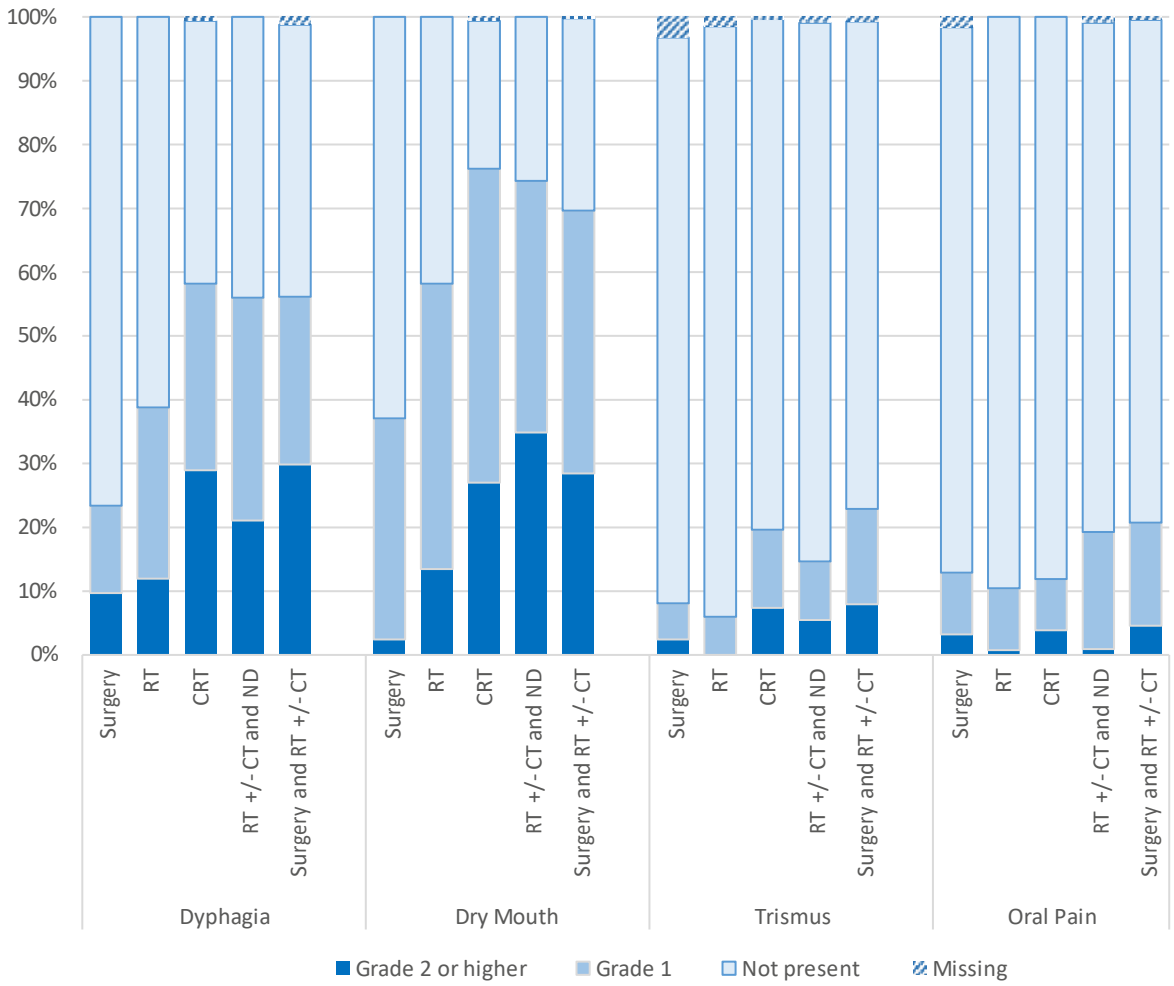

Figure 11 – Distribution of severity grades for four toxicities by treatment received
Grades are referring to the CTCAE Version 5; RT: radiotherapy; CT: chemotherapy; CRT: chemo radiotherapy; ND: neck dissection

9.6. Comparison of toxicities between treatment modalities

When adjusting for sex, age, UICC stage, and tumor sub-site, no strong evidence for a difference between the treatment groups was found for oral pain or trismus (Table 12 and Figure 12). However, the surgical treatment group had weak evidence of being more likely to be free of trismus or only have it at a CTCAE severity of 1 compared to survivors who had 'surgery and RT +/- CT' (OR: 3.7, 95% CI: 1.0-13.6). Of the 134 survivors treated with RT only, no one had trismus at a CTCEA severity of 2 or more.

Survivors who had only had surgery were considerably more likely to be free of dry mouth problems with dry mouth only have minor symptoms compared to survivors who had 'surgery and RT +/- CT' (OR: 15.4, 95% CI 4.6-51.7), but wide confidence interval indicates how imprecise this estimate is. There is some indication that survivors who had only RT are also more likely to be free of dry mouth than survivors who had had 'surgery and RT +/- CT' (OR: 1.9, 95% CI: 1.0-3.6).

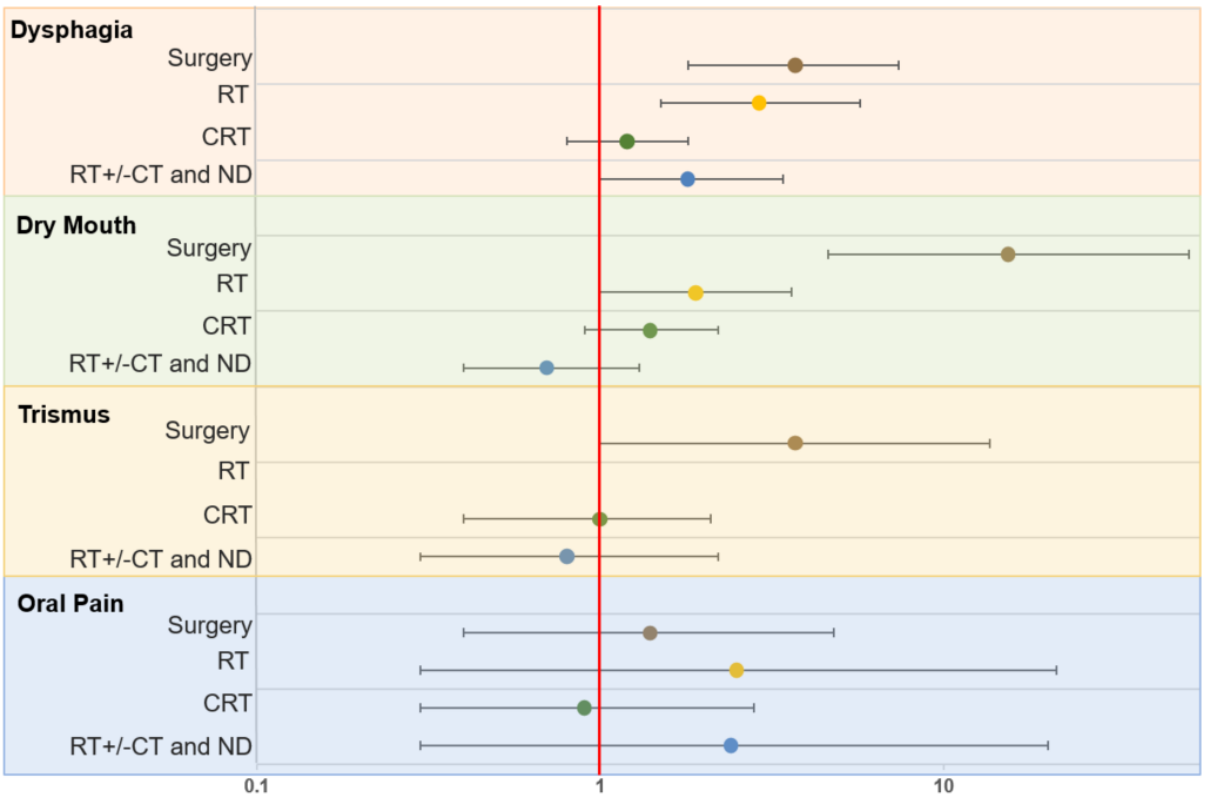

Figure 12 – Odds of being toxicity-free or having only mild symptoms for four toxicities by treatment

Notes: RT: Radiotherapy; CT: Chemotherapy; CRT: Chemo-radiotherapy; ND: Neck dissection; CI: confidence interval;
Reference group is 'surgery and RT +/- CT';
Odds are of being free of the toxicity or having it only at a CTCEA severity of 1 (mild symptoms);
The red line indicates the point at which the odds are the same between the specific treatment group and the 'Surgery and RT +/- CT' treatment group.
X-axis is the log scale.

In terms of dysphagia, survivors in the surgery only treatment group (OR: 3.7, 95% CI: 1.8-7.4) and the RT treatment group (OR: 2.9, 95% CI: 1.5-5.7) were more likely than those in the 'surgery and RT +/- CT' group to be free of dysphagia or only have it at a CTCEA severity of 1 compared to survivors who had had 'surgery and RT +/- CT'. Weak evidence was found indicating that survivors who had 'RT +/- CT and ND' more likely than those in the 'surgery and RT +/- CT' to be free of dysphagia or only have mild symptoms (OR: 1.8, 95% CI: 1.0-3.4).

Table 12 – Odds of being toxicity-free or having only mild symptoms for four toxicities by treatment

Toxicity	Treatment	Odds Ratio (95%CI)
Oral Pain	RT +/- CT and ND	2.4 (0.3-20.1)
	CRT	0.9 (0.3-2.8)
	RT	2.5 (0.3-21.3)
	Surgery	1.4 (0.4-4.8)
Trismus	RT +/- CT and ND	0.8 (0.3-2.2)
	CRT	1.0 (0.4-2.1)
	RT	-
	Surgery	3.7 (1.0-13.6)
Dry Mouth	RT +/- CT and ND	0.7 (0.4-1.3)
	CRT	1.4 (0.9-2.2)
	RT	1.9 (1.0-3.6)
	Surgery	15.4 (4.6-51.7)
Dysphagia	RT +/- CT and ND	1.8 (1.0-3.4)
	CRT	1.2 (0.8-1.8)
	RT	2.9 (1.5-5.7)
	Surgery	3.7 (1.8-7.4)

Notes: RT: radiotherapy; CT: chemotherapy; CRT: chemo-radiotherapy; ND: neck dissection; CI: confidence interval;
Reference group is 'surgery and RT +/- CT';
Odds are of being free of the toxicity or having it only at a CTCEA severity of 1 (mild symptoms);

In summary, the main differences were found for survivors who had received only surgery and only RT treatment for dry mouth and dysphagia toxicities, whereby these survivors were more likely to be free of these problems or only have minor symptoms compared to survivors who had been treated with multimodal therapies.

10. Discussion

This analysis investigated differences in HRQoL outcomes and physician-assessed toxicities in HNC survivors who were at least five years post-diagnosis. Significant, clinically meaningful differences in long-term survivors of head and neck cancer in light of the treatment received were found for seven HRQoL scales. Differences were also found for two of the four clinician-assessed toxicities analyzed. Where differences were found at this late assessment time point, even after controlling for sex, age, UICC stage and diagnosis group, survivors who had undergone mono-therapy treatment had better outcomes than survivors who had had multi-therapy treatments, a finding that other researchers have also reported.[127] Outcomes were particularly better for survivors who had been treated only with surgery.

