Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Priti Shah Date

Follow-up Imaging and Survival in Head and Neck Cancer Patients
By

Priti Shah
MPH

Epidemiology

_____
Dr. Michael Goodman, MD, MPH
Committee Chair

Follow-up Imaging and Survival in Head and Neck Cancer Patients

By

Priti Shah

B.S.
University of North Carolina at Chapel Hill
2010

Thesis Committee Chair: Dr. Michael Goodman, MD, MPH

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2017

Abstract

Follow-up Imaging and Survival in Head and Neck Cancer Patients
By Priti Shah

An important part of post-diagnosis follow-up and care for head and neck cancers (HNC) is surveillance imaging aimed at early detection of disease recurrence. This study investigates if imaging initiated at least 6 months post- diagnosis of HNC leads to better overall survival. The data for analyses were obtained from the Surveillance Epidemiology and End Results (SEER)-Medicare Linkage file. The person time intervals that included imaging by X-ray, computed tomography (CT) and/or positron emission tomography (PET) were compared to the reference intervals that did not include any imaging. The outcome, disease-specific survival, was ascertained during the follow-up and was used as a proxy for HNC recurrence. A total of 25,403 patients diagnosed with HNC between 1992 and 2007 were included in the study and contributed 100,988 person- months of follow-up. After adjusting for relevant covariates using a time-dependent extended Cox model, the cancer-specific mortality rate following imaging was 2.58 times higher (95% confidence interval: 2.38-2.79) than the corresponding rate without imaging. These findings indicate that post-diagnosis imaging among HNC patients, as documented in Medicare claims, is likely performed for clinical rather than surveillance reasons. A proper analysis of the association between surveillance imaging and disease prognosis requires more detailed information about indications for testing among asymptomatic patients. Imaging in the current analysis is probably a surrogate for disease severity and/or recurrence.

Follow-up Imaging and Survival in Head and Neck Cancer Patients

By

Priti Shah

B.S.
University of North Carolina at Chapel Hill
2010

Thesis Committee Chair: Dr. Michael Goodman, MD, MPH

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2017

ACKNOWLEDGEMENTS

This study was supported by Amy Chen, Kevin Ward, Nicole Regan.

TABLE OF CONTENTS

1. CHAPTER I: BACKGROUND

Head and neck cancers (HNC) are a group of diverse malignancies originating in the oral cavity, pharynx, larynx, tonsils, thyroid, salivary glands, parotid glands, and sinuses (1, 2). HNC is the sixth most common cancer category globally with approximately 630,000 new cases diagnosed each year (3, 4). In the U.S., the incidence of cancers of the oral cavity, larynx, and pharynx for the period 2009-2013 was estimated to be 14.3 cases per 100,000persons/year. While incidence of oral and pharyngeal cancers has increased on average by 0.6% annually, the incidence of laryngeal cancers has been decreasing by an estimated 2.4% each year (5, 6).

The mortality rate of HNC seems to be declining but to different extents depending on the primary site and stage at diagnosis. While the death rate of laryngeal cancers has declined on average by 2.3% each year for the past 10 years, the death rate of oral and pharyngeal cancers has not significantly changed during this time (6). The annual age-adjusted mortality rate of oral, pharyngeal, and laryngeal cancers collectively is approximately 3.5 per 100,000 persons and account for 2.3% of all cancer deaths in the U.S(6).

Risk of HNC appears to vary by different population groups. Men are more than twice as likely to develop oral and pharyngeal cancers compared to women with age-adjusted rates of 22.3 and 7.3 per 100,000 persons for men and women, respectively. Another risk factor for HNC is race with white men experiencing an increased risk of oral and pharyngeal cancers and black men having higher risk of laryngeal cancers. Similar to other cancers, the risk of HNC also increases with age. The median ages of individuals diagnosed with oral and laryngeal cancers are 62 and 65 years, respectively (6).

Other known risk factors strongly associated with HNC include tobacco use and overconsumption of alcohol, with a dose response and synergistic impact of the two leading to a 30-fold increase in HNC risk among heavy smokers and drinkers compared to persons that neither smoke nor consume alcohol. (1, 7-18). Recently, infectious agents such as Human papillomavirus (HPV) and Epstein-Barr virus (EBV), have also been strongly associated with

these cancers (1, 9, 17, 19). Evidence suggests HPV causes HNC and accounts for increased mortality as evident through a case-control study with HPV-positive SCC tumors at a 59% higher risk of death compared to HPV-negative SCC of the head and neck (17, 20).

