**SUPPLEMENTARY MATERIALS**

*Esophageal second primary tumors in patients with head and neck squamous cell carcinoma: incidence, risk factors and overall survival*

**SUPPLEMENTARY MATERIAL A - BACKGROUND**

Head and neck squamous cell carcinoma (HNSCC) patients have an increased risk of esophageal second primary tumors (ESPTs)1–3. ESPT is one of the most common second primary tumors in HNSCC patients, together with second primary tumors in the head and neck region and lungs1–3. Simultaneous occurrence of these malignancies is often explained by field cancerization of the entire upper aero-digestive tract with similar exogenous risk factors, most importantly alcohol and tobacco4,5.

The reported occurrence of ESPTs in HNSCC patients varies widely depending on the populations studied (0-22%)6. Asian studies report the highest occurrence of ESPTs. In non-Asian studies, the occurrence of ESPTs is lower, but still increased7. However, the number of non-Asian studies on the occurrence of ESPTs is limited and the reported risk varies widely, between 0.8% and 11.5%2,7–12.

Patients with HNSCC alone have a poor prognosis with an overall 5-year survival rate of 46%13. Concomitant presence of ESPTs is suggested to further deteriorate survival14. For patients with solely esophageal cancer, early stage disease is associated with a better prognosis than more advanced tumor stages14,15. Therefore, endoscopic esophageal surveillance of HNSCC patients might improve early detection of ESPTs and thereby possibly improve survival.

Currently, no formal surveillance program for ESPTs has been implemented for HNSCC patients in the western world. Although multiple studies acknowledge the added value of routine surveillance for ESPTs in high-risk populations, the value of endoscopic esophageal surveillance has not clearly been established because of several uncertainties6,16. First of all, the reported occurrence of ESPTs varies between and within regions. Secondly, the accuracy of identification of esophageal lesions with endoscopic surveillance remains unclear. Also, the stage at which ESPTs will be detected during endoscopic surveillance is uncertain but of high importance, since surveillance is only valuable if ESPTs are found in an early stage and can be treated curatively. Finally, the impact of detection and treatment of ESPTs on the prognosis of HNSCC patients remains to be determined.

With this retrospective cohort study, we aim to contribute to the debate on the role of endoscopic esophageal surveillance for Western HNSCC patients, by determining: (1) the incidence of ESPTs in HNSCC patients; (2) risk factors for development of ESPTs in HNSCC patients; and (3) the effect of the presence of ESPTs on overall survival of HNSCC patients. We hypothesize that HNSCC patients have an increased risk of ESPTs and that the presence of ESPTs in HNSCC patients is associated with worse overall survival.

**SUPPLEMENTARY MATERIAL B - METHODS**

Study design

This single-center, retrospective observational cohort study was performed in an academic, large regional referral center for patients with head and neck cancer in The Netherlands. The Medical Ethics Committee of the University Medical Center Utrecht evaluated the study protocol and stated that the Medical Research Involving Human Subjects Act does not apply to this study (reference no. 17-291/C). Patients were not involved in the design of the study. Data management was performed in Redcap17 and the manuscript was written according to the STROBE guidelines18.

Patients

All patients diagnosed with and/or treated for head and neck cancer in the University Medical Center Utrecht are prospectively registered in a database. For the current study, all patients that received the diagnosis and treatment for head and neck cancer between January 2003 and December 2012 were identified in this database. Patients were included if they had a histopathologically confirmed HNSCC. Patients were excluded in case of: (1) anatomical localization of HNSCC not exposed to the main risk factors alcohol and tobacco (nasopharynx, maxillary sinus, skin), or with unknown primary sites; (2) HNSCC not being the primary tumor (primary tumor located outside the head and neck region); (3) histopathological type of cancer other than squamous cell carcinoma (adenocarcinoma, melanoma, lymphoma, etc.); (4) carcinoma in situ; (5) previous diagnosis of esophageal cancer; (6) insufficient data on the primary tumor in the medical record.

