First Clinical Report on Comparative Treatment and Survival Outcomes in Second Cancers after Primary Head and Neck Cancer: A Population-Based Study

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Abstract
Introduction
To compare patients’ survival of second primary malignancy (SPM) after head and neck squamous cell carcinoma (HNSCC).

Methods
The Surveillance, Epidemiology, and End Results (SEER) database was utilized (1973-2011). The Kaplan-Meier method with log-rank test was used to compare the overall survival (OS) and cause-specific survival (CSS) among treatment methods from the time of diagnosis of SPMs. Cox proportional regression models were used to adjust the impact for risk factors on CSS.

Results
A total of 3,038 patients were identified (5-yr OS 22.6% (21.0-24.3%)). For head and neck (HN) SPMs, the patients who received 'conservative surgery with radiation' had the best 5-yr OS (65.2% (48.9-86.9%)); and the 'conservative surgery' group had the best 5-yr CSS (89.9% (85.6-94.5%)). For lung SPMs, the 'radical surgery' group showed the best survival (2-yr OS 60.8% (56.0-66.1%), 2-yr CSS 70.6% (65.8-75.8%), respectively). Esophagus SPMs had poor prognosis, with no difference among the treatment groups. In lung SPMs, younger age (p<0.001) and black race (p<0.05) were most favorable CSS predictors.

Conclusions
The prognosis of SPMs after HNSCC is worse compared with corresponding primary tumor. Conservative surgery with or without radiation showed the most favorable outcomes in HN SPMs.

Introduction
Head and neck (HN) cancer patients are known to be at significantly elevated risk of second primary malignancies (SPMs), compared with the matched population and SPMs are the leading cause of mortality (30% [1-2]) among long-term HNSCC survivors. Effective and successful SPM treatment is therefore a crucial part of long-term HNSCC management.

The concept of 'field cancerization', which was first introduced by Slaughter, et al. [3] in 1953, has been used to explain the high occurrence of SPMs in HNSCC. The classic view of 'field cancerization' is that exposure of environmental carcinogens, such as tobacco and alcohol use, may induce premalignant disease in large mucosal area and elevate the secondary cancer risk throughout the aero-digestive tract. Additional studies have further confirmed that some SPMs share a similar genetic pattern with the index tumor [4]. Other risk factors, such as aging and human papillomavirus (HPV)-seronegative status, etc. have been proven to significantly increase the incidence of SPMs [5-6]. The most common site of HNSCC SPMs is lung, followed by HN, and esophagus [5, 7-8], attributing to about 60% of all SPMs combined.

Patients who develop an SPM tend to have a significantly worse survival, compared to those who do not[7]. Head and neck SPMs have a relatively better prognosis than SPMs arising in lung or esophagus, with a 5-yr survival of 61%, 19%, and 0%, respectively [2, 9]. Lung SPM patients after an HNSCC primary tumor have a worse prognosis compared with the matched general population with primary lung cancer, regardless of the histology [10]. All these findings highlight the importance of better understanding and management of...
In this population-based study, we aim to compare the survival outcomes across treatment types in HNSCC patients who developed an HN, lung, or esophagus SPM and to determine whether there is any association between risk factors and the survival in SPM patients.

**Materials And Methods**

**The Surveillance, Epidemiology, and End Results program and Multiple Primary–Standardized Incidence Ratios session**

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the US, which routinely collects data on patient demographics, tumor site, morphology, stage at diagnosis, course of treatment, and follow-up for vital status, with quality control routinely performed since 1973 and now covers approximately 28% of the US population[11]. The NCI does not require institutional board approval for the use of SEER data.

The Standardized Incidence Ratios’ (MP-SIR) session is a session under the SEER program, in which a defined cohort of people previously diagnosed with cancer is followed through time to compare their subsequent primary cancer experience to the matching general population[12]. By extracting the detailed information of the secondary cancers, one can also look into the risk factors, management techniques, and survival outcomes of specific SPMs[13].

**Study population and treatment categories**

The SEER*Stat 8.2.1 software package (SEER, National Cancer Institute, MD, USA) and the MP-SIR session were used to identify patients who were diagnosed with a primary HNSCC and then developed SPMs between 1973 and 2011 in the nine registries of the SEER program. Patients with HNSCC were defined using the International Classification of Diseases for Oncology, third edition (ICD-O–3), histology codes for squamous cell carcinoma (8070-8078), and subsite codes for head and neck cancer (oral cavity, oropharynx, hypopharynx, larynx, and nasopharynx). All patients included were in ‘active follow-up’ or ‘originally inactive, then active follow-up’ as defined in the database. Given the relatively small study population for each SPM subsite, the stage at presentation was categorized according to the SEER historic stage A codes as ‘localized’ (localized without lymph node involvement or distant metastases, N0M0), ‘regional’ (locally advanced or lymph node-positive without distant metastases, N+M0), or ‘distant’ (distant metastases, any N M1)[14]. SPM was defined as an invasive solid tumor developing ≥2 months after an index HNSCC as per National Cancer Institute criteria[15]. Patients with HN, lung, and esophagus SPMs were drawn from the case listing sheet, and the ones who died from the index tumor, developed a third malignancy, or had an unstaged disease were excluded.