More modest but significant associations between HNC and diet have been observed with increased risk associated with consumption of red/processed meat and decreased risk associated with consumption of fibers (1, 9, 11, 17, 21-24). Global studies of diet and oral cancers also show that consumption of fruits and vegetables may lower the risk of oral cancers by 50%-70%. Other nutrients associated with such a diet including high intake of beta-carotene, vitamin C, and vitamin E also lower the risk of oral cancers (25). Genetic predisposition to HNC is also associated with specific types of cancers. For instance, individuals with family history of Fanconi anemia and Dyskeratosis congenita are at high risk of developing laryngeal cancers (26, 27). Genetic mutations of tumor suppressor genes such as p21 and oncogenes such as p16 or p53 have been strongly associated with HNC of various sites (25, 28). Vaccinations against infections caused by HPV are also promoted to reduce the risk of developing oral and neck cancers(29).

Environmental exposures such as solar ultraviolet radiation and occupational exposures like formaldehyde and tar are also strongly associated with oral cancers, specifically the lip (13, 30, 31). A meta-analysis of 27 studies showed farmers with an 88% higher risk of developing lip cancer compared to non-farmers (32). Furthermore, migrants from high-to-low- income countries also adopt the risk of HNC of their host countries further suggesting an environmental or lifestyle exposure (18).

The signs and symptoms also vary broadly across different HNC sites and stages. For many HNC, there may appear to be persistent, painful sores or bleeding lesions that do not heal. More advanced stage cancers may present with difficulty chewing, swallowing, speaking, or breathing (8, 33). Although there is no gold standard for screening for HNC, many providers and dentists initially perform visual screening of tumors during routine visits and follow-up with a needle aspiration biopsy and confirm by diagnostic imaging such as chest X-ray, computed

tomography (CT), magnetic resonance imaging (MRI), Positron Emission Tomography (PET), or combination of scans (6, 28, 33-36).

Treatment, management, and prognosis for HNC depend on many factors including cancer stage, grade, size, and location along with other patient characteristics. Treatment options include surgical resection, chemotherapy, and radiation with the goal of curing while preserving the original organ of the tumor (37, 38). There is sufficient evidence to suggest combination of surgery and radio and/or chemotherapy concurrently is most effective particularly in treating more advanced stage HNC (33, 34, 39). A combination of these treatments is often successful with good prognosis for squamous cell carcinomas of the head and neck (40). Depending on the site of the cancer, post-operative care may also involve restorative treatment. For instance, patients undergoing laryngectomy also undergo speech therapy, trachea-esophageal puncture (a surgical connection between trachea and esophagus that is created by puncturing the tracheostomy site to allow air to move from lungs to the mouth to create sounds and speech as patient moves his/her tongue and mouth), electrolarynx (an electrical device that is placed on the neck to create sounds to form a mechanical voice), and other trainings (26). Because having one malignancy increases the chances of cancer recurrence in the primary organ or in a second primary site especially within the first 2 years of treatment, ongoing care also includes follow-up examinations (26, 28, 41).

The five-year relative survival rates for HNC range from 20% to 90% depending on the site and stage of the disease, however, even early-stage cancers are considered to be at high risk for recurrence, which in turn is associated with increased mortality (10, 38).

There are many risk factors associated with HNC recurrence. In addition to sex, age, and race, other demographic criteria such as income are often associated the advanced stage HNC (37). Studies have shown that primary prevention efforts including smoking cessation, reduction of alcohol consumption, and safe sex practices can decrease the risk of developing both recurrent cancers and cancers to secondary sites (29, 42, 43). Taking oral isotretinoin has also been

effective in prevention of second primary tumor for individuals previously diagnosed with HNC (44). Long-term care for cancer survivors focuses on preventing recurrent HNC and second primary cancers.