Methods and definitions

Data on patient characteristics, primary HNSCC characteristics, ESPT characteristics, treatment and follow-up were collected from hospital records, including endoscopy, surgery, multidisciplinary meeting, and pathology reports.

The diagnosis of HNSCC was confirmed by evaluation of the original pathology report. In case of multiple tumor registrations per patient in the database, the first diagnosis of HNSCC was used and following HNSCCs were registered as second primary HNSCCs. HNSCCs were classified according to the 8th edition of the clinical TNM classification and stage in accordance with the AJCC 8th edition. Anatomical site of the HNSCC was categorized in four groups: (1) larynx; (2) oral cavity; (3) oropharynx; (4) hypopharynx.

The diagnosis of ESPT had to be confirmed with histopathological evaluation of endoscopic biopsies. In addition to medical chart review of all endoscopy and pathology reports, the Dutch nationwide pathology database *(PALGA)* was screened to detect esophageal neoplasia diagnosed in other medical centers in The Netherlands. ESPTs were defined according to the criteria defined by Warren and Gates and included both synchronous carcinomas, diagnosed simultaneously or within 6 months of the index tumor, and metachronous carcinomas, diagnosed after 6 months of the index tumor19.

Regarding follow-up time, information on vital status and date of death was requested in the Dutch Personal Records Database *(Basisregistratie Personen)* for all included patients on April 30 2019, since the hospital registry on vital status and date of death was incomplete. The follow-up period started at the date of HNSCC diagnosis and ended at the date of an event (ESPT diagnosis or death, depending on the specific research question), date of Dutch population registry check (30-4-2019), or moment of last follow-up in the hospital if the Dutch population registry check was not possible (n=2).

The following outcome parameters were evaluated: 1) Cumulative incidence of ESPT in HNSCC patients; 2) Risk factors for ESPT in HNSCC patients; and 3) Overall survival for HNSCC patients with and without ESPT.

Statistics

Statistical analysis was performed in R (Version 3.6.2 for Mac, R Foundation for Statistical Computing, Vienna, Austria). For baseline descriptive statistics, means were calculated with standard deviations (SD) for normally distributed variables and medians with 25th-75th percentiles (p25-p75) for variables with a skewed distribution. Categorical variables were presented as percentages of total. A 2-sided *P* value of < .05 was considered significant.

Missing values were present for covariates, no outcome variables were missing. Missing data were handled by creating 44 multiple imputed datasets (reflecting the percentage of incomplete observations) by iterative (25) chained equations using the *mice* package based on all potentially informative variables including the outcome20, under the missing at random assumption. Since the imputed datasets were used to perform cox regression analysis, Nelson Aalen estimators for survival time and time to ESPT were also included in the imputation process21. Analyses were performed on each imputed dataset and estimates were pooled using Rubin’s rules to include both within and between imputation components of variation22.

Cumulative incidences for ESPT with death as a competing risk were calculated using the *cmprsk* package23. Subsequently, cumulative incidences were calculated per primary HNSCC location, tobacco use and alcohol consumption. The crude incidence rate for ESPT was calculated as the number of ESPTs divided by the number of person years a patient was at risk of developing ESPT and the age-standardized rates using the Eurostat 2013 European standard population and WHO World standard population.

Risk factors for ESPT were evaluated using Fine and Grey competing risk regression analysis, and we used propensity scores as co-variable in these models to obtain estimates of the independent prognostic value of each variable of interest because the limited number of ESPT events precluded direct co-variable adjustment. Propensity scores were calculated per co-variable of interest (age, sex, HNSCC location, smoking and alcohol) including all but the co-variable of interest as covariates. Logistic regression was used to calculate the propensity score for binary variables (sex, smoking, alcohol) and multinomial regression analysis for variables with multiple categories (age in tertiles, HNSCC location). For binary exposure variables, possible non-linearity of the propensity scores with the outcome was accommodated for by using restricted cubic splines with 5 knots in the Fine and Grey models. For exposure variables with multiple categories and thus multiple propensity scores, non-linearity could not be accommodated for given the sparse outcome which prohibited the inclusion of too many parameters in the regression models. Checks for acquired balance for the selected co-variables by the propensity score were performed by using the propensity score to obtain inversed probability weights, and by then obtaining the C-indexes of the refitted propensity model in the pseudo-population as based on these weights24. For multinomial variables (HNSCC location and age in tertiles) these C-indexes were calculated per level. All C-indexes were below 0.6 indicating adequate achieved balance.