Two SEER variables ‘Site specific surgery (1983-1997)’ and ‘Surgery of the primary site (1988+)’ were recoded together to define and categorize the surgical treatment received. Radiation therapy (RT) was limited to ‘Beam radiation’ (SEER code 1) and ‘Combination of beam and implants or isotopes’ (SEER code 4). For HN SPMs, treatment categories were defined as: ‘conservative surgery (CS, SEER codes 10-30, including electroautery, cryosurgery, laser surgery, local excision, partial pharyngectomy, tonsillectomy, and partial laryngectomy, etc., but excluded excisional biopsy)’, ‘radical surgery (RS, SEER codes 40-90, including radical excision with/without lymph nodes dissection, total laryngectomy, and pharyngolaryngectomy, etc.)’, ‘radiation (RT)’, ‘conservative surgery with radiation (CSRT)’, ‘radical surgery with radiation (RSRT)’, and ‘no treatment’ group. We acknowledge that for pharynx, in ‘Surgery of the primary site (1998+)’ manual, code 30 also includes total pharyngectomy. However, for simplicity, we categorized it in the CS group. CS and CSRT groups (including local tumor destruction as laser ablation, cryosurgery, electroautery, and photodynamic therapy with/without radiation) were excluded from lung and esophagus SPMs because of atypical treatment patterns and very small patient number. For lung SPMs, RS was defined as SEER codes 20-90, including wedge resection, segmental resection, lobectomy, pneumonectomy, radical pneumonectomy, and extended pneumonectomy. For esophagus SPMs, RS was defined as SEER codes 40-90 in the ‘Site specific surgery (1983–1997)’ manual and 30-90 in the ‘Surgery of the primary site (1998+)’ manual and included partial/total esophagectomy with/without laryngectomy and/or gastrectomy.

**Statistical analysis**

Descriptive statistics were calculated to characterize the study cohort in relation to demographic factors, social-economic status, and tumor characteristics. The primary endpoint was cancer-specific survival (CSS). For CSS, the patients with deaths due to causes other than cancer were censored. A secondary endpoint was overall survival (OS). Time for both CSS and OS was calculated as time in months from the diagnosis of the SPM tumor to the date of death from any cause, or to the date of last follow-up if a patient did not have a recorded death. Kaplan-Meier survival analyses were performed to evaluate CSS and OS by SPM tumor staging and treatment group, stratified by SPM subsite. All analyses were used to produce relevant survival estimates and to employ the log-rank test for comparison of CSS/OS between the different groups of interest.
Unadjusted Cox proportional hazards regression analyses were performed to evaluate the impact of all demographic, social-economic, and tumor factors on CSS, stratified by SPM subsite. Multivariable Cox proportional hazards regression analyses was then performed with all variables included that were significant at the 0.20 alpha level from the unadjusted analyses. ‘Age at index tumor’ and ‘year of index tumor’ were excluded because of their collinearity with corresponding SPM data. Competing-risks survival regression was also performed to check the multivariable CSS hazard ratios by accounting for the competing event of death due to causes other than cancer (based on Fine and Gray’s proportional subhazards model). All p-values are two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals (CI) for unadjusted and adjusted HRs and subhazard ratios were calculated to assess the precision of the obtained estimates. All analyses were performed using R-3.2.0 for Windows 64 bit (R-statistics.com, Vienna, Austria).

Results

Description of study population

A total of 3,138 patients with a median follow-up of 12 months were identified, of which, 1,056 patients developed an HN SPM (33.7%), 1,717 patients developed a lung SPM (54.7%), and 265 patients developed an esophagus SPM (8.4%). The patient and tumor characteristics are summarized in Table 1. The median age for index and secondary tumor was 61 years, and 69 years, respectively. The median time interval from the diagnosis of an index tumor to an SPM was 70 months (range 2-242 months). It was found that 51.5% had a localized or regional (42.7%) index tumor. In patients with lung SPMs, 45.1% of patients (N=775) had distant disease at diagnosis (Table 1).
### Year at diagnosis of SPM

| Year      | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|-----------|-----------|-----------|-----------|-----------|
| N/A       | 56 (1.8)  | 474 (15.6)| 1126 (37.1)| 1382 (45.5)|
| N/A       | 45 (4.3)  | 206 (19.7)| 723 (42.1)| 507 (48.0)|
| N/A       | N/A       | 37 (11.5) | 107 (40.4)| 797 (46.4)|
| N/A       | N/A       | 69 (26.0)| 61 (23.0)| 78 (29.4)|

### Median Months since Index Tumor (mo)

| Year      | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|-----------|-----------|-----------|-----------|-----------|
| N/A       | 70.00     | 73.00     | 70.00     | 73.00     |
| N/A       | 68.00     | 36.40     | 70.60     | 66.40     |

### Marital Status

| Status    | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|-----------|-----------|-----------|-----------|-----------|
| Unmarried | 1176 (38.7)| 372 (35.2)| 698 (40.7)| 106 (40.0)|
| Married   | 1730 (56.9)| 606 (57.4)| 976 (56.8)| 148 (55.8)|
| Unknown   | 132 (4.3) | 78 (7.4)  | 43 (2.5)  | 11 (4.2)  |