While there is evidence to suggest follow-up imaging as a critical component of follow-up care, the frequency of imaging post-treatment is unclear. HNC patients are at higher risk of recurrence within the first 2 years of diagnosis, however there is insufficient understanding of risk of recurrence within the 2-year-period to make consistent recommendations for providers and patients. An important part of post diagnosis follow-up for HNC is surveillance imaging aimed at early detection of disease recurrence (45-47). Majority of second primary tumors are detected once patients become symptomatic, however routine, surveillance imaging is also a source of identifying such tumors (42). While some providers do not recommend routine screening for cancers such as nasopharyngeal for asymptomatic patients, other clinicians perform surveillance imaging (38, 41). The American Cancer Society (ACS) created guidelines for follow-up care based on a systematic review of the literature and created Level of Evidence (LOE) criteria to indicate strength of evidence based on study designs and methodologies of the studies. LOE ranges from 1 as strong evidence from meta-analyses of randomized clinical trials (RCTs) to 2A which indicates lower-level evidence that is based on consensus from an expert panel from National Comprehensive Cancer Network (NCCN). According to the ACS's guidelines for HNC survivorship, "it is recommended that primary care clinicians: a) should individualize clinical follow-up care provided to HNC survivors based on age, specific diagnosis, and treatment protocol as recommended by the treating oncology team (LOE = 2A) ; b) should conduct a detailed cancer-related history and physical examination every 1–3 mo for the first y after primary treatment, every 2–6 mo in the second y, every 4–8 mo in y 3–5, and annually after 5 y (LOE = 2A) c) should confirm continued follow-up with otolaryngologist or HNC specialist for HN-focused examination (LOE = 2A)" which further illustrates the need for evidence-based, consistent guidelines (66). Thus, despite accepted practice of surveillance imaging, which may

include X-ray, computed tomography (CT) and/or positron emission tomography (PET) scan, the optimal frequency and timing at which to perform follow-up evaluations based on strong level of evidence remains unclear (47-54). Moreover, the benefits of post-diagnosis surveillance imaging, in terms of improving prognosis and extending survival of HNC patients, are a matter of debate (46, 49).

Much of the existing uncertainty regarding post diagnosis surveillance imaging can only be resolved with the data from RCTs with strong level of evidence. Due to ethical considerations, however, no such trials are available. In the absence of RCTs, observational studies can be utilized to estimate the association between surveillance imaging and post HNC survival. Population-based observational data are particularly useful since they are less susceptible to non-random selection (55-57).

One such population-based data source is the Surveillance, Epidemiology, and End Results (SEER) Program created by the National Cancer Institute (NCI). A major limitation to SEER is that it does not include information on imaging and follow-up. This limitation can be addressed, at least for older patients, by linking SEER data with information on Medicare claims.

By using the SEER-Medicare linkage data, the relationship between imaging and survival as a proxy for cancer recurrence can be assessed. The objective of this paper is to examine the association between HNC imaging and survival of previously-diagnosed HNC patients.

2. CHAPTER II: MANUSCRIPT

TITLE, AUTHORS, ABSTRACT

Follow-up Imaging and Survival in Head and Neck Cancer Patients

By Priti Shah, Michael Goodman, Amy Chen, Yuan Liu, Renjian Jiang, Kevin Ward

An important part of post-diagnosis follow-up care for head and neck cancers (HNC) is surveillance imaging aimed at early detection of disease recurrence. This study investigates if imaging initiated at least 6 months post- diagnosis of HNC leads to better overall survival. The data for the analyses were obtained from the Surveillance Epidemiology and End Results (SEER)-Medicare Linkage file. The main independent variable in this analysis was time-dependent. The person time intervals that included imaging by X-ray, computed tomography (CT) and/or positron emission tomography (PET) were considered exposed. The outcome, disease-specific survival, was ascertained during the follow-up and was used as a proxy for HNC recurrence. A total of 14,936 patients diagnosed with HNC between 1992 and 2007 were included in the study and contributed 100,988 person- months of follow-up. After adjusting for relevant covariates using a time-dependent extended Cox model, the rate of cancer-specific death following imaging was 2.58 times higher (95% confidence interval: 2.38-2.79) than the corresponding rate without imaging. These findings indicate that post-diagnosis imaging among HNC patients, as documented in Medicare claims, is likely performed for clinical rather than surveillance reasons. A proper analysis of the association between surveillance imaging and disease prognosis requires more detailed information about indications for testing among asymptomatic patients. Imaging in the current analysis is probably a surrogate for disease severity and/or recurrence.