Overall survival for HNSCC patients with and without ESPTs within 6 months after HNSCC diagnosis were first calculated using the Kaplan Meier method, landmarking on 6 months to prevent immortal time bias. Next, the effect of ESPT on overall survival in HNSCC patients was evaluated with multivariable cox regression analysis, with ESPT included as a time varying covariate, again to avoid immortal time bias25, and adjusted for covariates age, sex, body mass index (BMI), smoking, alcohol use, HNSCC stage, HNSCC differentiation grade, HNSCC location, primary treatment for HNSCC, and presence of multiple primary HNSCCs at time of HNSCC diagnosis using restricted cubic splines with 5 knots for the continuous variables age and BMI. The proportional hazard assumption was checked with Schoenfeld residuals plots and the cox.zph function from the *survival* package. Strata were used for categorical variables in the multivariable model where the proportional hazard assumption did not hold (HNSCC stage, HNSCC location, primary treatment for HNSCC, smoking, presence of multiple primary HNSCCs), and the continuous variable age (after categorization in tertiles).

**SUPPLEMENTARY MATERIAL C – STRENGTHS AND LIMITATIONS**

Strengths of this cohort study are the prospective registration of all HNSCC patients in a large referral center and thorough data collection and verification based on review of all medical records, the Dutch nationwide pathology database and the Dutch Personal Records Database. The additional data on esophageal cancer diagnoses from the Dutch nationwide pathology database assured that we were also informed on esophageal cancer diagnosed in other medical centers. Given the differences in spatial distribution of ESPT in HNSCC patients, our findings add important information to prior studies that were mostly conducted in Asian countries. Nevertheless, several potential limitations should also be addressed. First, this study was performed in single-center setting, which is considered to have limited consequences on the generalizability of the study results since the hospital is a large regional referral center. Secondly, since the cause of death was rarely reported in the medical record and the Dutch Personal Records Database does not contain information on the cause of death, survival analysis for disease-specific survival could not be performed. Overall survival however, was considered the most important outcome. Moreover, the percentage of missing data was substantial for the covariates smoking and alcohol, which was dealt with by using multiple imputation, and HPV, which was not regularly evaluated during the inclusion period of this study and was left out of the analysis altogether. The overall percentage of observed data points however, was very high (97%). Furthermore, even though we present a large cohort, the number of ESPTs was limited to 47. Therefore, propensity score adjusted multivariable competing risk regression analysis was used for risk factor identification instead of adjusting for all separate covariates to allow multivariable analysis in the context of sparse outcome. Lastly, retrospective data collection on smoking and alcohol might underestimate risk behavior, but despite this uncertainty alcohol was still a significant predictor for ESPT.