### % At Least Bachelors Degree (2000)

| %       | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|---------|-----------|-----------|-----------|-----------|
| ≤25     | 1187 (39.1)| 397 (37.6)| 701 (40.8)| 89 (33.6)|
| >25     | 1851 (60.9)| 659 (62.4)| 1016 (59.2)| 176 (66.4)|

### Median Family Income (in Ks, 2000)

| Income   | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|----------|-----------|-----------|-----------|-----------|
| ≤50      | 949 (31.2)| 329 (31.2)| 542 (31.6)| 78 (29.4)|
| >50      | 2089 (68.8)| 727 (68.8)| 1175 (68.4)| 187 (70.6)|

### % Families below Poverty (2000)

| Poverty | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|---------|-----------|-----------|-----------|-----------|
| ≥10     | 599 (19.7)| 195 (18.5)| 328 (19.1)| 76 (28.7)|
| <10     | 2439 (80.3)| 861 (81.5)| 1389 (80.9)| 189 (71.3)|

### Index Tumor Staging

| Stage   | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|---------|-----------|-----------|-----------|-----------|
| Localized | 1564 (51.5)| 645 (61.1)| 813 (47.4)| 106 (40.0)|
| Regional | 1297 (42.7)| 359 (34.0)| 795 (46.3)| 143 (54.0)|
| Distant  | 177 (5.8) | 52 (4.9) | 109 (6.3) | 16 (6.0) |

### SPM Tumor Staging

| Stage   | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|---------|-----------|-----------|-----------|-----------|
| Localized | 1136 (37.4)| 619 (58.6)| 420 (24.5)| 97 (36.6)|
| Regional | 981 (32.3)| 366 (34.7)| 522 (30.4)| 93 (35.1)|
| Distant  | 921 (30.3)| 71 (6.7) | 775 (45.1)| 75 (28.3)|

### Treatment

| Modality | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|----------|-----------|-----------|-----------|-----------|
| CS       | 270 (8.9) | 270 (25.6)| N/A       | N/A       |
| RS       | 471 (24.4)| 307 (29.1)| 384 (22.4)| 50 (18.9)|
| RT       | 909 (29.9)| 163 (15.4)| 623 (36.3)| 123 (46.4)|
| CSRT     | 45 (1.5) | 45 (4.3) | N/A       | N/A       |
| RSRT     | 204 (6.7) | 83 (7.9) | 85 (5.0) | 36 (13.6)|
| None     | 869 (28.6)| 188 (17.8)| 625 (36.4)| 56 (21.1)|

### Vital Status

| Status   | 1973-1980 | 1981-1990 | 1991-2000 | 2001-2011 |
|----------|-----------|-----------|-----------|-----------|
| Alive    | 630 (20.7)| 403 (38.2)| 202 (11.8)| 25 (9.4)|
Noncancer Deaths 685 (22.5) 360 (34.1) 289 (16.8) 36 (13.6)
SPM Specific Deaths 1572 (51.7) 209 (19.8) 1168 (68.0) 195 (73.6)
Unknown Cause Deaths 151 (5.0) 84 (8.0) 58 (3.4) 9 (3.4)

TABLE 1: Descriptive Characteristics by SPM Subsite (1973-2011)

Overview of SPM survival by subsite
The study cohort had a median OS of 14 months (13-15 months) and a median CSS of 22 months (20-26 months). HN SPMs (Table 2) 5-yr OS was 44.0%, (40.7-47.5%) and 5-yr CSS 75.6%, (72.4-78.9%). Patients with esophagus SPM had a 5-yr OS and 5-yr CSS less than 10.0%. The SPM staging was closely correlated with survival, except esophageal SPMs where there was no survival difference between localized versus non-localized SPMs (Figures 1A-1C).

| Site      | 5-yr OS (%) | 95% CI | 5-yr CSS (%) | 95% CI | HR (CSS) |
|-----------|-------------|--------|--------------|--------|----------|
| All Sites | 22.6        | 21.0-24.3 | 38.8        | 36.8-40.9 | NA       |
| HN (R)    | 44.0        | 40.7-47.5 | 75.6        | 72.4-78.9 | 1.000    |
| Lung      | 12.4        | 10.8-14.2 | 20.5        | 18.3-23.0 | 6.152*** |
| Esophagus | 4.9         | 2.7-8.9  | 8.7         | 5.1-14.8  | 7.051*** |

TABLE 2: Overview of Survival Outcomes by Subsite
Abbreviations: CI, confidence interval; CSS, cause-specific survival; HN, head and neck; HR, hazard ratio; OS, overall survival; R, reference.
***p<0.001

FIGURE 1: Cause-specific Survival by Stage
A. Cause-specific survival of HN SPMs by SPM Staging (Log-rank <0.001)
B. Cause-specific survival of lung SPMs by SPM Staging (Log-rank <0.001)
C. Cause-specific survival of esophagus SPMs by SPM Staging (Log-rank<0.001)
** p<0.01, *** p<0.001 compared with corresponding localized SPMs