INTRODUCTION

Head and neck cancers (HNC) are a group of diverse malignancies originating in the oral cavity, pharynx, larynx, tonsils, thyroid, salivary glands, parotid glands, and sinuses (1, 2). In 2002 HNC represented the sixth most common cancer category globally with approximately 630,000 new cases diagnosed that year (3, 4). The five-year survival rates for HNC range from 20% to 90% depending on the site and stage of the disease, however, even early-stage cancers are still considered to be at high risk for recurrence, which in turn is associated with increased mortality (10, 38).

An important part of post-diagnosis follow-up for HNC is surveillance imaging aimed at early detection of disease recurrence (45-47). Despite the accepted practice of surveillance imaging, which may include X-ray, computed tomography (CT) and/or positron emission tomography (PET) scan, the optimal frequency and timing at which to perform follow-up evaluations remain unclear (47-54). Moreover, the benefits of post-diagnosis surveillance imaging, in terms of improving prognosis and extending survival of HNC patients, are a matter of debate (46, 49).

Much of the existing uncertainty regarding post-diagnosis surveillance imaging can be resolved with the data from randomized clinical trials. Due to ethical considerations, however, no such trials are available. In the absence of randomized clinical trials, observational studies can be utilized to estimate the association between surveillance imaging and post HNC survival. Population-based observational data are particularly useful since they are less susceptible to non-random selection (55-57).

One such population-based data source is the Surveillance, Epidemiology, and End Results (SEER) Program created by the National Cancer Institute (NCI). A major limitation of SEER is that it does not include information on imaging and follow-up. This limitation can be addressed, at least for older patients, by linking SEER data with information from Medicare claims. With these considerations in mind, the objective of this paper is to use linked SEER-

Medicare data to examine the association between HNC imaging and survival of previously-diagnosed cancer patients both overall and by cancer site.

METHODS

Data Source

The SEER program is a consortium of population-based cancer registries created by the National Cancer Institute (58). It represents diverse geographic areas across the United States. SEER collects data on newly diagnosed cancer cases from 18 population-based cancer registries (59). The data include details on patient demographic information, tumor characteristics, first course of cancer treatment, vital status, follow-up, and (if applicable) cause of death (59, 60).

Medicare is federal health insurance for persons 65 year or older, persons with end-stage renal disease, and persons with some disability. Approximately 97% of the elderly are eligible for Medicare (61, 62) and 94% of SEER patients 65 years or older have been linked to Medicare (57). Medicare collects information on all the services at the time of each beneficiary's visit with a healthcare provider. Claims data include the International Classification of Diseases (ICD) diagnostic codes, procedures and treatments, comorbidities, and billing information (57, 60).

Study Population

SEER-Medicare linkage claims for the years 1992-2007 were used to identify eligible patients over 65 years of age who were newly diagnosed with cancers of the larynx, lip and oral cavity, nasopharynx, pyriform sinuses and hypopharynx, tonsil, oropharynx, or salivary glands. Eligible cases were identified using the International Classification of Diseases for Oncology Third revision (ICD-O-3) codes C00.3-C00.9, C01.9, C02.0 - C06.9, C07.9, C08.0 - C14.9, C30.0, and C31.1- C32.9.

Patients were excluded if they 1) experienced death within 6 months post-diagnosis (n=7396); 2) were identified based on autopsy or death certificate (n=659), 3) had in-situ, distant, or unknown stage disease (n=3507), 4) had another cancer prior to HNC (n=7490) or had a cancer

that followed HNC within 2 years (n=2949), 5) had missing month of diagnosis or month of death (n=534), and 6) were of race/ethnicity other than non-Hispanic White or Black (n=1217). With respect to Medicare enrollment, patients were excluded if they were not enrolled continuously one year before or 2 years after HNC diagnosis, or if deceased, lacked continuous enrollment up to death (n=69,792). After exclusion criteria, a total of 14,936 patients diagnosed with HNC between 1992 and 2007 were included in the study and contributed 100,988 person- months of follow-up.

Analytic variables

The main exposure variable of primary interest in this analysis was time-dependent. The person time intervals that contained imaging by X-ray, computed tomography (CT) and/or positron emission tomography (PET) were considered exposed, and the corresponding person time prior to imaging was considered non-exposed. The main dependent variable was HNC-specific survival. The follow-up started 6 months post-diagnosis in an effort to differentiate between surveillance and imaging performed as a part of diagnostic or immediate post-treatment workup. The follow-up was extended until death or the end of 2010. Subjects who died from causes other than HNC were censored.