**SUPPLEMENTARY TABLE 1** – Baseline characteristics

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | All patients (N=1708) | Missing values, n (%) | Patients with ESPT (N=47) | Missing values, n (%) | Patients without ESPTs (N=1661) | Missing values, n (%) |
| Patient characteristics at time of HNSCC diagnosis |  |  |  |  |  |  |
| Male sex, n (%) | 1131 (66.2) | 0 (0) | 37 (79) | 0 (0) | 1094 (65.9) | 0 (0) |
| Age, mean (SD) | 64.4 (11.5) | 0 (0) | 61.9 (7.2) | 0 (0) | 64.5 (11.6) | 0 (0) |
| Body mass index, mean (SD) | 24.4 (4.6) | 151 (8.8) | 22.9 (4.7) | 2 (4.3) | 24.5 (4.6) | 149 (9.0) |
| Smoking quantity in pack years, n (%)  0  <10  10-20  >20 | 309 (28.4)  31 (2.9)  90 (8.3)  656 (60.4) | 622 (36.4) | 1 (3.7)  1 (3.7)  1 (3.7)  24 (88.9) | 20 (42.6) | 308 (29.1)  30 (2.8)  89 (8.4)  632 (59.7) | 602 (36.2) |
| Alcohol quantity in IE/day, n (%)  0  1-2  3-4  5-8  >8 | 592 (37.5)  329 (20.8)  318 (20.2)  256 (16.2)  83 (5.3) | 130 (7.6) | 5 (11.9)  3 (7.1)  15 (35.7)  17 (40.5)  2 (4.8) | 5 (10.6) | 587 (38.2)  326 (21.2)  303 (19.7)  239 (15.6)  81 (5.3) | 125 (7.5) |
| PrimaryHNSCC tumor and treatment characteristics |  |  |  |  |  |  |
| >1 primary HNSCC tumor at time of diagnosis, n (%) | 195 (11.4) | 0 (0) | 8 (17.0) | 0 (0) | 187 (11.3) | 0 (0) |
| Location, n (%)  Larynx  Oral cavity  Oropharynx  *HPV positive/negative/unknown\*\**  Hypopharynx | 416 (24.4)  877 (51.3)  308 (18.0)  *31/67/210*  107 (6.3) | 0 (0) | 5 (10.6)  23 (48.9)  17 (36.2)  *0/5/42*  2 (4.3) | 0 (0) | 411 (24.7)  854 (51.4)  291 (17.5)  *31/62/1568*  105 ( 6.3) | 0 (0) |
| Differentiation grade, n (%)  Well  Moderate  Poor  Undifferentiated | 103 (6.1)  997 (58.8)  154 (9.1)  441 (26.0) | 13 (0.8) | 2 (4.3)  28 (59.6)  6 (12.8)  11 (23.4) | 0 (0) | 101 (6.1)  969 (58.8)  148 (9.0)  430 (26.1) | 13 (0.8) |
| *Clinical* TNM Classification 8th edition, n (%)  T1  T2  T3  T4  N0  N1  N2  N3  M0  M1 | 577 (33.8)  544 (31.9)  192 (11.2)  395 (23.1)  1201 (70.3)  154 (9.0)  325 (19.0)  28 (1.6)  1689 (98.9)  19 (1.1) | 0 (0) | 17 ( 36.2) 13 ( 27.7) 6 ( 12.8) 11 ( 23.4)  34 ( 72.3)  6 ( 12.8)  6 ( 12.8)  1 ( 2.1)  47 (100)  0 (0) | 0 (0) | 560 (33.7)  531 (32.0)  186 (11.2)  384 (23.1)  1167 (70.3)  148 ( 8.9)  319 (19.2)  27 ( 1.6)  1642 (98.9)  19 ( 1.1) | 0 (0) |
| Stage according to the AJCC 8th edition, n (%)  I  II  III  IV | 525 (30.7)  400 (23.4)  203 (11.9)  580 (34.0) | 0 (0) | 17 ( 36.2)  9 ( 19.1)  7 ( 14.9)  14 ( 29.8) | 0 (0) | 508 (30.6) 391 (23.5)  196 (11.8)  566 (34.1) | 0 (0) |
| Primary treatment, n (%)  No treatment  Radiotherapy alone  Chemoradiotherapy  Surgery | 56 (3.3)  555 (32.5)  153 (9.0)  943 (55.2) | 1 (0.1) | 2 ( 4.3)  14 ( 29.8)  6 ( 12.8)  25 ( 53.2) | 0 (0) | 54 (3.3)  541 (32.6)  147 (8.9) 918 (55.3) | 1 (0.1) |
| Neoadjuvant treatment before surgery, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Adjuvant therapy after surgery, n (%)  No adjuvant treatment  Chemotherapy  Radiotherapy  Chemoradiotherapy | N=943 (765 N/A)  505 (53.6)  3 (0.3)  387 (41.0)  48 (5.1) | 0 (0) | N=25 (22 N/A)  13 (52.0)  1 (4.0)  11 (44.0)  0 (0) | 0 (0) |  | 0 (0) |
| Endoscopy performed after HNSCC diagnosis, n (%)  Indications:   * ESPT screening * Upper gastrointestinal bleeding/anemia * Duodenal feeding tube * Percutaneous endoscopic gastrostomy * Other | 484 (28.3)  21 (1.2)  29 (1.7)  13 (0.8)  337 (19.7)  84 (4.9) | 0 (0) | 14 (29.8)  0 (0.0)  0 (0.0)  7 (14.9)  26 (55.3) | 0 (0) | 7 (0.4)  29 (1.7)  13 (0.8)  330 (19.9)  58 (3.5) | 0 (0) |