Correlation between treatment type and site-specific survival
For HN SPMs, surgical resection was the most frequently performed treatment (RS 29.1% and CS 25.6%, Table 1). Patients who received CSRT had 2-yr OS of 87.1% (77.1-98.4%) and a 5-yr OS 65.2% (48.9-86.9%), while patients who received CS showed a 5-yr CSS of 89.9% (85.6-94.5%). The RSRT group had 5-yr CSS of 57.9% (46.2-72.6%) (Table 3). Interestingly, the 'no treatment' group revealed a comparable survival to RS (5-yr CSS 74.5% (67.6-82.1%)), especially in localized SPMs (unadjusted HR of 0.548 (p<0.1)) (Table 4).

| SPM Site | Treatment | 2-yr OS (95% CI) (%) | 5-yr OS (95% CI) (%) | 2-yr CSS (95% CI) (%) | 5-yr CSS (95% CI) (%) | HR (CSS) |
| --- | --- | --- | --- | --- | --- | --- |
| HN | CS | 78.3 (73.2-83.8) | 57.2 (50.7-64.6) | 93.0 (89.6-96.5) | 89.9 (85.6-94.5) | 0.295*** |
| | RS (R) | 61.3 (55.9-67.1) | 35.3 (29.9-41.6) | 84.5 (80.0-89.2) | 72.1 (65.8-78.9) | 1.000 |
| | RT | 60.0 (52.6-68.4) | 35.9 (28.3-45.4) | 72.0 (64.8-80.0) | 67.4 (59.5-76.3) | 1.375 |
| | CSRT | 87.1 (77.1-98.4) | 65.2 (48.9-86.9) | 97.5 (92.8-100.0) | 82.1 (66.7-100.0) | 0.364* |
| | RSRT | 62.4 (52.4-74.2) | 36.0 (26.3-49.2) | 81.4 (72.6-91.1) | 57.9 (46.2-72.6) | 1.484 |
| | None | 63.8 (56.9-71.4) | 47.7 (40.4-56.3) | 79.9 (73.8-86.5) | 74.5 (67.6-82.1) | 1.017 |
| Lung | Treatment | 1-yr OS (95% CI) (%) | 2-yr OS (95% CI) (%) | 1-yr CSS (95% CI) (%) | 2-yr CSS (95% CI) (%) | HR (CSS) |
| --- | --- | --- | --- | --- | --- | --- |
| | RS (R) | 73.2 (68.9-77.9) | 60.8 (56.0-66.1) | 81.3 (77.3-85.5) | 70.6 (65.8-75.8) | 1.000 |
| | RT | 35.1 (31.5-39.2) | 15.0 (12.3-18.2) | 40.4 (36.5-44.7) | 22.0 (18.5-26.0) | 3.765*** |
| | RSRT | 75.6 (66.8-85.5) | 36.3 (27.1-48.6) | 78.9 (70.4-88.3) | 39.2 (29.5-52.1) | 1.969*** |
| | None | 16.4 (13.6-19.7) | 7.1 (5.26-9.65) | 21.0 (17.8-24.9) | 11.6 (8.92-15.1) | 6.542*** |
| Esophagus | Treatment | 1-yr OS (95% CI) (%) | 2-yr OS (95% CI) (%) | 1-yr CSS (95% CI) (%) | 2-yr CSS (95% CI) (%) | HR (CSS) |
| --- | --- | --- | --- | --- | --- | --- |
| | RS (R) | 51.9 (39.7-67.8) | NA | 61.4 (48.8-77.3) | NA | 1.000 |
| | RT | 36.9 (29.1-46.8) | NA | 44.0 (35.5-54.5) | NA | 1.277 |
| | RSRT | 35.5 (22.5-55.9) | NA | 47.8 (32.7-69.9) | NA | 1.080 |
| | None | 26.1 (16.7-40.9) | NA | 29.4 (19.1-45.3) | NA | 2.019** |

| TABLE 3: Survival of SPMs by Subsite |

Abbreviations: SPM, second primary cancer; CS, conservative surgery; RS, radical surgery; RT, radiation therapy; CSRT, conservative surgery with radiation; RSRT, radical surgery with radiation; HN, head and neck; R, reference; OS, overall survival; CSS, cause-specific survival; HR, hazard ratio; CI: confidence interval.

. p<0.1, * p<0.05, ** p<0.01, ***p<0.001
**TABLE 4: Cause Specific Survival of SPMs by Subsite and Stage**

Abbreviations: SPM, second primary cancer; CS, conservative surgery; RS, radical surgery; RT, radiation therapy; CSRT, conservative surgery with radiation; RSRT, radical surgery with radiation; HN, head and neck; R, reference; OS, overall survival; CSS, cause-specific survival; HR, hazard ratio; CI, confidence interval.

. p<0.1, * p<0.05, ** p<0.01, ***p<0.001

- **Lung**
  - In the lung SPM cohort, 591 patients (83.5%) were diagnosed with a regional or distant disease and radiation was the most commonly used treatment. It was found that 384 cases (22.4%) (232 localized, 60.4%) received surgical resection as the only treatment (Table 1). The RS group had a 2-yr OS of 60.8% (56.0-66.1) and 2-yr CSS of 70.6% (65.8-75.8%), followed by the RSRT group (Table 3), which remained to be the most superior when categorized into stages (Table 4).