Good “apples to apples” comparisons with the literature are difficult, in part because studies extending beyond five years post diagnosis are not common but also because only unadjusted results may have been reported, the reported results are based on study participants with mixed treatment regimes, the number of study participants is very small or a combination of all three. Even when studies report outcomes grouped by treatment, the grouping of treatments may be different to the treatment groups in our study. Most of the studies discussed below reported results specific to a tumor sub-site. Nevertheless, some context for and comparisons to our findings can be gained from the literature.

10.1. Health-related quality of life in long-term head and neck cancer survivors

10.1.1. Dry mouth

The largest HRQoL differences between survivors who had undergone different treatment regimes in our study were found for *dry mouth,* with the greatest difference between survivors who had had surgery only versus CRT. Tsai et al. investigated 242 survivors of nasopharynx cancer at five to 13 years after treatment, and 66% has received CRT and 34% RT.[91] The authors reported an unadjusted mean score for dry mouth of 48 (SD: 31), which is similar to our unadjusted mean score among the survivors treated with CRT. The survivors in our study treated with RT also had a high dry mouth burden, including in the adjust models, and it would seem that the survivors treated with RT in Tsai study also had a considerable burden given that the study’s over mean finding. Tsai’s study collective was entirely nasopharynx cancer survivors in contrast to our mixed HNC diagnoses, suggesting that this diagnosis may play less of a role in dry mouth than the treatment given. Aghajanzadeh et al.’s examination of survivors with mixed HNC diagnoses at five years post treatment showed a high dry mouth burden, with means of 67 (95%CI 56-78) among survivors with diagnosed trismus and 52 (95%CI 45-59) among survivors with no trismus.[65] These findings are higher than both the unadjusted scores and adjusted scores found in our analysis and quite a bit higher than the adjusted results. The 129 survivors included in this Swedish study who completed the five-year follow-up were predominantly oropharynx cancer and oral cavity cancer survivors (77%), had received a mix of treatments (with 84% having had multi-modal treatment - no one had surgery only), and 69% had a stage III or IV tumor at diagnosis. Our survivor collective had 56% oropharynx and oral cavity cancer survivors, approximately the same proportion of multi-modal treatment, and 58% stage III and IV tumors. This provides evidence that oropharynx and oral cavity diagnoses may be associated with a greater dry mouth burden in the long-term, but the difference in tumor size distribution between the studies may be more important, given that there were similar proportions of multimodal treatment. A greater tumor size may require more aggressive levels treatment, leading to more toxicities.

In a retrospective chart review of 164 oropharynx survivors, Ranta et al. concluded that there were no significant treatment-related *dry mouth* differences between single modality and multi-modality treatment groups using the EORTC QLQ-H&N35, with respective median scores of 66.7 and 33.3.[127] However, these seem like unusual median values given that the article also reports mean values between 80 and 90 for dry mouth these treatment groups, which is considerably higher than our findings. On the other hand, over 90% of study participants had had multi-modal therapy, so perhaps the effect on dry mouth was more drastic. However, it is possible the authors miscalculated the scores. Despite the author's not concluding significant differences for dry mouth between the monotherapy and multimodal therapy groups, wherever differences were identified in other scales, the survivors in the monotherapy group were doing better.

Data from 2013 on 26 survivors of oral cavity and oropharynx cancer reported a high *dry mouth* burden (mean score of 46) at eight to 11 years post-diagnosis, which is in line with our unadjusted findings.[64] No information on the treatment distribution is reported, but these survivors had received a mix of surgery and surgery with adjuvant RT.[64] Abendstein and colleagues reported an unadjusted mean *dry mouth* score of 48 among 167 HNC survivors at five years post-diagnosis, 55% of whom had had only surgery or only RT.[66] Similarly, Nordgren et al. published data from Sweden and Norway reporting unadjusted mean *dry mouth* scores of 49 among 59 long-term oral cavity cancer survivors, 66 among 36 long-term pharyngeal cancer survivors, and 41 among 46 long-term survivors or laryngeal cancer.[58–60] The *dry mouth* outcomes for the oral cavity cancer survivors were also reported by treatment, with surgery only having the least burden (a mean of approximately 24) while the RT only and multi-modal treatment groups had considerably higher burden (mean scores of approximately 60).[58] Neither the adjusted means nor the unadjusted means in our analysis showed such an equality of dry mouth problems between RT only and the multi-modal groups. Possible reasons for this is the considerable difference in the distribution of tumor size between the survivors treated with RT in their study and ours; Nordgren et al.'s study had 73% with stage III and IV tumors treated with RT, whereas only 24% of survivors treated with RT in the Late Tox Study had this stage. As well, the technology of radiotherapy has improved between the times the survivors in their study and our study were treated.[128] Also supporting our results, *dry mouth* represented the symptom with the greatest burden among the survivors reported in the literature cited here.

A study from the United Kingdom examining HRQoL at five to ten years post-treatment among 38 oral cavity and oropharynx cancer survivors treated with primary surgery reported that 40% of survivors reported having *dry mouth* "quite a bit" or "very much".[90] The authors used 30 of the questions from the EORTC QLQ-H&N35 but did not calculate scores for the domains. Nevertheless, given that the majority reported no problems or little problems with dry mouth, it is likely the calculated mean score would not have been notably high. Most these survivors

had been treated with surgery only, which would be in line with our findings of low dry mouth burden in survivors who had had only surgery.

Our study found considerably less dry mouth burden among survivors of mixed HNC treated with RT or adjuvant RT than a Taiwanese study on 640 survivors of mixed HNC.[93] At a mean of 48 (SD: 31), their higher average dry mouth burden may be due to the higher tumor burden in their survivors treated with RT, with 67% stage III and IV tumors. These survivors may have received a higher dose of RT than the survivors in our study. Supporting the evidence that radiation treatment is associated with long-term dry mouth problems is also found in a Dutch study on 39 survivors of mixed HNCs assessed at a mean of 9.6 years after treatment.[89] The authors used a self-designed questionnaire and concluded that 64% of survivors still experienced moderate to severe permanent dry mouth.

Published population norm data for the EORTC QLQ-H&N35 report mean values of 12.0 (SD: 22.6) for *dry mouth,* meaning that survivors with surgery only in our study had a similar *dry mouth* symptom burden to that of the general public, in both the unadjusted and adjusted models, while the other treatment groups had a considerably greater burden.[74]

10.1.2. Sticky saliva

Our analysis showed that the treatment-specific burden for *sticky saliva* was lowest for the survivors treated with surgery only and the highest for those treatment with CRT. As in our analysis, the published literature shows that long-term sticky saliva problems are less burdensome than problems with dry mouth, but are still a considerable problem. Unadjusted mean sticky saliva scores among the 129 five-year survivors examined by Aghajanzedeh et al. ranged from 63 (95%CI 43-82) among survivors with trismus to 39 (95%CI 31-46) among survivors without trismus, which are higher than our results.[65] This could be due to the higher distribution of tumor size in their study. Oskam et al.'s small collective of 27 oral cavity and oropharynx cancer survivors reported an unadjusted mean of 42 for sticky saliva among survivors at eight to 11 years post-treatment, while Nordgren et al.'s three studies focusing on specific cancer sub-sites reported similar means of 33 and 34 respectively for survivors of oral cavity cancer and larynx cancer, and a considerably higher mean of 47 for survivors of pharynx cancer [58–60,64]. This notably higher unadjusted mean score of 47 compared to our highest mean finding could be related to the fact that 84% of the pharynx cancer survivors in Nordgren et al.'s study had stage III or IV disease, whereas in our analysis this percentage was 61%, or perhaps the treatment group compositions are too different to produce a similar result: 38% the pharynx study survivors had mono-therapy compared to 24% in tour study.

In a long term study on 30 survivors who had primarily been diagnosed at an early stage treated with surgery only, sticky saliva function at eight years post-treatment was found to be similar to functioning at diagnosis.[87]

An estimated of sticky saliva score from a Swedish general population reported a mean of 5.9 (SD: 16.5), which is within range of the adjusted scores in our analysis for the surgery only and RT only treatment groups.[74] However, it is considerably lower than our unadjusted scores, particularly for the treatment groups other than surgery alone, which is only 8 points higher. This could mean that the sticky saliva burden experienced by long-term survivors of HNC after mono-surgery treatment could be due to factors unrelated to the surgical treatment.

10.1.3. Opening mouth

Our analysis found the third largest single difference between treatment groups for *opening mouth*. The adjusted scores did not differ much compared to unadjusted, implying that the effect of sex, age, UICC stage and diagnosis group was not particularly strong for this outcome, which was not the case for *dry mouth* and *sticky saliva*. Long-term results in the literature show remarkable differences. Leung et al.'s cross-sectional evaluation of HNC survivors at a minimum of two years after treatment on average reported a higher degree of *opening mouth* problems compared to all our treatment groups (mean: 33, SD: 32).[93] At least 46% of these survivors had had multi-modal therapy and it is not clear if any had only monotherapy therapy treatment. This study population was also comprised of nearly 50% nasopharynx cancer survivors, which was a much smaller proportion of our study population and could be an explanation for the higher burden found. Oskam et al.'s long-term assessment point at 8 to 11 years after diagnosis found even greater average difficulties in opening mouth (mean: 41).[64] Their population was predominately oropharynx cancer at the start of their study, but information on the diagnosis and treatment composition of the long-term survivors was not reported. What was reported is the 77% of the 27 survivors had tumors stages III or IV at diagnosis, which is more than our study population and could be a reason for our lower symptom burden. An older study by Rogers et al. that also included oropharynx and oral cavity cancer survivors found 83% of survivors reported having troubles opening their mouth wide not at all or only a little.[90] This study did not convert the answers to the QLQ-H&N35 into scores, but it seems this population had quite a low burden.

A considerably low mean result of 8 was reported by Nordgren et al. at five years in 2003, which is similar to the low burden found by our unadjusted mean findings of 8 and 13 for the surgery and RT treatment groups.[60] The similarity could be because 85% of the larynx survivor collective had only had RT. Much higher scores were more recently reported for a survivor collective with mixed diagnoses and predominantly multi-modal treatment, with unadjusted mean scores of 48 for survivors with clinically diagnosed trismus and 13 for those without a

trismus diagnosis.[65] Clinical trismus was defined as a maximum difference of ≤ 35 mm between the upper and lower incisors and three time points. Given the purposeful separation of the survivors in this regard, it is surprising the mean opening mouth score for the survivors with trismus was not even higher. Perhaps this is an indication that survivors with trismus learn to manage the symptom and are better able to cope. The two other publications by Nordgren et al. report similar mean results of 27 and 28 for long-term oral cavity/oropharynx cancer survivors and pharynx cancer survivors, respectively, which are slightly higher than our results for the survivors with multi-modal treatment but not remarkably so.[58,59]

Our study provides evidence that long-term HNC survivors who had surgery alone on average experience problems opening their mouths to an extent approaching the low level reported by a general population, while other treatment groups tend to experience this symptom at a greater burden.