The patient-related covariates used in the analyses included age (66-70, 71- 75 or >75 years), Charlson comorbidity index (0, 1 or 2), area-based socioeconomic status (0-5%, 6-20% or >20% of residents in a census tract living in poverty), race (white or black), sex (male or female), and marital status (married or not). The disease-related covariates included primary site, stage (localized or regional) and grade (I/II, III/IV, or unknown). The B-cell tumors (n=4) were included in the grade III/IV category. Cancer-directed treatment variables included receipt of surgery, chemotherapy, and/or radiation.

Statistical Analyses

In a series of descriptive analyses, patients who did and did not receive diagnostic imaging were compared with respect to all covariates of interest. Association between surveillance imaging and survival was examined using Cox proportional hazard models. The survival analyses were based on extended Cox models in which pre-imaging interval among HNC patients was included with the non-exposed group, while post-imaging follow-up started after the patients had the procedure. A counting process data format was utilized to analyze the time-dependent imaging variable to create a dataset with patients having two records or observations if they had imaging. To explore the heterogeneity of results, each analysis was performed separately by site (lip and oral cavity, salivary glands, tonsils and oropharynx, nasopharynx, pyriform sinus and hypopharynx, and larynx) and stage (localized and regional). The overall model then included all patients with primary site and stage used as covariates. The results of all Cox models were expressed as hazard ratios (HRs) along with the 95% confidence intervals (CI). Extended Kaplan- Maier estimator was used to graphically present the results of the overall Cox model. The most parsimonious multivariable model was selected using backward elimination methods. Analyses were conducted using statistical software SAS 9.4 (SAS Institute Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Description of study population

We identified 14,936 patients diagnosed with localized or regional HNC in the SEER-Medicare linkage dataset. The most common HNC sites were lip/oral cavity (N=5670 38.0%) and larynx (N=5302, 35.5 %). Nearly 30% (N=4,469) of all patients did not have imaging performed within the 6-month to 2-year window after the diagnosis. As shown in Table 1, the distributions of demographic variables were similar among patients who did and did not undergo imaging. With respect to tumor-specific characteristics (Table 2) the group that underwent

imaging procedures included a greater proportion of patients with regional stage disease (52% versus 43%), a lower proportion with tumor grades I or II (55% versus 58%), and greater proportions with surgery (66% versus 53%), chemotherapy (26% versus 10%) and radiation (80% versus 56%).

Survival analyses

There were 4,555 deaths during the study period. The median survival time was 48 months without imaging and 36 months with imaging (Figure 1). In the site-specific analyses, the imaging category consistently experienced higher mortality compared to the no-imaging category with HR (95% CI) estimates ranging from 1.60 (1.31-1.96) for cancers of tonsils and oropharynx to 3.13 (2.44-4.02) for cancers of the salivary glands. The corresponding analyses of the association between imaging and mortality stratified by stage produced HRs of 3.62 (95% CI: 3.16-4.14) and 2.18 (95% CI: 1.98-2.39) for localized and regional disease, respectively.

The results of the overall multivariable analysis that included all cases are shown in Table 5. All variables except gender and surgical treatment were retained in the final model. After adjusting for age, race, marital status, comorbidities, neighborhood poverty level, primary site of tumor, tumor stage and grade, and treatment, rate of cancer-specific death following imaging was 2.58 times higher (95% CI 2.38-2.79) than the corresponding rate without imaging.

DISCUSSION

Using SEER-Medicare linkage data, we observed that that imaging during follow-up was associated with lower HNC survival. This observation goes against our *a priori* expectation, but appears to be consistent in both the overall and the site-specific analyses, and does not differ by stage, and with or without adjustment for possible confounders.

Perhaps the most notable feature of this study is the large and diverse population-based sample that was not affected by non-participation bias and allowed several multivariable and stratified analyses of sufficient statistical power. Another distinguishing characteristic of this

study is the ability to overcome the important methodological challenge of immortal time bias. Immortal time bias is of particular concern in the analyses of the association between a particular diagnostic or treatment procedure and survival. In our case, patients included in the exposed imaging group have to survive until the test, and therefore, during the period between the diagnosis and the procedure death cannot occur. In contrast, patients in non-exposed group do not have a minimum survival requirement, and as a result, their follow-up does not include the "immortal" period (63). A prolonged interval between diagnosis and imaging may have resulted in a spurious survival advantage in the exposed group. It is possible to address this type of bias by starting follow-up after some delay following the immediate post-diagnosis period, and by performing time-dependent analysis; both of these approaches were employed in our study.