- **Esophagus**
  - In the esophagus SPM group, (Tables 2-3), 1-yr OS was 51.9%, (39.7-67.8%) and 1-yr CSS was 61.4%, (48.8-77.3%), which was observed in RS group (Table 3).

**Impact on survival**

In the multivariable model (Table 5), 'SPM staging' was an independent predictor of CSS among all three subsites. 'Index tumor staging' was also adversely correlated with survival except for esophagus SPMs. Younger age at diagnosis and being black were correlated with better survival outcome in lung SPM patients.
| Factors                  | HN HR (95% CI) | Lung HR (95% CI) | Esophagus HR (95% CI) |
|-------------------------|---------------|-----------------|-----------------------|
| Age of SPM              | 1.012 (0.999-1.026) | 1.011** (1.005-1.018) | 1.000 (0.999-1.001) |
| Months since Index Tumor| 1.000          |                  | 0.999-1.001           |
| Gender                  |                |                 |                       |
| Male (referent)         | 1.000          | 1.000           |                       |
| Female                  | 0.760 (0.540-1.072) | 0.926 (0.810-1.057) |                       |
| Ethnicity               |                |                 |                       |
| White (R)               | 1.000          | 1.000           |                       |
| Black                   | 1.226 (0.736-2.042) | 0.783* (0.629-0.975) |                       |
| Other                   | 0.763 (0.333-1.749) | 0.982 (0.722-1.337) |                       |
| Marital Status          |                |                 |                       |
| Unmarried (R)           | 1.000          | 1.000           |                       |
| Married                 | 0.827 (0.609-1.124) | 0.914 (0.808-1.033) | 0.767 (0.560-1.031)  |
| Unknown                 | 0.964 (0.535-1.735) | 0.966 (0.658-1.417) | 1.005 (0.430-2.349)  |
| % At Least Bachelors Degree |                |                 |                       |
| ≤25 (R)                 | 1.000          |                 |                       |
| >25                     | 1.144 (0.757-1.730) |               |                       |
| Median Family Income (K) |                |                 |                       |
| ≤50 (R)                 | 1.000          | 1.000           |                       |
| >50                     | 1.269 (0.761-2.118) | 0.931 (0.820-1.057) |                       |
| % Families below Poverty |                |                 |                       |
| >=10 (R)                | 1.000          |                 |                       |
| <10                     | 0.797 (0.507-1.254) |               |                       |
| Index Tumor Staging     |                |                 |                       |
| Localized (R)           | 1.000          | 1.000           | 1.000                 |
| Regional                | 1.569** (1.168-2.107) | 1.186** (1.048-1.341) | 1.122 (0.834-1.509)  |
| Distant                 | 2.180** (1.252-3.793) | 1.171 (0.904-1.518) | 0.626 (0.325-1.205)  |
| SPM Tumor Staging       |                |                 |                       |
| Localized (R)           | 1.000          | 1.000           | 1.000                 |
| Regional                | 2.804*** (2.009-3.914) | 1.985*** (1.642-2.400) | 1.127 (0.795-1.598)  |
| Distant                 | 5.247*** (3.384-8.138) | 3.427*** (2.826-4.156) | 1.714** (1.182-2.484) |
| Treatment               |                |                 |                       |
| CS                      | 0.429** (0.257-0.715) |               |                       |
| RS (R)                  | 1.000          | 1.000           | 1.000                 |
| RT                      | 1.233 (0.842-1.807) | 2.428*** (1.976-2.978) | 1.200 (0.802-1.795)  |
| CSRT                    | 0.430 (0.156-1.189) |           | NA                  |
| RSRT                    | 1.027 (0.656-1.607) | 1.469* (1.073-2.012) | 1.013 (0.598-1.718)  |
| None                    | 1.385 (0.924-2.076) | 3.475*** (2.793-4.323) | 1.624* (1.010-2.612) |