10.1.4. Swallowing

Our adjusted mean scores for the surgery and RT groups showed low problems with *swallowing*, while the multi-modal treatment groups were higher, but not dramatically so. Nevertheless, the symptom burden among multi-model treatment groups in particular was notably greater than what can be expected in a non-cancer population, indicating that some survivors are struggling with swallowing in the long term.[74] A mean *swallowing* score of 7 was reported by the 53 long-term survivors of larynx cancer reported by Nordgren et al., most of whom had RT only, which is not far off our mean findings for the RT only group.[60] Abendstein et al.'s mix of HNC long-term survivors, most of whom had been treated with mono-therapy, reported a mean *swallowing* score of 14, which is slightly more than the burden found in our study for survivors treated with RT or surgery only.[66] Perhaps the somewhat greater burden was found because 45% of the study population had multi-modal therapy. A study with a similar distribution of treatments but only including oral cavity cancer survivors also reported an unadjusted mean swallowing of 13.[58] Other examples of long-term *swallowing* burden reported in the literature indicate a greater problems with this. One of the highest long-term *swallowing* scores was reported for 36 survivors of pharynx cancer, with an unadjusted mean of 27.[59] This is out of range of the unadjusted and adjusted confidence intervals for the highest scores among the CRT group found in our analysis, but 84% of the patients first enrolled at diagnosis in the pharynx cancer article had stage III and IV tumors, whereas our study had 61%. A larger study that also found a higher burden for swallowing reported a mean burden of 30 (SD: 21), but this population also mostly comprised cancers of the pharynx and 67% had stage III or IV tumors at diagnosis.[93] It is possible the larger tumor size required more aggressive treatment, resulting in increased swallowing problems compared to our study, or perhaps the key function

of the pharynx in swallowing and the effect of a having a tumor of any size there is the underlying reason for greater swallowing burden.

A 2017 study by Yan et al. on oral cavity cancer survivors using the UQ-QoL reported very good swallowing function.[87] Their study population was 70% surgical monotherapy, which supports our finding of low problems swallowing in our surgery only group. Interesting, the study did not include any pharynx cancer survivors and the majority of the long-term survivor population at stage I and II tumors at diagnosis. Rogers et al. also reported good swallowing functioning among oral cavity and oropharynx cancer survivors at five to 10 years after treatment.[90]

Our study provides evidence that long-term HNC survivors who had been treated with multi-modal treatment are still experiencing noticeable difficulties with swallowing on average.

10.1.5. Senses problems

Our analysis showed minimal limitations among the survivors in this area, but again the survivors who had received multi-modal treatment had the highest burden. Aghajanzadeh et al.'s cohort of survivors reported higher unadjusted mean scores, particularly for the survivors with trismus (mean: 31; 95% CI: 22-40).[65] Sixty-two percent of the survivors in the Aghajanzadeh study had CRT, and at least some of the surgery treatment group also had CRT, meaning more survivors had CT than in our analysis. This is relevant because a range of chemotherapy drugs are known to be associated with altered sense of taste and to a lesser extent smell.[129] Leung et al.'s assessment of survivors of most pharynx cancer survivors also found notable difficulties with *senses* (mean: 27 (SD: 24) higher than any treatment group in our study.[93] Again, this could be related to the different tumor stage distribution, the dominance of nasopharynx cancer survivors in their study or the distribution of treatments. Other unadjusted mean scores reported in the literature are lower, and more in line with our results. The five year assessments among three Swedish-Norwegian studies on pharynx cancer survivors at (mean: 24), oral cavity survivors (mean: 18), and larynx cancer survivors (mean: 13) are all mostly in range of our findings.[58–60] However, these values show an increased burden compared to our findings for the surgery only group. Again it is difficult to draw comparisons between our findings with results from mixed treatment groups, but it is interesting that the lowest score of 13 was found among a population of survivors 85% of whom had been treated RT only, whereas the highest score of 24 reported was among 36 survivors of mixed HNCs of whom only 17% had had only RT.[65] This spread in light of treatments is also evident in our findings, with survivors who had monotherapy having fewer problems with *senses* than those who had multi-modal therapy. A recently published study specifically looking at problems with taste in the short term among 61 HNC patients treated with RT found that by the fourth week of treatment, 77% reported moderate or severe problems.[130] The survivors in our study

who had had RT only reported a low symptom burden for smell and taste, suggesting it is possible that taste problems may improve or disappear eventually or that patients find the sensory problems less burdensome in the long-term even if still present.

Problems with senses in the general population have shown to be of a minimal burden, and our analysis shows that the association between treatment and *problem with senses* is most noticeable in the 'surgery and RT +/- CT' group, as all the other treatment groups had adjusted means that were similar to the general population example.[74]

10.1.6. Pain

The results in this analysis showed that survivors in the surgery only group reported a clinically meaningfully smaller burden concerning *pain in the mouth* compared to survivors who had undergone 'surgery and RT +/- CT'. As well, the RT only treatment group had lower scores than the multi-modal groups. A cohort of larynx cancer survivors, 85% of whom had been treated with RT only, reported one of the lowest burdens of long-term *mouth pain*, with an unadjusted mean of 4.[60] Interestingly, a mean of 3.4 (SD: 9.3) was also reported by a general population sample,[74] suggesting that larynx cancer survivors treated by RT may not have a significant problem with long-term *oral pain*. Our survivor collective was only 19% larynx cancer survivors, which was the third largest group after oropharynx and oral cavity cancer. Oskam's long-term follow-up of 27 oropharynx and oral cavity cancer survivors found a considerably higher burden for *oral pain* at 8-11 years post treatment (mean: 25). The role of tumor stage could be the reasons for this difference, with 77% had were stage III or IV at diagnosis.[64] A similar score was reported among long-term HNC survivors with trismus at five years post treatment.[65] Unadjusted scores among cohorts of oral cavity and pharynx cancer survivors, each of which had a greater than 50% proportion of multi-modal treatment, were similar to our results [58,59].

Although our results showed some differences between treatment groups, there was no meaningful differences in the reported n*eed for pain medication* between the groups. Although there may be a difference in the *pain* burden between the treatment groups, the overall *pain* burden appears to be quite low compared to the symptoms discussed so far.

10.1.7. Fatigue

In both unadjusted and adjusted models, our analysis showed that the surgery only and RT only groups had a lower *fatigue* burden compared to the 'surgery and RT +/- CT' group. As well, the maximum difference in the treatment scores between the unadjusted and adjusted models for *fatigue* was very small, meaning that adjusting for sex, age, UICC stage, and diagnosis group did change results much. Long-term *fatigue* burden reported in the literature

is largely uniform and corresponds particularly well to the multi-modal treatment scores in our analysis. For example, long-term mean unadjusted *fatigue* burden in eight studies only ranged between 25 and 31, based on a mix of cancer types and treatments [58–60,64,66,90–92]. This range is comparable to the both the unadjusted and adjusted means in our analysis for the multi-modal treatments and is not much higher than the monotherapy results. The study that examined long-term HNC survivors in light of the presence of trismus reported a notably higher *fatigue* burden for the survivors with trismus at five years post-treatment (mean: 37; 95%CI: 23-50).[65]

None of the mean scores in this analysis nor those reported here from the literature fall above the threshold of clinical relevance as defined by Giesinger et al., which is 39.[131] This is a suggested cut off below which clinical intervention should be considered for *fatigue*. Nolte et al. reported population means for the QLQ-C30 domains in a large international cohort of 15,386 members of the general population in 11 countries.[54] Notably, the mean result for *fatigue* was 30 (SD: 26), meaning that the Late Tox survivor population with multi-modal treatment reported a similar *fatigue* burden as a general population sample on average. Given this, the relative uniformity in the long-term literature, the similarity between the adjusted and unadjusted results in our analysis, as well the scores found in the general population, it seems that *fatigue* is not a long-term outcome particularly associated with treatment.

10.1.8. Other HRQoL Domains

The results for HRQoL domains where no differences were found between treatment groups are also of interest. Across all treatment groups, all functional outcomes in adjusted models were above the threshold for likely requiring clinically intervention, except for *emotional functioning,* which had mean adjusted values below Giesinger et al.'s suggested cut off of 71 for the multi-modal treatment groups and the surgery only group.[131] The functional outcomes were also similar or better than the population functional means estimated by Nolte et al., with the exception of the multi-modal treatment groups for *social functioning* (Nolte et al.'s population mean was 86.2 (SD:24.1) [54]. When our data are compared to the population means estimated by Hammerlid et al., the survivors in our study are functioning less well for *social functioning* and *emotional functioning* across all treatment groups.[74] Hammerlid et al.'s results are based on a Swedish population and the number of participants is only a tenth of the multi-national population included by Nolte, which could be a reason for the discrepancy. Overall, the long-term survivors seem to fare quite well in the functional domains, but the trend of having better scores in the mono-therapy groups compared to the multi-therapy is still present. *Social functioning* in our analysis was worse than the long-term *social functioning* reported by several long-term studies, including Nordgren et al.'s collective of oral cavity cancer survivors (mean: 81), Abendstein et al.'s study on a mix HNC population (mean: 82), and Oskam et al.'s

collective of oropharynx and oral cavity cancer survivors (mean: 77) [58,64,66]. This is particularly noticeable among the multi-therapy treatment groups, which could represent an opportunity where suitable interventions could be helpful.

Differences in *dyspnea* in unadjusted and adjusted models did not have notable differences in light of treatment group, but the adjusted models had considerably lower means, implying that the factors associated with *dyspnea* may not include treatment received. The adjusted results were similar to the long-term burden reported by Oskam et al. (mean: 6; SD: 4)), but notably different than the results reported by Nordren et al. (means of 19, 25, and 18), and Rogers et al. (mean: 24) which are more in line with our unadjusted results [58–60,64,90].

Sexuality did not have strong evidence for a clinically meaningful difference between the treatment groups, but the adjusted models showed a considerable down adjustment for all groups. This implies the associated factors for sexual problems may not include treatment. The burden of sexual problems found in our study was similar to unadjusted long-term problems in *sexuality* reported for a cohort of long-term survivors of oral cancer (mean: 29), but noticeably lower (fewer problems) than results reported for pharynx cancer survivors (mean: 44), and two mixed populations of HNC survivors (means: 37 and 38) [59,59,64,66]. Whether these differences are due to the type of cancer, a different mix of tumor stages or anomalies due to small sample sizes is not possible to know. A general population mean estimate measured in a Swedish population for this domain is 19, meaning that long-term HNC survivors may have similar problems with *sexuality* compared to the general population.

Financial difficulties results were notably high among all treatment groups, particularly in the adjusted models. Examples of *financial difficulties* scores in the literature show that problems may increase from baseline to six months later and 12 months later, but that by 24 months this is less of a problem for some survivors.[4,5,56] A low burden at five years of survivorship (mean: 12) was reported by Abendstein et al. in 2005 among a collective of survivors with mixed HNC sub-sites and treatments, and a more recent study reported mean of 17.6 among survivors with trismus.[65,66] The extent of long-term financial problems in HNC survivors and reasons behind them are not clear and would be a valuable topic to investigate further.

10.2. Toxicities in long term survivors

Our analysis found differences between the treatment groups in the odds of a HNC survivor having clinical signs of dysphagia or dry mouth as rated by a physician, but did not find differences for trismus and oral pain. Similar to some of the HRQoL results, the survivors who had been treated with surgery only were more likely to have little to no clinical problems with dysphagia or dry mouth.

Long-term studies on physician-rated toxicities in this survivor population where 'long term' is defined as five years or more post-diagnosis are rare, as demonstrated by a literature review which included only three articles.[117] One example included only nasopharynx cancer survivors (n=242) who were between five and 13 years post-diagnosis. The authors reported that 40.5% had dysphagia and 55.8% had dry mouth at a grade 2 or higher, both of which are considerably higher than our findings.[91] Most of the survivors in the nasopharynx study had received CRT (34% had only RT), but our CRT treatment group had proportionally fewer survivors with grade 2 or higher dysphagia (28.9%). Physician-confirmed dry mouth occurred for a considerably greater proportion of the nasopharynx cancer survivors than in our study as well, so it could be that nasopharynx cancer survivors are particularly prone to these toxicities. The nasopharynx cancer survivor study is a single center in Taiwan, so there could be something unique to treatment techniques or management of side effects there as well. A second study on late toxicities in 789 nasopharynx cancer patients and survivors from China did not assess dysphagia, but the occurrence of trismus was retrospectively examined and no cases of trismus were found higher than a grade 1.[119] This is in considerable contrast to the 7.4% of grade 2 or higher trismus events identified in our study among the CRT treatment groups. A possible reason for this difference could be the mix of sub-sites in our study versus the single diagnosis in the Chinese study, particularly because nasopharynx is so unique in HNC that it was not included in a recent European Clinical Practice Guideline for head and neck cancer.[13] Therefore nasopharynx comparisons to other HNC sites may not be suitable. However, the proximity of a nasopharynx tumor to the muscles involved in opening one's mouth would imply that the Chinese study could be expected to find more trismus than in a survivor group with mixed diagnoses. Differences could also be due to the nature of retrospective studies, which are prone to information bias.