Abbreviations: **HNSCC** head and neck squamous cell carcinoma; **ESPT** esophageal second primary tumor; **SD** standard deviation; **HPV** human papilloma virus; **AJCC** American Joint Committee on Cancer

\* Baseline characteristics of 1 of the 44 imputed datasets for variables with missing values.Missingness at random was plausible when comparing patients with and without missing values; 56% complete cases, 97% observed data points.

\*\* HPV status had too many missing values for multiple imputation. This was not regularly measured during the inclusion period of this study.

**SUPPLEMENTARY TABLE 2 –** Tumor and treatment characteristics of the esophageal second primary tumors

|  |  |  |
| --- | --- | --- |
| Esophageal second primary tumor and treatment characteristics (N=47) | | Missing values, n (%) |
| Histopathological subtype, n (%)  Esophageal squamous cell carcinoma Esophageal adenocarcinoma | 43 (91.5)  4 (8.5) | 0 (0) |
| Location of esophageal second primary tumor, n (%)  Cervical esophagus  Proximal intrathoracic esophagus (18-24cm)  Mid esophagus (24-32cm)  Distal esophagus (32-40cm) | 1 (2.4)  7 (16.7)  16 (38.1)  18 (42.8) | 5 (10.9) |
| Details on esophageal second primary tumor available, n (%) | 35 (74.5) | 0 (0) |
| Clinical TNM Classification, n (%)  T1  T2  T3  T4  N0  N1  N2  N3  M0  M1 | 10 (34.6)  3 (10.3)  13 (44.8)  3 (10.3)  16 (51.6)  15 (48.4)  0 (0)  0 (0)  25 (78.1)  7 (21.9) | 6 (17.1)  4 (11.4)  3 (8.6) |
| Differentiation grade, n (%)  Well  Moderate  Poor | 1 (4.5)  13 (59.1)  8 (36.4) | 13 (37) |
| Curative treatment performed, n (%)  Yes (of which 5 curative endoscopic resections)  No | 23 (65.7)  12 (34.3) | 0 (0) |

NB: No association between the above mentioned characteristics of esophageal second primary tumors was statistically significant associated with mortality.

**SUPPLEMENTARY TABLE 3 -** Risk factors for esophageal second primary tumors

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Number of patients | Number of ESPTs | Univariable HR (95%-CI) following multiple imputation | Adjusted HR (95%-CI)\*  following multiple imputation |
| Age in years\*\*  15-59  60-69  70-96 | 589  575  544 | 17  22  8 | Reference  1.33 (0.71-2.50)  0.51 (0.22-1.17) | Reference  1.36 (0.72-2.58)  0.88 (0.36-2.16) |
| Sex  Female  Male | 577  1131 | 10  37 | Reference  1.91 (0.95-3.85) | Reference  1.43 (0.71-2.91) |
| HNSCC location  Larynx  Oral cavity  Oropharynx  Hypopharynx | 416  877  308  107 | 5  23  17  2 | Reference  2.17 (0.83-5.69)  4.73 (1.75-12.79)  1.56 (0.30-8.09) | Reference  2.81 (1.07-7.40)  4.03 (1.49-10.91)  1.18 (0.22-6.15) |
| Smoking in pack years  0  >0 | 325  1383 | 1  46 | Reference  9.92 (1.38-71.52) | Reference  3.34 (0.40-27.74) |
| Alcohol in IE/day  <3  >=3 | 962  746 | 8  39 | Reference  6.12 (2.84-13.20) | Reference  3.25 (1.33-7.93) |