These methodological strengths notwithstanding, the main limitation of the current analysis is the inability to distinguish between imaging tests performed for surveillance and diagnostic purposes. A true surveillance imaging test has to be performed in the absence of any clinical symptom or suspicion of recurrence. Unfortunately, the Medicare claims data do not provide information on the reasons for which a particular imaging test was performed. It is likely that many of the procedures among the exposed category were performed because the patients presented with signs or symptoms of recurrent cancer. As result, the observed increase in mortality in the imaging category likely represents a spurious, "reverse" causation whereby patients with more severe disease and/or imminent recurrence were more likely to undergo testing than those who were symptom free.

It appears that in the absence of randomized clinical trials, the only way of establishing the effect of surveillance imaging on HNC prognosis is through identification and exclusion of patients whose follow-up testing was carried out in response to clinical signs or symptoms. In a retrospective study this can be achieved through detailed review and abstraction of medical records. While detailed record abstraction of all eligible cohort members may not be feasible due to unrealistic time requirements and prohibitively high costs, a more efficient design

alternative is a case-control study nested within an established cohort with access to electronic medical records including clinical notes. A recent case-control study of screening colonoscopy nested within the Kaiser Permanente Integrated Health Care Systems in Northern and Southern California offers a useful example that can be applied to address other research questions, including questions related to the effectiveness of surveillance imaging among HNC survivors (64).

Several previous studies focused on the optimal frequency and type of follow-up imaging for HNC. As summarized previously elsewhere (51), it appears that the current literature does not provide direct evidence in support of post-diagnosis surveillance. The most recent American Cancer Society HNC Surviroship Cancer Guideline points out the current recommendations are consensus-based rather than evidence-based (65).

In conclusion, these SEER-Medicare linkage data do not support the use of post-diagnosis imaging as an effective means of improving prognosis among HNC patients. On the other hand, our findings should not be interpreted as definitive evidence against post-diagnosis surveillance in this population because many (perhaps most) tests captured in the Medicare claims were likely performed for clinical rather than surveillance reasons. A proper analysis of the association between surveillance imaging and disease prognosis requires more detailed information about indications for testing among asymptomatic patients. Imaging in the current analysis is probably a surrogate for disease severity and/or recurrence.

REFERENCES

1. Mao L, Hong WK, Papadimitrakopoulou VA. Focus on head and neck cancer. *Cancer Cell* 2004;5(4):311-6.
2. Argiris A, Eng C. Epidemiology, staging, and screening of head and neck cancer. *Cancer Treat Res* 2003;114:15-60.
3. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55(2):74-108.
4. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol* 2009;45(4-5):309-16.
5. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65(2):87-108.
6. SEER Cancer Stat Facts: Oral Cavity and Pharynx Cancer. Bethesda, MD: National Cancer Institute. (http://seer.cancer.gov/statfacts/html/oralcav.html). (Accessed 01/07/2017).
7. Saman DM. A review of the epidemiology of oral and pharyngeal carcinoma: update. *Head Neck Oncol* 2012;4:1.
8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66(1):7-30.
9. LaVecchia C, Tavani A, Franceschi S, et al. Epidemiology and prevention of oral cancer. *Oral Oncol* 1997;33(5):302-12.
10. Sankaranarayanan R, Masuyer E, Swaminathan R, et al. Head and neck cancer: A global perspective on epidemiology and prognosis. *Anticancer Res* 1998;18(6B):4779-86.
11. Sturgis EM, Wei QY, Spitz MR. Descriptive epidemiology and risk factors for head and neck cancer. *Semin Oncol* 2004;31(6):726-33.
12. Hashibe M, Brennan P, Chuang SC, et al. Interaction between Tobacco and Alcohol Use and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidemiol Biomarkers Prev* 2009;18(2):541-50.
13. Seijas-Tamayo R, Fernandez-Mateos J, Klain JCA, et al. Epidemiological characteristics of a Spanish cohort of patients diagnosed with squamous cell carcinoma of head and neck: distribution of risk factors by tumor location. *Clin Transl Oncol* 2016;18(11):1114-22.
14. Franceschi S, Talamini R, Barra S, et al. SMOKING AND DRINKING IN RELATION TO CANCERS OF THE ORAL CAVITY, PHARYNX, LARYNX, AND ESOPHAGUS IN NORTHERN ITALY. *Cancer Res* 1990;50(20):6502-7.
15. Hashibe M, Brennan P, Benhamou S, et al. Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: Pooled analysis in the international head and neck cancer epidemiology consortium. *J Natl Cancer Inst* 2007;99(10):777-89.
16. Blot WJ, McLaughlin JK, Winn DM, et al. SMOKING AND DRINKING IN RELATION TO ORAL AND PHARYNGEAL CANCER. *Cancer Res* 1988;48(11):3282-7.
17. 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):709-20.
18. Torre LA, Bray F, Siegel RL, et al. Global Cancer Statistics, 2012. *CA-Cancer J Clin* 2015;65(2):87-108.
19. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. *JAMA* 2012;307(7):693-703.