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CS showed the highest CSS after adjusting for all the covariates in all HN SPMs (HR 0.429 compared with RS, p<0.01, Table 5) and by stages (localized SPM HR 0.430, regional SPM HR 0.249 compared with RS, p<0.05, Table 6). Patients with localized HN SPM who received no treatment showed a comparable CSS versus RS (HR 0.685, p>0.1) (Table 6). Surgical intervention was superior compared to all the other groups in lung SPMs. However, in esophagus SPMs, no survival difference was observed among treatment types (Table 5).
| Factors                  | Localized |          | Regional |          |
|-------------------------|-----------|----------|----------|----------|
|                         | HR        | 95% CI   | HR       | 95% CI   |
| **Gender**              |           |          |          |          |
| Male (R)                | 1.000     |          |          |          |
| Female                  | 0.609     | 0.368-1.008 |          |          |
| **Ethnicity**           |           |          |          |          |
| White (R)               | 1.000     |          |          |          |
| Black                   | 0.997     | 0.411-2.422 |          |          |
| Other                   | 2.124     | 0.504-8.952 |          |          |
| **Marital Status**      |           |          |          |          |
| Unmarried (R)           | 1.000     |          |          |          |
| Married                 | 0.545*    | 0.326-0.911 |          |          |
| Unknown                 | 0.858     | 0.371-1.983 |          |          |
| **% At Least Bachelors Degree** |   |      |          |          |
| ≤25 (R)                 | 1.000     |          |          |          |
| >25                     | 1.608*    | 1.052-2.457 |          |          |
| **% Families below Poverty** | |    |          |          |
| ≥10 (R)                 | 1.000     |          |          |          |
| <10                     | 0.787     | 0.418-1.480 |          |          |
| **Index Tumor Staging** |           |          |          |          |
| Localized (R)           | 1.000     |          | 1.000    |          |
| Regional                | 1.944*    | 1.151-3.282 | 1.618*   | 1.072-2.442 |
| Distant                 | 3.854***  | 1.774-8.374 | 1.395    | 0.432-4.511 |
| **Treatment**           |           |          |          |          |
| CS                      | 0.430*    | 0.220-0.838 | 0.249*   | 0.075-0.821 |
| RS (R)                  | 1.000     |          | 1.000    |          |
| RT                      | 1.218     | 0.593-2.502 | 1.443    | 0.861-2.417 |
| CSRT                    | 0.566     | 0.132-2.423 | 0.404    | 0.958-1.704 |
| RSRT                    | 1.112     | 0.329-3.764 | 1.068    | 0.595-1.918 |
| None                    | 0.685     | 0.342-1.373 | 2.375**  | 1.299-4.341 |

**TABLE 6: Multivariable Analysis of Impact of Factors on HN SPM CSS by Stage**

Abbreviations: SPM, second primary cancer; CS, conservative surgery; RS, radical surgery; RT, radiation therapy; CSRT, conservative surgery with radiation; RSRT, radical surgery with radiation; HN, head and neck; R, reference; CSS; cause-specific survival; HR, hazard ratio; CI: confidence interval.

. p<0.1, * p<0.05, ** p<0.01, ***p<0.001

**Discussion**

Our population-based study showed outcomes of various treatment modalities for SPMs after primary HN SCC. Based on the results of our study, it seems that aggressive surgical approaches with adjuvant radiation may be the better option compared to more conservative approaches in most patients except esophageal
SPMs.

Our study (Supplementary 1) confirmed that the burden of SPMs is elevated in HNSCC patients, with a standardized incidence risk (SIR) of 1.90 (p<0.05) and an absolute excess risk (AER) of 167 per 10,000 person years (PYR) compared to the age-, gender-, and calendar year-matched normal population.

Our study found a 5-yr OS of 22.6% from the time of diagnosis of SPM (Table 2), which is significantly lower than the recent reports on >60% 5-yr OS for HN cancers [16-17]. In addition, SPMs arising in the lung and esophagus had a 5-yr OS of 12.4% and 4.9%, respectively, which is significantly worse than those with an HN SPMs (Table 2) and worse than the reported corresponding primary cancer survival as well [18-19].

For HN SPMs, the management is sometimes complicated by the effects of prior treatment, including anatomical changes, risk of re-irradiation, as well as the multifocal nature of these tumors [20]. Thus, often, they are managed similarly as recurrent diseases. In our study cohort, 66.8% HN SPM patients underwent some sort of surgical resection (Table 1). The unequal survival across conservative and radical surgery groups in HN SPMs was somewhat unexpected, especially in regional SPMs. To our knowledge, there are no studies specifically comparing the outcomes between conservative and radical approaches in HN SPMs. Evidence from observational series in primary and recurrent HN tumors suggests that conservative procedures may be able to offer an alternative option for carefully selected patients [21-22]. For example, Ganly, et al. [22] reported that for early-stage recurrent glottis larynx tumors, partial laryngectomy gives a significantly greater 5-yr survival compared with total laryngectomy. Collectively, our findings raise important questions for surgical treatment selection in HN SPMs after HNSCC.

Interestingly, patients who did not receive any intervention for HN SPMs showed a comparable outcome to surgery (5-yr CSS 88.0%, CSS HR 0.685, p>0.05) (Tables 3-5, Supplementary 2). We are not sure of the reason for this finding except that the retrospective nature of data limits information about histology, chemotherapy or other interventions. A possible explanation may be that ‘no intervention’ preserves the immunological status of the patient to fight cancer progression and such patients may be better if left untreated.

Patients with lung SPMs showed best outcomes when treated with RS alone while patients who received RT only were found to have the worst outcomes (Tables 3-5). This may be due either to advanced stage of presentation or due to conventional RT techniques in the years considered in this data collection. Conventional RT has traditionally been considered inferior to surgical resection in lung cancer treatment outcomes. However, in the last decade, increasing utilization of novel RT techniques such as stereotactic body radiation therapy (SBRT) has resulted in excellent local controls for early stage cancer, and future long term outcome data will likely result in significantly better RT outcomes, compared to conventional RT [23]. Lung SPM patients who had RSRT fared worse compared with those who underwent surgery alone (Tables 3, 5). Some studies in primary lung cancer treatment have shown that postoperative RT may not improve OS [24-25]. A randomized trial from France [26] reported that the non-cancer-related death increased with the RT dose delivered per fraction.