Abbreviations: **ESPTs** esophageal second primary tumors; **HR** hazard ratio; **CI** confidence interval; **HNSCC** head and neck squamous cell carcinoma

\* Multivariable competing risk regression analysis for esophageal second primary tumors with death as a competing risk, adjusted using propensity scores.

\*\* Age in tertiles was used to accommodate propensity score adjustment in the multivariable analysis: age 15-59, age 60-69, age 70-96.

**SUPPLEMENTARY TABLE 4** - Overall survival of head and neck squamous cell carcinoma patients with versus without an esophageal second primary tumor

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Effect estimate** | **95%-CI** | ***P* value** |
| HR for overall survival\*  Unadjusted  Adjusted\*\* | 3.81  3.36 | 2.76 – 5.28  2.16 – 5.22 | < .001  < .001 |

Abbreviations: **HR** hazard ratio; **CI** confidence interval  
  
\* Multivariable cox regression analysis following multiple imputation with esophageal second primary tumor as a time-varying covariate  
\*\* Adjusted for covariates age, sex, body mass index, smoking, alcohol use, head and neck squamous cell carcinoma (HNSCC) stage, HNSCC differentiation grade, HNSCC location, primary treatment for HNSCC, and presence of multiple primary HNSCCs at time of HNSCC diagnosis

**SUPPLEMENTARY TABLE 5** – Subgroup analysis for overall survival with versus without esophageal second primary tumors in head and neck squamous cell carcinoma patients

|  |  |  |  |
| --- | --- | --- | --- |
| **Effect modifiers** | **HR for overall survival with versus without ESPT\*** | **95%-CI** | **P value for interaction** |
| Sex  Male  Female | 3.37  3.34 | 2.03-5.60  1.39-8.02 | .99 |
| Age  < = 65 years  > 65 years | 2.73  4.94 | 1.66-4.49  2.50-9.74 | .16 |
| Alcohol  <3 IE / day  >= 3 IE / day | 9.41  2.88 | 3.03 – 29.27  1.78 – 4.68 | .06 |
| Smoking  0 PY  >0 PY | 10.96  3.53 | 0.97-123.82  2.32-5.37 | .37 |
| HNSCC stages  1-2  3-4 | 3.53  3.13 | 2.04-6.12  1.84-5.35 | .75 |
| HNSCC location\*\*  Oral cavity, tongue, palate, gum  Oropharynx | 3.47  1.81 | 1.89-6.37  0.85-3.86 | .18 |
| HNSCC differentiation  Well  Moderate  Poor  Undifferentiated | 1.23  3.07  9.46  4.06 | 0.12-12.33  1.77-5.35  1.44-62.29  1.69-9.72 | .54 |
| Multiple primary HNSCCs  No  Yes | 3.71  2.16 | 2.38-5.79  0.86-5.40 | .30 |

Abbreviations: **HR** hazard ratio; **ESPTs** esophageal second primary tumors; **CI** confidence interval; **HNSCC** head and neck squamous cell carcinoma

\* Multivariable cox regression analysis adjusted for age, sex, body mass index, smoking, alcohol use, head and neck squamous cell carcinoma (HNSCC) stage, HNSCC differentiation grade, HNSCC location, primary treatment for HNSCC, and presence of multiple primary HNSCCs.  
\*\* Subgroup analysis for HNSCC locations larynx and hypopharynx was not possible due to limited number of esophageal second primary tumors in these subgroups.

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