A retrospective study reporting toxicities in 57 HNC survivors with eight or more years follow-up using the Late Effects of Normal Tissues (LENT) - Subjective, Objective, Management, and Analytic (SOMA) grading system[132] found that the proportion of survivors with grade 2 and 3 dysphagia was greater at five to eight years after diagnosis compared to the years before.[133] At eight years follow-up 14% had dysphagia at grade 2 or 3, which is less than our findings. This could be due to differences in the grading systems, with the CTAEA grades for this outcome being milder. For example, grade 1 dysphagia according to the CTCAE entails being symptomatic but still being able to eat a regular diet, whereas the subjective grade 1 description of dysphagia in the LENT-SOMA schema means difficulty eating solid food. The authors also concluded that the survivors had decreasing dry mouth severity over the follow-up time, but that the prevalence remains high in the long-term, with 20% having grade 2 dry mouth after eight years. This is a similar proportion as our study. These findings underline the

importance of studies on long-term survivors, as the survivor's experience in the long-term may be different than the years immediately after treatment.

10.3. Strengths

One of the main strengths of our study is the large number of participating survivors. To our knowledge, this is the largest examination of outcomes at five years survival and beyond. This analysis also has representation from 11 countries, increasing the diversity of the survivors. The use of well-established, validated questionnaires increases the validity of the results and will allow future studies to compare results to our findings. This study has added substantial HRQoL and toxicity information for HNC survivors on what can be expected in the long-term and an indication of differences depending on treatment received.

10.4. Limitations

There are several limitations to this analysis. Defining treatments groups is inherently difficult due to the complex nature of treatment and our treatment groups are broadly defined. Information about the order of treatments was not collected, nor whether survivors in the 'surgery and RT +/- CT' group were primary surgery patients with adjuvant therapy or were primary radiotherapy patients with subsequent surgery. This would have an implications for the dosage of radiation received, as primary radiation patients are treated at a higher dose than adjuvant radiotherapy patients, and higher radiation doses are known to cause more side effects than lower.[100] We have no information about the radiation dose administered and therefore are not able to make any conclusions about how higher or lower RT doses affect HRQoL in the long-term.

The cross-section design of the study means drawing conclusions of causality is not possible. Future studies that include oropharynx cancer patients or survivors would be wise to collect HPV status and consider analyzing HPV+ oropharyngeal cancer as a separate entity from HPV- oropharyngeal cancer. We did not collect HPV status information in our study because the survivors in our study were diagnosed at time when HPV was not as common.

This study likely suffers from healthy survivor bias, in particular because a physical clinical examination was necessary for participation. It is likely, and indeed is known to have occurred, that survivors who are not healthy enough to make an extra trip to the hospital were not included in the study. Therefore the frequency of toxicities may be under reported and the HRQoL data may be missing input from survivors who are not doing as well. Therefore our estimates may be biased towards optimistic outcomes. At some sites, such as in Portugal, the survivors were enrolled as part of routine long-term check-ups, but in most sites, the clinical

visit entailed an extra visit to the hospital to participate. We were not able to calculate an accurate overall response proportion due to missing information on the number of eligible survivors contacted, and some sites were not allowed to state even basic demographic information about any survivors who refused to participate. Future studies should consider mechanisms to reach the survivors who are most struggling in order to gain a full picture of HNC survivorship. It is also possible that the questionnaires used have missed assessing issues that are important to cancer survivors, such as health distress and positive and negative health outlooks, all three of which have been included in the EORTC QLQ-SURV100 Survivorship module,[134] and skin and shoulder problems, which have been included in the updated version of the EORTC HNC module.[50]

This study considered a ten-point or greater difference in a HRQoL domain between treatment groups as being clinically relevant. It is important to consider that this is a broad rule of thumb that may not be ideal for all scales. Work on determining domain-specific minimal important differences has been done, but the work is complicated with no accepted gold standard for methodology.[135,136] Therefore the results of this study should be regarded as an indication of where differences are likely to be, but not necessarily an indication of the definitive magnitude of the differences.

11. Conclusion

This examination of the HRQoL and toxicity outcomes among a large group of long-term HNC survivors shows that survivors who had been treated with multimodal therapy had poorer outcomes on average than those who had been treated with monotherapy. Specifically, after adjustment for sex, age, tumor stage and sub-site, clinically meaningfully worse outcomes were found for *fatigue, mouth pain, swallowing, senses, opening mouth, dry mouth,* and *sticky saliva* among some comparisons between multimodal and monotherapy groups. For clinically assessed dysphagia and dry mouth, a similar picture emerged, with survivors who underwent monotherapy being more likely to be free of these problems (or only having them at a low severity) in the long-term compared to survivors who had multi-modal therapy. No differences were found between treatment groups for clinically assessed trismus and oral pain. Our conclusions on the specific problems experienced in the long term by HNC survivors could offer a starting point to inform patients on what they can expect in the long-term and how their treatment may impact their life as a survivor. As well clinicians could tailor specific follow-up programs, so that outcomes more likely to be present in certain treatment groups are more systemically assessed and support offered.

Given the range of aspects that can affect HRQoL and toxicity outcomes in HNC patients, including the specific diagnosis, the tumor stage, the nature and extent of the treatment and

the timing of the assessment, future studies could focus on more specific aspects, such as comprehensively examining outcomes for a specific tumor sub site or a specific treatment. As well, studies in this survivor group should consider ways to reach survivors who may not be willing to attend a clinical visit, perhaps by offering an alternative stream with no toxicity assessment so that least the HRQoL data could be collected or assessment via video conference, as a way to ensure that the voices of a complete cross-section of survivors are included. A complete picture of the HRQoL and symptoms experienced by these survivors will only increase in importance as treatments advance and evolve, and the expectation that a newly diagnosed patient will survive their disease continues to improve.

12. List of Abbreviations

2DRT: two dimensional radiotherapy

3DRT: three dimensional radiotherapy

ADL: activities of daily living

ASI: age standardized incidence

CCI: Charlson Comorbidity Index

CI: Confidence interval

CT: chemotherapy

CTCAE: Common Terminology Criteria for Adverse Events

CRT: chemoradiotherapy

EORTC: European Organisation for the Research and Treatment of Cancer

HAM: highest adjusted mean

HNC: Head and neck cancer

HRQoL: Health-related quality of life

IARC: International Agency for Research on Cancer

ICD-10: international classification of disease, tenth edition

IMRT: intensity modulated radiotherapy

LENT: Late Effects of Normal Tissues

mm: millimeters

MDASI: MD Anderson Symptom Inventory

MDASI-HN: MD Anderson Symptom Inventory Head and Neck module

NA: not assessed

ND: neck dissection

PROMs: patient-report outcome measures

QLG: Quality of life group

QoL: Quality of life

RT: radiotherapy

SAS: Statistical Analysis Software

SD: standard deviation

SOMA: Subjective, Objective, Management, and Analytic

UICC: Union for International Cancer Control

US: United States

UW-QoL: University of Washington Quality of Life Questionnaire

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14. References

1. Mascarella A, Morand G, Hier P, et al. Dealing with the Vicissitudes and Abject Consequences of Head and Neck Cancer: A Vital Role for Psycho-Oncology. *Curr Oncol*. 2022;29(9):6714-6723.
2. Chen SC. Oral Dysfunction in Patients With Head and Neck Cancer: A Systematic Review. *J Nurs Res JNR*. 2019;27(6):e58. doi:10.1097/jnr.0000000000000363
3. Loorents V, Rosell J, Salgado Willner H, Borjeson S. Health-related quality of life up to 1 year after radiotherapy in patients with head and neck cancer (HNC). *Springerplus*. 2016;5(1):669. doi:10.1186/s40064-016-2295-1
4. Scott SI, Kathrine Ø Madsen A, Rubek N, et al. Long-term quality of life & functional outcomes after treatment of oropharyngeal cancer. *Cancer Med*. 2021;10(2):483-495. doi:10.1002/cam4.3599
5. Verdonck-de Leeuw IM, Buffart LM, Heymans MW, et al. The course of health-related quality of life in head and neck cancer patients treated with chemoradiation: a prospective cohort study. *Radiother Oncol*. 2014;110(3):422-428. doi:10.1016/j.radonc.2014.01.002
6. Doran M, Semple C, Moorhead A, McCaughan E. A qualitative systematic review of the social eating and drinking experiences of patients following treatment for head and neck cancer. *Support Care Cancer*. 2021;29(9):4899-4909.
7. Gillison ML, Koch WM, Capone RB, et al. Evidence for a Causal Association Between Human Papillomavirus and a Subset of Head and Neck Cancers. *J Natl Cancer Inst*. 2000;92(9):709-720.
8. Jethwa AR, Khariwala SS. Tobacco-related carcinogenesis in head and neck cancer. *Cancer Metastasis Rev*. 2017;36(3):411-423. doi:10.1007/s10555-017-9689-6
9. Kawakita D, Matsuo K. Alcohol and head and neck cancer. *Cancer Metastasis Rev*. 2017;36(3):425-434. doi:10.1007/s10555-017-9690-0
10. Gupta B, Ariyawardana A, Johnson NW. Oral cancer in India continues in epidemic proportions: evidence base and policy initiatives. *Int Dent J*. 2013;63(1):12-25. doi:10.1111/j.1875-595x.2012.00131.x
11. Chow LQ. Head and Neck Cancer. *N Engl J Med*. 2020;382(1).
12. Barsouk A, Aluru JS, Rawla P, Saginala K, Barsouk A. Epidemiology, Risk Factors, and Prevention of Head and Neck Squamous Cell Carcinoma. *Med Sci*. 2023;11(42).
13. Machiels JP, René Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(11):1462-1475. doi:10.1016/j.annonc.2020.07.011
14. Hashim D, Genden E, Posner M, Hashibe M, Boffetta P. Head and neck cancer prevention: from primary prevention to impact of clinicians on reducing burden. *Ann Oncol*. 2019;30(5):744-756. doi:10.1093/annonc/mdz084
15. Verdonck-de Leeuw I, Dawson C, Licitra L, et al. European Head and Neck Society recommendations for head and neck cancer survivorship care. *Oral Oncol*. 2022;133:106047. doi:10.1016/j.oraloncology.2022.106047
16. Staffieri A, Sebastian P, Kapre M, Varghese BT, Kazi R. *Essentials of Head and Neck Cancer*. Byword Books Private Limited; 2012.
17. León X, Garciía J, López M, Rodrigiez C, Gutierrez A, Quer M. Risk of onset of second neoplasms and successive neoplasms in patients with a head and neck index tumour. *Acta Otorrinolaringol Esp Engl Ed*. 2020;71(1):9-15.