Conventional treatment options for esophagus cancer include surgical resection [27], preoperative concurrent chemoradiotherapy or neoadjuvant chemotherapy followed by resection [28-29]. Our study failed to demonstrate the superiority of any one treatment option over another in the management of esophageal SPMs.

In the diagnostic time-controlled multivariable analysis, ‘SPM staging’ was found to be the survival predictor among all SPMs (Table 5). Blacks did better than whites in lung SPMs (Table 5). However, we acknowledge that race was unequally distributed in our study cohort (155 blacks vs. 1497 whites), which could potentially affect statistical results. Interestingly, consistent with prior studies [30], being married was found favorable in HN and lung SPMs in univariate analysis (Supplementary 3) but not in esophageal SPMs.

As in any SEER-based study, limitations [11, 14] of our study include incomplete information on adjuvant therapy, systemic treatment information, risk factors, coding reliability, and patient migration. However, we hope that the large patient numbers and the information that is available is enough to give us an idea about the management options in this subgroup of patients, and this may be useful for clinical decision making as well as generating a hypothesis for a prospective trial.

Conclusions

SPMs after an index HNSCC are considerably common and negatively impact the survival. The overall prognosis of SPMs after HNSCC has significantly improved over the years but is still poor compared with corresponding primary tumors. In HN SPMs and lung SPMs, conservative surgery with or without adjuvant radiation may be the best treatment option. Esophageal SPMs showed equivalent outcomes irrespective of the type of treatment. Some SPMs can potentially be left untreated or be managed conservatively.

Appendices
| Subsite                        | Observed Cases | Expected Cases | SIR Rate  | 95% CI     | Excess Risk per 10,000 PYR |
|-------------------------------|----------------|----------------|-----------|------------|--------------------------|
| All Sites                     | 20,081         | 10556.71       | 1.90*     | 1.88-1.93  | 167.31                   |
| Lung and Bronchus             | 5,972          | 1716.62        | 3.48*     | 3.39-3.57  | 74.75                    |
| Head and Neck                 | 4,233          | 403.55         | 10.49*    | 10.18-10.81| 67.27                    |
| Oral Cavity and Pharynx       | 3,714          | 276.47         | 13.43*    | 13.00-13.87| 60.39                    |
| Larynx                        | 519            | 127.08         | 4.08*     | 3.74-4.45  | 6.88                     |
| Esophagus                     | 972            | 135.58         | 7.17*     | 6.73-7.63  | 14.69                    |

**TABLE 7: Sup 1. Elevated Risk of SPM after HNSCC by Subsite**

Abbreviations: CI: confidence interval; HNSCC, head and neck squamous cell carcinoma; PYR, persons year at risk; SIR, standardized incidence ratio; SPM, second primary cancer.

*P<0.05

| Treatment | All Stages | Localized | HR (95% CI) | HR (95% CI) | HR CSS |
|-----------|------------|-----------|-------------|-------------|--------|
| Untreated |            |           | 5-yr OS (%) | 5-yr CCS (%)| CSS (%)|
|           | 47.7 (40.4-56.3) | 74.5 (67.6-82.1) | 1.217 | 59.5 (50.9-69.6) | 88.0 (81.8-94.7) | 0.826 |
| Treated   | 43.2 (39.6-47.1) | 75.8 (72.3-79.4) | 1.000 | 51.3 (46.5-56.6) | 86.4 (82.7-90.4) | 1.000 |

**TABLE 8: Sup 2. Survival Between Treated and Untreated HN SPMs**

Abbreviations: CI: confidence interval; CSS: cause-specific survival; HN, head and neck; HR, hazard ratio; OS, overall survival; R, reference; SPM, second primary cancer.

| Factors | HN | Lung | Esophagus |
|---------|----|------|-----------|
| Age of Index Tumor | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| ≤45 (referent) | 1.00 | 1.00 | 1.00 |
| 46-55 | 1.609 (0.883-2.931) | 1.095 | 0.805 (0.419-1.546) |
| 56-65 | 2.814*** (1.607-4.930) | 1.145 | 0.921 (0.490-1.732) |
| 66-75 | 1.952* (1.069-3.564) | 1.288 | 0.769 (0.397-1.492) |
| >75 | 1.098 (0.475-2.538) | 1.498* | 1.241 (0.526-2.925) |

| Age of SPM | HR (95% CI) | HR (95% CI) | HR (95% CI) |
|------------|-------------|-------------|-------------|
| ≤45 (referent) | 1.00 | 1.00 | 1.00 |
| 46-55 | 2.420 (0.716-8.178) | 2.133 (0.932-4.881) | 0.515 (0.195-1.360) |
| 56-65 | 3.055 (0.959-9.732) | 2.135 (0.952-4.791) | 0.684 (0.274-1.706) |
| 66-75 | 4.676** (1.477-14.811) | 2.219 (0.991-4.967) | 0.648 (0.281-1.608) |