18. Beckham TH, Leeman JE, Xie P, et al. Long-term survival in patients with metastatic head and neck squamous cell carcinoma treated with metastasis-directed therapy. *Br J Cancer*. 2019;121(11):897-903. doi:10.1038/s41416-019-0601-8

19. Conway DI, Purkayastha M, Chestnutt IG. The changing epidemiology of oral cancer: definitions, trends, and risk factors. *Br Dent J*. 2018;225(9):867-873. doi:10.1038/sj.bdj.2018.922

20. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: An overview. *Int J Cancer*. Published online April 5, 2021. doi:10.1002/ijc.33588

21. Braakhuis BJM, Leemans CR, Visser O. Incidence and survival trends of head and neck squamous cell carcinoma in the Netherlands between 1989 and 2011. *Oral Oncol*. 2014;50(7):670-675. doi:10.1016/j.oraloncology.2014.03.008

22. *Krebs in Deutschland Für 2017/2018 [Cancer in Germany for 2017/2018]*. Robert Koch Institute (Editor) and the Association of the Epidemiologcal Cancer Registries in Germany (Editor); 2021.

23. Cancer in Norway 2018 - Cancer incidence, mortality, survival and prevalence in Norway. Published online 2019.

24. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-86. doi:10.1002/ijc.29210

25. Park JO, Nam IC, Kim CS, et al. Sex Differences in the Prevalence of Head and Neck Cancers: A 10-Year Follow-Up Study of 10 Million Healthy People. *Cancers*. 14(10).

26. Ferlay J, Ervik M, Colombet M, et al. *Global Cancer Observatory: Cancer Today*. International Agency for Research on Cancer; 2020. Accessed July 1, 2023. https://gco.iarc.fr/today

27. Bayer O, Krüger M, Koutsimpelas D, et al. [Changes in Incidence and Mortality Trends of Head and Neck Cancer in Rhineland-Palatinate, 2000-2009]. *Laryngorhinootologie*. 2015;94(7):451-458. doi:10.1055/s-0034-1390455

28. Lewis A, Kang R, Levine A, Maghami E. The New Face of Head and Neck Cancer: The HPV Epidemic. *Oncol Williston Park N*. 2015;29(9):616-626.

29. Veyer D, Wack M, Grard O, et al. HPV detection and genotyping of head and neck cancer biopsies by molecular testing with regard to the new oropharyngeal squamous cell carcinoma classification based on HPV status. *Pathology (Phila)*. 2019;51(4):421-425. doi:10.1016/j.pathol.2019.02.002

30. Mifsud M, Eskander A, Irish J, et al. Evolving trends in head and neck cancer epidemiology: Ontario, Canada 1993-2010. *Head Neck*. 2017;39(9):1770-1778. doi:10.1002/hed.24829

31. Young D, Xiao CC, Murphy B, Moore M, Fakhry C, Day TA. Increase in head and neck cancer in younger patients due to human papillomavirus (HPV). *Oral Oncol*. 2015;51(8):727-730. doi:10.1016/j.oraloncology.2015.03.015

32. Vokes EE, Agrawal N, Seiwert TY. HPV-Associated Head and Neck Cancer. *J Natl Cancer Inst*. 2015;107(12):djv344. doi:10.1093/jnci/djv344

33. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst*. 2008;100(4):261-269. doi:10.1093/jnci/djn011

34. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17-48. doi:10.3322/caac.21763

35. Pulte D, Brenner H. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. *Oncologist*. 2010;15(9):994-1001. doi:10.1634/theoncologist.2009-0289

36. Dittberner A, Friedl B, Wittig A, et al. Gender Disparities in Epidemiology, Treatment, and Outcome for Head and Neck Cancer in Germany: A Population-Based Long-Term Analysis from 1996 to 2016 of the Thuringian Cancer Registry. *Cancers*. 2020;12(11). doi:10.3390/cancers12113418

37. Ringash J. Survivorship and Quality of Life in Head and Neck Cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2015;33(29):3322-3327. doi:10.1200/JCO.2015.61.4115

38. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7-30. doi:10.3322/caac.21387

39. Bell K, Ristovski-Slijepcevic S. Cancer survivorship: why labels matter. *J Clin Oncol Off J Am Soc Clin Oncol*. 2013;31(4):409-411. doi:10.1200/JCO.2012.43.5891

40. Ganz PA. A Teachable Moment for Oncologists: Cancer Survivors, 10 Million Strong and Growing! *J Clin Oncol*. 23(24):5458-5460.

41. Rogers SN, Gwanne S, Lowe D, Humphris G, Yueh B, Weymuller EA. The addition of mood and anxiety domains to the University of Washington quality of life scale. *Head Neck*. 2002;24(6):521-529. doi:10.1002/hed.10106

42. Rogers SN, Lowe D, Yueh B, Weymuller EA. The physical function and social-emotional function subscales of the University of Washington Quality of Life Questionnaire. *Arch Otolaryngol Head Neck Surg*. 2010;136(4):352-357. doi:10.1001/archoto.2010.32

43. Hassan SJ, Weymuller EA Jr. Assessment of quality of life in head and neck cancer patients. *Head Neck*. 1993;15(6):485-496.

44. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer*. 2000;89(7):1634-1646. doi:10.1002/1097-0142(20001001)89:7<1634::aid-cncr29>3.0.co;2-v

45. Cleeland C. The M. D. Anderson Symptom Inventory User Guide. Accessed October 19, 2023. https://www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/MDASI_userguide.pdf

46. Rosenthal DI, Mendoza TR, Chambers MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. *Head Neck*. 2007;29(10):923-931. doi:10.1002/hed.20602

47. Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. *Arch Otolaryngol Head Neck Surg*. 2001;127(7):870-876.

48. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.

49. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. *J Clin Oncol Off J Am Soc Clin Oncol*. 1999;17(3):1008-1019. doi:10.1200/JCO.1999.17.3.1008

50. Singer S, Amdal CD, Hammerlid E, et al. International validation of the revised European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module, the EORTC QLQ-HN43: Phase IV. *Head Neck*. 2019;41(6):1725-1737. doi:10.1002/hed.25609

51. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139-144. doi:10.1200/jco.1998.16.1.139

52. Ellis MA, Sterba KR, Day TA, et al. Body Image Disturbance in Surgically Treated Head and Neck Cancer Patients: A Patient-Centered Approach. *Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg*. 2019;161(2):278-287. doi:10.1177/0194599819837621

53. So WKW, Chan RJ, Chan DNS, et al. Quality-of-life among head and neck cancer survivors at one year after treatment--a systematic review. *Eur J Cancer Oxf Engl 1990*. 2012;48(15):2391-2408. doi:10.1016/j.ejca.2012.04.005

54. Nolte S, Liegl G, Petersen MA, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. *Eur J Cancer*. 2019;107:153-163. doi:10.1016/j.ejca.2018.11.024

55. Tribius S, Raguse M, Voigt C, et al. Residual deficits in quality of life one year after intensity-modulated radiotherapy for patients with locally advanced head and neck cancer: Results of a prospective study. *Strahlenther Onkol*. 2015;191(6):501-510. doi:10.1007/s00066-015-0824-4

56. Roick J, Danker H, Dietz A, Papsdorf K, Singer S. Predictors of changes in quality of life in head and neck cancer patients: a prospective study over a 6-month period. *Eur Arch Otorhinolaryngol*. 2020;277(2):559-567. doi:10.1007/s00405-019-05695-z

57. Singer S, Danker H, Guntinas-Lichius O, et al. Quality of life before and after total laryngectomy: results of a multicenter prospective cohort study. *Head Neck*. 2014;36(3):359-368. doi:10.1002/hed.23305

58. Nordgren M, Hammerlid E, Bjordal K, Ahlner-Elmqvist M, Boysen M, Jannert M. Quality of life in oral carcinoma: a 5-year prospective study. *Head Neck*. 2008;30(4):461-470. doi:10.1002/hed.20735

59. Nordgren M, Jannert M, Boysen M, et al. Health-related quality of life in patients with pharyngeal carcinoma: a five-year follow-up. *Head Neck*. 2006;28(4):339-349. doi:10.1002/hed.20334

60. Nordgren M, Abendstein H, Jannert M, et al. Health-related quality of life five years after diagnosis of laryngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 2003;56(5):1333-1343.

61. Nallani R, Smith JB, Penn JP, et al. Decision regret 3 and 6 months after treatment for head and neck cancer: Observational study of associations with clinicodemographics, anxiety, and quality of life. *Head Neck*. 2022;44(1):59-70. doi:10.1002/hed.26911

62. Pateman KA, Cockburn NL, Batstone MD, Ford PJ. Quality of life of head and neck cancer patients in urban and regional areas: An Australian perspective. *Aust J Rural Health*. 2018;26(3):157-164. doi:10.1111/ajr.12340

63. Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer*. 2000;36(14):1796-1807.

64. Oskam IM, Verdonck-de Leeuw IM, Aaronson NK, et al. Prospective evaluation of health-related quality of life in long-term oral and oropharyngeal cancer survivors and the perceived need for supportive care. *Oral Oncol*. 2013;49(5):443-448. doi:10.1016/j.oraloncology.2012.12.005

65. Aghajanzadeh S, Karlsson T, Tuomi L, Engström M, Finizia C. Trismus, health-related quality of life, and trismus-related symptoms up to 5 years post-radiotherapy for head

and neck cancer treated between 2007 and 2012. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2023;31(3):166. doi:10.1007/s00520-023-07605-w

66. Abendstein H, Nordgren M, Boysen M, et al. Quality of life and head and neck cancer: a 5 year prospective study. *Laryngoscope*. 2005;115(12):2183-2192. doi:10.1097/01.Mlg.0000181507.69620.14
67. Infante-Cossio P, Torres-Carranza E, Cayuela A, Hens-Aumente E, Pastor-Gaitan P, Gutierrez-Perez JL. Impact of treatment on quality of life for oral and oropharyngeal carcinoma. *Int J Oral Maxillofac Surg*. 2009;38(10):1052-1058. doi:10.1016/j.ijom.2009.06.008
68. Iriya PM de O, Romaniszen LW, Fernandes TMF, Poleti ML. Health-related quality of life of patients with squamous cell carcinoma: a comparison according to tumor location. *Braz Oral Res*. 2017;31:e105. doi:10.1590/1807-3107BOR-2017.vol31.0105
69. Rathod S, Gupta T, Ghosh-Laskar S, Murthy V, Budrukkar A, Agarwal J. Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. *Oral Oncol*. 2013;49(6):634-642. doi:10.1016/j.oraloncology.2013.02.013
70. Al-Mamgani A, van Rooij P, Verduijn GM, Meeuwis CA, Levendag PC. Long-term outcomes and quality of life of 186 patients with primary parotid carcinoma treated with surgery and radiotherapy at the Daniel den Hoed Cancer Center. *Int J Radiat Oncol Biol Phys*. 2012;84(1):189-195. doi:10.1016/j.ijrobp.2011.11.045
71. Al-Mamgani A, Mehilal R, van Rooij PH, Tans L, Sewnaik A, Levendag PC. Toxicity, quality of life, and functional outcomes of 176 hypopharyngeal cancer patients treated by (chemo)radiation: the impact of treatment modality and radiation technique. *Laryngoscope*. 2012;122(8):1789-1795. doi:10.1002/lary.23387
72. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014;11(10):597-609. doi:10.1038/nrclinonc.2014.127
73. Servaes P, Verhagen C, Bleijenberg G. Fatigue in cancer patients during and after treatment: prevalence, correlates and interventions. *Eur J Cancer Oxf Engl 1990*. 2002;38(1):27-43. doi:10.1016/s0959-8049(01)00332-x
74. Hammerlid E, Adnan A, Silander E. Population-based reference values for the European Organization for Research and Treatment of Cancer Head and Neck module. *Head Neck*. 2017;39(10):2036-2047. doi:10.1002/hed.24870
75. Leemans M, Longobardi Y, Dirven R, et al. Improving Hands-Free Speech Rehabilitation in Laryngectomized Patients with a Moldable Adhesive. *The Laryngoscope*. 2023;133(11):2965-2970. doi:10.1002/lary.30636
76. Nayak SG, Sharan K, George A. Attributes of Psychosocial Distress from the Perspectives of Head-and-Neck Cancer Patients - A Thematic Analysis. *Indian J Palliat Care*. 2023;29(2):181-185. doi:10.25259/IJPC_185_2022
77. Rhoten BA. Head and Neck Cancer and Sexuality: A Review of the Literature. *Cancer Nurs*. 2016;39(4):313-320. doi:10.1097/NCC.0000000000000289
78. Stone MA, Lissenberg-Witte BI, de Bree R, et al. Changes in Sexuality and Sexual Dysfunction over Time in the First Two Years after Treatment of Head and Neck Cancer. *Cancers*. 2023;15(19):4755. doi:10.3390/cancers15194755
79. McDowell L, Gough K, Fua T, et al. A longitudinal study evaluating sexual health outcomes and prioritization in patients undergoing chemoradiation for human papillomavirus-associated oropharyngeal cancer. *Int J Radiat Oncol Biol Phys*. Published online October 19, 2023:S0360-3016(23)08013-6. doi:10.1016/j.ijrobp.2023.10.006

80. Singer S, Danker H, Dietz A, et al. Sexual problems after total or partial laryngectomy. *The Laryngoscope*. 2008;118(12):2218-2224. doi:10.1097/MLG.0b013e318182cdc6

81. Krebbers I, Pilz W, Vanbelle S, Verdonschot RJCG, Baijens LWJ. Affective Symptoms and Oropharyngeal Dysphagia in Head-and-Neck Cancer Patients: A Systematic Review. *Dysphagia*. 2023;38(1):127-144. doi:10.1007/s00455-022-10484-8

82. Hutcheson KA, Holsinger FC, Kupferman ME, Lewin JS. Functional outcomes after TORS for oropharyngeal cancer: a systematic review. *Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg*. 2015;272(2):463-471. doi:10.1007/s00405-014-2985-7

83. Scott SI, Madsen AKØ, Rubek N, et al. Dysphagia and QoL 3 Years After Treatment of Oropharyngeal Cancer With TORS or Radiotherapy. *The Laryngoscope*. 2023;133(8):1893-1898. doi:10.1002/lary.30410

84. Tamer R, Chen Y, Xu X, Xie C, Swai J. Short-Term Quality of Life, Functional Status, and Their Predictors in Tongue Cancer Patients After Anterolateral Thigh Free Flap Reconstruction: A Single-Center, Prospective, Comparative Study. *Cancer Manag Res*. 2020;12:11663-11673. doi:10.2147/CMAR.S268912

85. Ursino S, Calistri E, De Felice F, et al. Patient-Reported Outcomes After Swallowing (SWOARs)-Sparing IMRT in Head and Neck Cancers: Primary Results from a Prospective Study Endorsed by the Head and Neck Study Group (HNSG) of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). *Dysphagia*. 2023;38(1):159-170. doi:10.1007/s00455-022-10434-4

86. Taylor K, Singer S. [Long-term Quality of Life in Head and Neck Cancer Patients]. *Onkol*. 2019;25(3):253-261. doi:10.1007/s00761-019-0528-y

87. Yan YB, Meng L, Liu ZQ, et al. Quality of life in long-term oral cancer survivors: an 8-year prospective study in China. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;123(1):67-75. doi:10.1016/j.oooo.2016.09.006

88. Herce-Lopez J, Rollon-Mayordomo A, Lozano-Rosado R, Infante-Cossio P, Salazar-Fernandez CI. Assessment of quality of life of oral cancer survivors compared with Spanish population norms. *Int J Oral Maxillofac Surg*. 2013;42(4):446-452. doi:10.1016/j.ijom.2012.11.014

89. Wijers OB, Levendag PC, Braaksma MM, Boonzaaijer M, Visch LL, Schmitz PI. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. *Head Neck*. 2002;24(8):737-747. doi:10.1002/hed.10129

90. Rogers SN, Hannah L, Lowe D, Magennis P. Quality of life 5-10 years after primary surgery for oral and oro-pharyngeal cancer. *J Craniomaxillofac Surg*. 1999;27(3):187-191.

91. Tsai WL, Huang TL, Liao KC, et al. Impact of late toxicities on quality of life for survivors of nasopharyngeal carcinoma. *BMC Cancer*. 2014;14:856. doi:10.1186/1471-2407-14-856

92. Bjordal K, Kaasa S, Mastekaasa A. Quality of life in patients treated for head and neck cancer: a follow-up study 7 to 11 years after radiotherapy. *Int J Radiat Oncol Biol Phys*. 1994;28(4):847-856. doi:10.1016/0360-3016(94)90104-x

93. Wan Leung S, Lee TF, Chien CY, Chao PJ, Tsai WL, Fang FM. Health-related quality of life in 640 head and neck cancer survivors after radiotherapy using EORTC QLQ-C30 and QLQ-H&N35 questionnaires. *BMC Cancer*. 2011;11:128. doi:10.1186/1471-2407-11-128

94. Dohopolski MJ, Diao K, Hutcheson KA, et al. Long-term Patient-Reported Outcomes in a Population-Based Cohort Following Radiotherapy vs Surgery for Oropharyngeal Cancer. *JAMA Otolaryngol-- Head Neck Surg*. 2023;149(8):697-707. doi:10.1001/jamaoto.2023.1323

95. Gross MD, Al Hussein Al Awamlh B, Hu JC. Assessing Treatment-Related Toxicity Using Administrative Data, Patient-Reported Outcomes, or Physician-Graded Toxicity: Where Is the Truth? *Semin Radiat Oncol*. 2019;29(4):333-337. doi:10.1016/j.semradonc.2019.05.007

96. National Institute of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0*; 2017 Available online: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (accessed 16 November 2023)

97. Russi EG, Corvò R, Merlotti A, et al. Swallowing dysfunction in head and neck cancer patients treated by radiotherapy: review and recommendations of the supportive task group of the Italian Association of Radiation Oncology. *Cancer Treat Rev*. 2012;38(8):1033-1049. doi:10.1016/j.ctrv.2012.04.002

98. Moroney LB, Helios J, Ward EC, et al. Patterns of dysphagia and acute toxicities in patients with head and neck cancer undergoing helical IMRT±concurrent chemotherapy. *Oral Oncol*. 2017;64:1-8. doi:10.1016/j.oraloncology.2016.11.009

99. Jensen AD, Krauss J, Weichert W, et al. Disease control and functional outcome in three modern combined organ preserving regimens for locally advanced squamous cell carcinoma of the head and neck (SCCHN). *Radiat Oncol Lond Engl*. 2011;6:122. doi:10.1186/1748-717X-6-122

100. Palazzi M, Tomatis S, Orlandi E, et al. Effects of treatment intensification on acute local toxicity during radiotherapy for head and neck cancer: prospective observational study validating CTCAE, version 3.0, scoring system. *Int J Radiat Oncol Biol Phys*. 2008;70(2):330-337. doi:10.1016/j.ijrobp.2007.06.022

101. Christianen MEMC, Verdonck-de Leeuw IM, Doornaert P, et al. Patterns of long-term swallowing dysfunction after definitive radiotherapy or chemoradiation. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2015;117(1):139-144. doi:10.1016/j.radonc.2015.07.042

102. Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol*. 2008;26(21):3582-3589. doi:10.1200/JCO.2007.14.8841

103. Hutchison AR, Cartmill B, Wall LR, Ward EC. Dysphagia optimized radiotherapy to reduce swallowing dysfunction severity in patients undergoing treatment for head and neck cancer: A systematized scoping review. *Head Neck*. 2019;41(6):2024-2033. doi:10.1002/hed.25688

104. Springborg LK, Møller MN. Submandibular gland excision: long-term clinical outcome in 139 patients operated in a single institution. *Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg*. 2013;270(4):1441-1446. doi:10.1007/s00405-012-2175-4

105. Strojan P, Hutcheson KA, Eisbruch A, et al. Treatment of late sequelae after radiotherapy for head and neck cancer. *Cancer Treat Rev*. 2017;59:79-92. doi:10.1016/j.ctrv.2017.07.003

106. Shaw R, Beasley N. Aetiology and risk factors for head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. 2016;130(S2):S9-S12. doi:10.1017/S0022215116000360

107. Marta GN, Silva V, de Andrade Carvalho H, et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2014;110(1):9-15. doi:10.1016/j.radonc.2013.11.010

108. Teguh DN, Levendag PC, Voet P, et al. Trismus in patients with oropharyngeal cancer: relationship with dose in structures of mastication apparatus. *Head Neck*. 2008;30(5):622-630. doi:10.1002/hed.20760

109. Wranicz P, Herlofson BB, Evensen JF, Kongsgaard UE. Prevention and treatment of trismus in head and neck cancer: A case report and a systematic review of the literature. *Scand J Pain*. 2010;1(2):84-88. doi:10.1016/j.sjpain.2010.01.006

110. Zhang B, Mo Z, Du W, Wang Y, Liu L, Wei Y. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. *Oral Oncol*. 2015;51(11):1041-1046. doi:10.1016/j.oraloncology.2015.08.005

111. Faravel K, Jarlier M, Senesse P, et al. Trismus Occurrence and Link With Radiotherapy Doses in Head and Neck Cancer Patients Treated With Chemoradiotherapy. *Integr Cancer Ther*. 2023;22:15347354221147284. doi:10.1177/15347354221147283

112. Kamstra JI, Jager-Wittenaar H, Dijkstra PU, et al. Oral symptoms and functional outcome related to oral and oropharyngeal cancer. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2011;19(9):1327-1333. doi:10.1007/s00520-010-0952-4

113. Khawaja SN, Scrivani SJ. Head and Neck Cancer-Related Pain. *Dent Clin North Am*. 2023;67(1):129-140. doi:10.1016/j.cden.2022.07.010

114. Epstein JB, Elad S, Eliav E, Jurevic R, Benoliel R. Orofacial pain in cancer: part II--clinical perspectives and management. *J Dent Res*. 2007;86(6):506-518. doi:10.1177/154405910708600605

115. Mirabile A, Airoldi M, Ripamonti C, et al. Pain management in head and neck cancer patients undergoing chemo-radiotherapy: Clinical practical recommendations. *Crit Rev Oncol Hematol*. 2016;99:100-106. doi:10.1016/j.critrevonc.2015.11.010

116. Trotti A, Bellm LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2003;66(3):253-262. doi:10.1016/s0167-8140(02)00404-8

117. Taylor K, Krueger M, Singer S. [Long-term Toxicities among Head and Neck Cancer Patients – A Systematic Review]. *Onkol*. 2021;27(14).