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| Months since Index Tumor (Categorical) | 2-36 (referent) | 37-72 | 73-108 | 109-144 (>108 for Esophagus) | 145-180 | >=181 |
|--------------------------------------|----------------|-------|--------|-----------------------------|---------|-------|
|                                      | 1.000          | 0.936 (0.644-1.361) | 0.900 (0.604-1.340) | 0.929 (0.589-1.466) | 0.667 (0.352-1.265) | 0.894 (0.546-1.464) |
|                                      |                | 1.112 (0.947-1.307) | 1.042 (0.874-1.242) | 1.183 . (0.969-1.445) | 1.121 (0.886-1.420) | 1.198 . (0.990-1.450) |
|                                      |                | 1.524* (1.043-2.228) | 1.107 (0.733-1.671) | 1.238 (0.844-1.816) |                |       |
| Gender                               | Male (referent) | 1.000 |       | 1.000 | 1.000 |       |
|                                      | Female         | 0.781 (0.564-1.080) |       | 1.092 (0.962-1.240) |       | 1.113 (0.786-1.576) |
| Ethnicity                            | White (referent)| 1.000 |       | 1.000 | 1.000 |       |
|                                      | Black          | 1.632 * (1.048-2.542) |       | 0.838 (0.676-1.038) |       | 1.142 (0.814-1.602) |
|                                      | Other          | 0.885 (0.437-2.222) |       | 0.956 (0.705-1.298) |       | 1.397 (0.829-2.354) |
| Year at diagnosis of index tumor     | 1973-1980 (referent) | 1.000 |       | 1.000 | 1.000 |       |
|                                      | 1981-1990      | 1.020 (0.736-1.412) |       | 0.943 (0.773-1.152) |       | 1.144 (0.799-1.638) |
|                                      | 1991-2000      | 0.465*** (0.316-0.683) |       | 0.913 (0.749-1.113) |       | 1.084 (0.713-1.647) |
|                                      | 2001-2011      | 0.131*** (0.056-0.303) |       | 0.585*** (0.484-0.738) |       | 0.396** (0.214-0.736) |
| Year at diagnosis of SPM             | 1973-1980 (referent) (NA for Lung) | 1.000 |       |       | 1.000 |       |
|                                      | 1981-1990 (referent for Lung) | 1.019 (0.584-1.778) |       | 1.000 |       | 0.834 (0.424-1.641) |
|                                      | 1991-2000      | 0.814 (0.470-1.409) |       | 1.041 (0.866-1.252) |       | 1.185 (0.614-2.287) |
|                                      | 2001-2011      | 0.248*** (0.135-0.453) |       | 0.789* (0.654-0.952) |       | 0.550 . (0.273-1.110) |
| Marital Status                       | Unmarried (referent) | 1.000 |       | 1.000 | 1.000 |       |
|                                      | Married        | 0.709* (0.534-0.943) |       | 0.881* (0.783-0.991) |       | 0.808 (0.604-1.081) |
|                                      | Unknown        | 0.774 (0.439-1.365) |       | 0.958 (0.655-1.403) |       | 0.739 (0.322-1.697) |
| % At Least Bachelors Degree          | ≤25            | 1.000 |       | 1.000 | 1.000 |       |
|                                      | >25            | 1.257 (0.929-1.648) |       | 1.011 (0.900-1.137) |       | 1.074 (0.793-1.454) |
| Median Family Income                 | ≤50            | 1.000 |       | 1.000 | 1.000 |       |
|                                      | >50            | 1.249 (0.919-1.696) |       | 0.922 (0.815-1.042) |       | 1.058 (0.771-1.452) |
| % Families below Poverty             | ≥10 (referent) | 1.000 |       | 1.000 | 1.000 |       |
|                                      | <10            | 0.800 (0.577-1.110) |       | 1.025 (0.883-1.191) |       | 1.003 (0.729-1.379) |
| Treatment | CSS (R) | RS | RT | CSRT | RSRT | None |
|-----------|---------|----|----|------|------|------|
| **Localized (referent)** | 1.000  | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| **Regional** | 1.733*** (1.304-2.302) | 1.096 (0.974-1.234) | 1.162 (0.868-1.557) | 3.219*** (2.378-4.358) | 2.262*** (1.885-2.715) | 1.146 (0.815-1.610) |
| **Distant** | 2.601*** (1.535-4.405) | 0.911 (0.706-1.176) | 0.643 (0.341-1.209) | 7.171*** (4.738-10.855) | 5.869*** (4.925-6.993) | 1.944*** (1.361-2.777) |

**TABLE 9: Sup 3. Univariate Analysis of Impact of Factors on CSS by Subsite**

Abbreviations: CI: confidence interval; CS, conservative surgery; CSS, cause-specific survival; CSRT, conservative surgery with radiation; HN, head and neck; HR, hazard ratio; OS, overall survival; R, reference; RS, radical surgery; RSRT, radical surgery with radiation; RT, radiation therapy; SPM, second primary cancer.

. p<0.1, * p<0.05, ** p<0.01, ***p<0.001

**Additional Information**

**Disclosures**

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