118. Takiar V, Ma D, Garden AS, et al. Disease control and toxicity outcomes for T4 carcinoma of the nasopharynx treated with intensity-modulated radiotherapy. *Head Neck*. 2016;38 Suppl 1:E925-33. doi:10.1002/hed.24128

119. Zeng L, Tian YM, Sun XM, et al. Late toxicities after intensity-modulated radiotherapy for nasopharyngeal carcinoma: patient and treatment-related risk factors. *Br J Cancer*. 2014;110(1):49-54. doi:10.1038/bjc.2013.720

120. EORTC Quality of Life Group Website. Head and Neck Cancer Survivors Project. https://qol.eortc.org/projectqol/head-and-neck-cancer-survivors/ (accessed 16 November 2023)

121. Evaluation Software Development Company. Computer-Based Health Evaluation System. Available online: https://ches.pro/ (accessed on 16 November 2023)

122. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8

123. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. *Cancer*. 1984;53(9):2002-2007. doi:10.1002/1097-0142(19840501)53:9<2002::aid-cncr2820530933>3.0.co;2-w

124. Pierre CS, Dassonville O, Chamorey E, et al. Long-term quality of life and its predictive factors after oncologic surgery and microvascular reconstruction in patients with oral or oropharyngeal cancer. *Eur Arch Otorhinolaryngol*. 2014;271(4):801-807. doi:10.1007/s00405-013-2592-z

125. Sobin LH, Gospodarowicz MK, Wittekind Ch, eds. *TNM Classification of Malignant Tumours*. 7th Edition. International Union Against Cancer; 2009.

126. Brierley JD, Gospodarowicz MK, Wittekind Ch, eds. *TNM Classification of Malignant Tumours*. 8th Edition. International Union Against Cancer; 2016.

127. Ranta P, Kinnunen I, Jouhi L, et al. Long-term Quality of Life After Treatment of Oropharyngeal Squamous Cell Carcinoma. *The Laryngoscope*. 2021;131(4):E1172-E1178. doi:10.1002/lary.29042

128. Hess CB, Chen AM. Global and health-related quality of life after intensity-modulated radiation therapy for head and neck cancer. *Expert Rev Anticancer Ther*. 2012;12(11):1469-1477. doi:10.1586/era.12.126

129. Buttiron Webber T, Briata IM, DeCensi A, Cevasco I, Paleari L. Taste and Smell Disorders in Cancer Treatment: Results from an Integrative Rapid Systematic Review. *Int J Mol Sci*. 2023;24(3). doi:10.3390/ijms24032538

130. Mathlin J, Courtier N, Hopkinson J. Taste changes during radiotherapy for head and neck cancer. *Radiogr Lond Engl 1995*. 2023;29(4):746-751. doi:10.1016/j.radi.2023.05.004

131. Giesinger JM, Loth FLC, Aaronson NK, et al. Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. *J Clin Epidemiol*. 2020;118:1-8. doi:10.1016/j.jclinepi.2019.10.003

132. LENT SOMA scales for all anatomic sites. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1049-1091. doi:10.1016/0360-3016(95)90159-0

133. Baudelet M, Van den Steen L, Tomassen P, et al. Very late xerostomia, dysphagia, and neck fibrosis after head and neck radiotherapy. *Head Neck*. 2019;41(10):3594-3603. doi:10.1002/hed.25880

134. van Leeuwen M, Kieffer JM, Young TE, et al. Phase III study of the European Organisation for Research and Treatment of Cancer Quality of Life cancer survivorship core questionnaire. *J Cancer Surviv Res Pract*. Published online January 27, 2022. doi:10.1007/s11764-021-01160-1

135. Musoro JZ, Coens C, Singer S, et al. Minimally important differences for interpreting European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 scores in patients with head and neck cancer. *Head Neck*. 2020;42(11):3141-3152. doi:10.1002/hed.26363

136. Singer S, Hammerlid E, Tomaszewska IM, et al. Methodological approach for determining the Minimal Important Difference and Minimal Important Change scores for the European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module (EORTC QLQ-HN43) exemplified by the Swallowing scale. *Qual Life Res*. 2022;31(3):841-853. doi:10.1007/s11136-021-02939-6

15. Appendices

15.1. Appendix 1 – Case report form

Collaborator/Institution:	**Country:**
Local patient ID:	**Date form was completed: (dd/mm/yyyy)**
Participation status 1 = participated 2 = ineligible 3 = declined	**If declined – why?** 1 = not enough time 2 = does not want to be reminded of cancer 3 = does not want to participate in studies 4 = other reason, namely …….. 9 = unknown, no reason provided
Age:	**Gender:** 1 = male 2 = female
Education (years at school) 1 = <10 years 2 = 10 years 3 = >= 10 years **Please document the total number of years of education at school, college, university, etc. Do not add years of apprenticeship.**	**Living situation** 1 = lives alone 2 = lives with partner +/- children 3 = lives without partner but with children 4 = lives with other people 9 = unknown
Smoking status 1 = never smoker 2 = former smoker 3 = current smoker If a current smoker, please enter the estimated number of cigarettes per day.	**Alcohol consumption** How often does the patient have a drink containing alcohol? 1 = Never 2 = Monthly or less 3 = Two to four times a month 4 = Two to three times a week 5 = Four to five times a week

Tumor site (ICD)	**TNM**	**UICC**
C ☐ C00 = lip C01 = base of the tongue, NOS C02 = other parts of the tongue C03 = gum C04 = floor of the mouth C05 = palate C06 = other parts of mouth C07 = parotid gland C08 = other salivary gland C09 = tonsil C10 = oropharynx C11 = nasopharynx C12 = pyriform sinus C13 = hypopharynx C14 = other sites of lip, OC, pharynx C30 = nasal cavity C31 = nasal sinuses C32 = larynx C77, C80 = unknown primary	T (1,2,3, or 4;9=unknown) ☐ N (0,1,2,3; 9=unknown) ☐ M (0 or 1; 9=unknown) ☐ If possible, write down the exact TNM. For example: cT2a/b cTNM: ……	1 = UICC I 2 = UICC II 3 = UICC III ☐ 4 = UICC IV 9 = unknown **Which TNM version was used?** ☐ 7 = version 7 (2009) 8 = version 8 (2016) **If possible, use version 8!**
Histology 1 = squamous cell carcinoma ☐ 2 = sarcoma 3 = other 9 = unknown	**Second primary** 0 = no 1 = yes 9 = unknown If yes, date: …….. dd/mm/yyyy	**if second primary, where?** 0 = lungs 1 = esophagus ☐ 2 = liver 4 = locoregional 3 = other, please specify ……
Current evidence of disease 0 = no 1= yes ☐ 9 = unknown	**Recurrence (ever since first diagnosis)** 0 = no ☐ 1 = yes 9 = unknown If yes, date: …….. dd/mm/yyyy	**Has the patient participated in a clinical trial?** 0 = no ☐ 1 = yes 9 = unknown

NOTE: for the Surgery, Chemotherapy, and Radiotherapy items, if the patient had more than one type of these treatments, note all treatments.

Treatment Information

Treatment scheme	**Surgery**	**Salvage Surgery**
☐ 1 = monotherapy surgery 2 = monotherapy RT 3 = monotherapy CT 4 = radiochemotherapy without surgery 5 = radiochemotherapy + surgery 6 = chemotherapy + surgery 7 = radiotherapy + surgery 9 = other, please specify: …….. Note: the order of treatments can be either way. For example, radiotherapy + surgery = first RT, then OP or first OP, then RT. Patients with a first treatment with surgery only, then recurred and received chemo-radiation being free of disease at the time of survey should be documented with a '5'.	☐ 0 = no surgery 1 = transoral/transnasal/ endoscopic without neck dissection 2 = transoral/transnasal/ endoscopic with neck dissection 3 = transcervical (with or without neck dissection) 4 = neck dissection only 5 = any intervention with regional flap reconstruction 6 = any intervention with free flap reconstruction 9 = unknown	☐ 0 = no 1 = yes 9 = unknown
Chemotherapy	**Radiotherapy**	**Targeted therapy**
☐ 0 = no CT 1 = induction CT 2 = concomitant CT 3 = monotherapy CT 9 = unknown	☐ 0 = no RT 1 = brachytherapy 2 = 2D conformal 3 = 3D conformal 4 = IMRT 5 = other, **please specify**: …… 9 = unknown	☐ 0 = none 1 = Cetuximab 2 = Pantiumumab 3 = Other, **please specify:** ……

Date of first diagnosis of head and neck cancer:

_____ /_____/_____

Note: please use dd/mm/yyyy

Performance status (Karnofsky)

100 = normal, activities, no complaints,
90 = able to carry on normal activities
80 = normal activities with effort
70 = cares for self, unable to carry on normal activity or do active work
60 = requires some assistance but able to care for most of own needs
50 = requires considerable assistance and frequent medical care
40 = disabled, requires special care and assistance
30 = severely disabled, hospitalization
20 = very sick, hospitalization, active support treatment necessary
10 = moribund

Charlson Comorbidity Index (please document the <u>current</u> situation):

One point:

_____Myocardial infarction (history, not ECG changes only)

_____Congestive heart failure

_____Peripheral vascular disease (includes aortic aneurysm >= 6 cm)

_____Cerebrovascular disease: stroke with mild or no residua or TIA

_____Dementia

_____Chronic pulmonary disease

_____Connective tissue disease

_____Peptic ulcer disease

_____Mild liver disease (without portal hypertension, includes chronic hepatitis)

_____Diabetes without end-organ damage (excludes diabetes controlled by diet alone)

Two points:

_____Hemiplegia

_____Moderate or severe renal disease

_____Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy) or´brittle diabetes

_____Tumor without metastasis (do not award points if > 5y from diagnosis)

_____Leukemia (acute or chronic)

_____Lymphoma

Three points:

_____Moderate of sever liver disease

Six points:

_____Metastatic solid tumor

_____AIDS (not just HIV positive)

Sum: Please add the points per disease.
For example, if a patient has congestive heart failure and milder liver disease and hemiplegia, it would be: 1 + 1 + 2 = 4

From the patient's point of view, what are **the top two** most serious long-term effects the patient is currently experiencing? Place a 1 and 2 next to the top 2 aspects below.

_____ Pain in the head/neck region

_____ Pain at a flap donor site

_____ Difficulty swallowing/eating
_____ Difficulty breathing
_____ Hoarseness or difficulty speaking
_____ Dry mouth
_____ Numbness in the face and/or neck
_____ Neck stiffness
_____ Fatigue
_____ Social isolation
_____ Sialorrhea
_____ Trismus
_____ Osteonecrosis
_____ Fistula
_____ Dissatisfaction with facial appearance

_____ Other:_____

This patient's consent form indicates that he/she:

1) ☐ gave written consent for his/her doctor's to be contacted.

☐ did not give written consent for his/her doctors to be contacted

2) ☐ gave written consent for his/her anonymized data to be sent to the EORTC in Brussels.

☐ did not give written consent for his his/her anonymized data to be sent to the EORTC in Brussels.

If you have any comments to add about this patient related to the information in this Case Report Form, please add them here: (*NOTE: there were more lines available to write comments in the copies given to the physicians to use)*

_____

_____

_____

15.2. Appendix 2 – EORTC QLQ-C30

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" answers. The information you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social life?	1	2	3	4
28. Has your physical condition or medical treatment caused you any financial difficulties?	1	2	3	4

For the following questions, please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

15.3. Appendix 3 – EORTC QLQ-H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had a painful throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you choked when swallowing?	1	2	3	4
39. Have you had problems with your teeth?	1	2	3	4
40. Have you had problems opening your mouth wide?	1	2	3	4
41. Have you had a dry mouth?	1	2	3	4
42. Have you had sticky saliva?	1	2	3	4
43. Have you had problems with your sense of smell?	1	2	3	4
44. Have you had problems with your sense of taste?	1	2	3	4
45. Have you coughed?	1	2	3	4
46. Have you been hoarse?	1	2	3	4
47. Have you felt ill?	1	2	3	4
48. Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you had trouble eating?	1	2	3	4
50. Have you had trouble eating in front of your family?	1	2	3	4
51. Have you had trouble eating in front of other people?	1	2	3	4
52. Have you had trouble enjoying your meals?	1	2	3	4
53. Have you had trouble talking to other people?	1	2	3	4
54. Have you had trouble talking on the telephone?	1	2	3	4
55. Have you had trouble having social contact with your family?	1	2	3	4
56. Have you had trouble having social contact with friends?	1	2	3	4
57. Have you had trouble going out in public?	1	2	3	4
58. Have you had trouble having physical contact with family or friends?	1	2	3	4
59. Have you felt less interest in sex?	1	2	3	4
60. Have you felt less sexual enjoyment?	1	2	3	4

During the past week:	No	Yes
61. Have you used pain-killers?	1	2
62. Have you taken any nutritional supplements (excluding vitamins)?	1	2
63. Have you used a feeding tube?	1	2
64. Have you lost weight?	1	2
65. Have you gained weight?	1	2

15.4. Appendix 4 – Tabular curriculum vitae

Personal Information

Address	[redacted]
Telephone	[redacted]
Email	[redacted]
Citizenship	[redacted]
Place and date of birth	[redacted]

Academic Education

- M.Sc. in Epidemiology - Johannes Gutenberg Universität, Mainz – (April, 2009). Master's thesis was written on Bisphosphonate Associated Osteonecrosis of the Jaws.
- B.Sc. in Health Information Science - University of Victoria, Canada - graduated with Distinction (2004) (http://hinf.uvic.ca).

Employment

- December 2016 – Present – **IMBEI (Institut für Medizinische Biometrie, Epidemiologie und Informatik), Mainz**
- September 2014 – November 2015 – **German Consortium for Translational Cancer Research (DKTK), Based in Mainz at the IMBEI**
- June 2009 – September 2014 – **IMBEI (Institut für Medizinische Biometrie, Epidemiologie und Informatik), Mainz**
- Nov. 2006 – July 2008 – **IMBEI (Institut für Medizinische Biometrie, Epidemiologie und Informatik), Mainz Germany**
- Sept. 2005 – Sept. 2006 – **Vancouver Island Health Authority – Victoria, Canada**
- May 2004 – Apr. 2005 – **Calgary Regional Health Authority – Calgary, Canada**
- Jan. 2003 − Apr. 2003 − **Canada Health Infoway – Montreal, Canada**
  - 2rd practicum required by the Health Information Science Degree Program.
- Apr. 2002 − Aug. 2002 − **NB Prescription Drug Program, Fredericton, Canada**
  - 1st practicum required by the Health Information Science Degree Program.

Publications

Singer S, Sievers L, Scholz I, **Taylor K**, Blanck J, Maier L (2023) Who seeks psychodynamic psychotherapy in community-based practices? Patient characteristics examined in a large sample of applications for reimbursement of psychotherapy in Germany. Psychodynamic Practice. 29(2):117-135.

Singer S, Sievers L, Scholz I, Taylor K, Blanck J, Maier L (2023) **Suicidal ideation and attempts in adults seeking outpatient psychodynamic psychotherapy**. Clin Psychol Psychother. 30(2):317-334.

Singer S, Engesser D, Wirp B, Lang K, Paserat A, Kobes J, Porsch U, Mittag M, **Taylor K**, Gianicolo G, Maier L (2022) **Effects of a statutory reform on waiting times for outpatient psychotherapy: A multicentre cohort study.** Counselling and Psychotherapy Res. 22(4):982-998.

Riccetti N, Blettner M, Taylor K, Wehler B, Gohrbandt B, Nestle U, Bals R, Stockinger M, Wehler T, Singer S, Eichler M (2022) **Quality of life in lung cancer survivors treated with Tyrosine-kinase-inhibitors (TKI): results from the multi-centre cross-sectional German study LARIS**. Cancer Res and Clin Oncol. 148(8):1943-1953.

Billaudelle F, Bayer O, Hechtner M, **Taylor K**, Lang J, Alt J, Fried M, Singer S (2022) **That was a tip from my physician"—Gender-specific pathways of patients and relatives to outpatient psychosocial cancer counselling centres—A qualitative study in Psycho-Oncology.** Psychooncology**.** 31(6):1022-1030.

Büttner M, Singer S, Hentschel L, Stephan Richter S, Hohenberger P, Kasper B, Dimosthenis, Andreou D, Pink D, **Taylor K**, Arndt K, Bornhäuser M, Schmitt J, Schuler MK, Eichler M (2022) **Financial toxicity in sarcoma patients and survivors in Germany: results from the multicentre PROSa study**. Supportive Care in Cancer 30:187-196.

Singer S, Hammerlid E, Tomaszewska I, Amdal CD, Bjordal K, Herlofson BB, Santos M, Castro Silva J, Mehanna H, Fullerton A, Brannan C, Gonzalez LF, Inhestern J, Pinto M, Arraras JI , Yarom N, Bonomo P, Baumann I, Galalae R, Nicolatou-Galitis O, Kiyota N, Raber-Durlacher J, Salem D, Fabian A, Boehm B, Krejovic-Trivic S, Chie WC, **Taylor K**, Simon C, Licitra L, Sherman AC, EORTC Quality of Life Group and the EORTC Head and Neck Cancer Group (2022) **Methodological approach for determining the Minimal Important Difference and Minimal Important Change scores for the European Organisation for Research and Treatment of Cancer Head and Neck Cancer Module (EORTC QLQ-HN43) exemplified by the Swallowing scale**. Qual Life Res. 31(3):841-853.

Singer S, Kojima E, Deppisch L, **Taylor K**, Wickert M, Riedel P, Alt J, Heß G, Hechtner M, Bayer O (2021) **What is the best time for psychosocial counselling from the perspective of cancer patients and their relatives? A multi-centre qualitative study**. Counselling and Psychotherapy Res. 22(3):558-568.

Amdal CD, Pe M, Falk RS, Piccinin C, Bottomley A, Arraras JI, Darlington AS, Hofsø K, Holzner B, Høyning Jørgensen NM, Kulis D, Rimehaug SA, Singer S, **Taylor K**, Wheelwright S, Bjordal K (2021) **Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review**. Qual Life Research.30(12):3367-3381.

Pokora R, Kutschbach S, Weigl M, Braun D, Epple A, Lorenz E, Grund S, Hecht J, Hollich H, Rietschel P, Schneider F, Sohmen R, **Taylor K**, Dienstbuehl I (2021) **Investigation of superspreading COVID-19 outbreak events in meat and poultry processing plants in Germany: A cross-sectional study**. PLOS One.16 (6) e0242456. https://doi.org/10.1371/journal.pone.0242456

Taylor K, Krüger M, Singer S (2021) **[Late Toxicity in Head and Neck Cancer Patients – A Systematic Review]**. Der Onkologe. Issue 4.

Gianicolo E, Russo A, Büchler B, **Taylor K,** Stang A, Blettner M (2021) **Gender specific excess mortality in Italy during the COVID-19 pandemic accounting for age**. Eur J Epidemiol. 36(2):213-218.

Bonomo P, Maruelli A, Saieva C, **Taylor K**, Singer S, Patelli Z, Rogers S, Mattavelli D, Simon C, Scotté F, Bueno de Oliveira T, Murphy, Rhoten BA, Tassini U, Fallon M, Nicolatou Gatidis O, Yarom N, Bergamini C , Bossi P (2020) **Assessing Preferences in Patients with Head and Neck Squamous Cell Carcinoma: Phase I and II of Questionnaire Development**. Cancers (Basel). 12(12):3577.doi: 10.3390/cancers12123577.

Büttner M, Locati L, Pinto M, Araújo C, Tomaszewska IM, Kiyota N, E Vidhubala, Brannan C, Hammerlid E, Husson O, Salem D, Ioannidis G, Gamper E, Arraras J, Andry G, Inhestern J, Theurer J,

Taylor K, Singer S (2020) **Quality of Life in Patients With Hypoparathyroidism After Treatment for Thyroid Cancer**. J Clin Endocrinol Metab 105(12):dgaa597. doi: 10.1210/clinem/dgaa597.

Gerlach C, **Taylor K**, Ferner M, Munder M, Weber M, Ramsenthaler (2020) **Challenges in the cultural adaptation of the German Myeloma Patient Outcome Scale (MyPOS): an outcome measure to support routine symptom assessment in myeloma care**. BMC Cancer. 20:245 https://doi.org/10.1186/s12885-020-06730-7

Leinert E, Kreienberg R, Wöckel A, Kühn T, Flock F, Felberbaum R, Janni W, **Taylor K**, Singer S, Schwentner L, BRENDA study group (2020) **Survivors of primary breast cancer 5 years after surgery: follow-up care, long-term problems, and treatment regrets. Results of the prospective BRENDA II-study**. Arch Gynecol Obstet. 301(3):761-767.

Taylor K, Singer S (2019) **[Long-term quality of like in patients with head and neck cancer – a systematic review]**. Der Onkologe. 25(3):253-261.

Taylor KJ, Singer S, May M, Durdu G, Petermann-Meyer A (2019) **Outcome comparison of integrated psycho-social care versus unstructured care – Results of an non-randomized open-label two arm trial.** European J Cancer Care. 28(5).

Singer S, Vogel HJ, Guntinas-Lichius O, Erdmann-Reusch B, Fuchs M, **Taylor K**, Meyer A, Keszte J (2019) **Multicenter prospective study on the use and outcome of rehabilitation after total laryngectomy in Germany**. Head Neck. 41(4): 1070-1079.

Schülein S, **Taylor KJ**, Braun B, Heyl V, Zoche H, Peek A, Solbach C, Schott S, Blettner M, Klug SJ (2018) **Evaluation of the methodological quality of articles on autologous breast reconstruction**. J Plast Reconstr Aesthet Surg. 71(9):1286-1294.

Schülein S, **Taylor KJ**, Schriefer D, Blettner M, Klug SJ (2017) **Participation in preventive health check-ups among 19,351 women in Germany**. Prev Med Rep. 26(6):23-26.

Schülein S, **Taylor KJ**, König J, Claus M, Blettner M, Klug SJ (2016) **Factors influencing uptake of HPV vaccination among girls in Germany**. BMC Public Health. 20(16):995.

Sagheb K, Sagheb K, **Taylor K**, Kumar VV, Al-Nawas B, Walter C (2015) **Sentinel Lymph Node Biopsy in T1/ T2 Squamous Cell Carcinomas of the Tongue, a Prospective Study**. Oncology Letters. 11(1):600-604.

Walter C, Sagheb K, Bitzer J, Rahimi-Nedjat RK, **Taylor KJ** (2014) **Analysis of reasons for osteonecrosis of the jaws**. Clin Oral Investig. 18(9):2221-2226.

Sagheb K, Sagheb Ka, **Taylor KJ**, Al-Nawas B , Walter C (2014) **Cervical metastases of squamous cell carcinoma of the maxilla: a retrospective study of 25 years**. Clin Oral Investig. 18(4):1221-1227.

Schulz P, Sagheb K, Sagheb K, Kumar V, **Taylor K**, Walter C (2013) **Malignant Neoplasms of the Upper Jaw: A 17 year retrospective study**. Int Poster J Dent Oral Med. 15 (2): 640.

Pabst AM, Ziebart T, Koch FP, **Taylor K**, Al-Nawas B, Walter C (2012) **The influence of bisphosphonates on viability, migration, and apoptosis of human oral keratinocytes–in vitro study**. Clin Oral Investig. 16 (1):87-93.

Klug SJ, **Taylor KJ**, Scheidemann-Wesp U, Lautz D, Güther B, Potthoff P, Blettner M (2010) **Participation in cervical cancer screening in Germany.** Prev Med. 51(5):431-432.

- End of CV -