20. Human Papillomavirus–Associated Cancers — United States, 2004–2008. *MMWR* 2012;61(15):258-61.
21. Bradbury BD, Brookhart MA, Winkelmayer WC, et al. Evolving statistical methods to facilitate evaluation of the causal association between erythropoiesis-stimulating agent dose and mortality in nonexperimental research: strengths and limitations. *Am J Kidney Dis* 2009;54(3):554-60.
22. Chuang SC, Jenab M, Heck JE, et al. Diet and the risk of head and neck cancer: a pooled analysis in the INHANCE consortium. *Cancer Causes Control* 2012;23(1):69-88.
23. Pavia M, Pileggi C, Nobile CGA, et al. Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. *Am J Clin Nutr* 2006;83(5):1126-34.
24. Steinmetz KA, Potter JD. VEGETABLES, FRUIT, AND CANCER .1. EPIDEMIOLOGY. *Cancer Causes Control* 1991;2(5):325-57.
25. Adami H, Hunter, D., Trichopoulos, D. . *The Textbook of Cancer Epidemiology*. Second Edition ed. New York, NY: Oxford University Press; 2008.
26. What Are the Key Statistics About Laryngeal and Hypopharyngeal Cancers? : American Cancer Society; 2014. (http://www.cancer.org/cancer/laryngeal-and-hypopharyngeal-cancer/about/key-statistics.html). (Accessed 01/07/2017 2017).
27. SEER Cancer Stat Facts: Larynx Cancer. Bethesda, MD: National Cancer Institute; 2016. (https://seer.cancer.gov/statfacts/html/laryn.html). (Accessed 01/07/2017).
28. Argiris A, Karamouzis MV, Raben D, et al. Head and neck cancer. *Lancet* 2008;371(9625):1695-709.
29. SEER Stat Fact Sheets: Oral Cavity and Pharynx Cancer. 2016.
30. Lindqvist C. RISK-FACTORS IN LIP CANCER - QUESTIONNAIRE SURVEY. *Am J Epidemiol* 1979;109(5):521-30.
31. Shangina O, Brennan P, Szeszenia-Dabrowska N, et al. Occupational exposure and laryngeal and hypopharyngeal cancer risk in central and eastern Europe. *Am J Epidemiol* 2006;164(4):367-75.
32. Acquavella J, Olsen G, Cole P, et al. Cancer among farmers: a meta-analysis. *Ann Epidemiol* 1998;8(1):64-74.
33. Poeta ML, Manola J, Goldwasser MA, et al. TP53 mutations and survival in squamous-cell carcinoma of the head and neck. *N Engl J Med* 2007;357(25):2552-61.
34. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2016. *CA-Cancer J Clin* 2016;66(1):7-30.
35. Sankaranarayanan R, Ramadas K, Thara S, et al. Long term effect of visual screening on oral cancer incidence and mortality in a randomized trial in Kerala, India. *Oral Oncol* 2013;49(4):314-21.
36. de Bree R, Deurloo EE, Snow GB, et al. Screening for distant metastases in patients with head and neck cancer. *Laryngoscope* 2000;110(3):397-401.
37. Hoffman HT, Karnell LH, Funk GF, et al. The National Cancer Data Base report on cancer of the head and neck. *Arch Otolaryngol Head Neck Surg* 1998;124(9):951-62.
38. Haddad RI, Shin DM. Recent advances in head and neck cancer. *N Engl J Med* 2008;359(11):1143-54.
39. Funk GF, Karnell LH, Robinson RA, et al. Presentation, treatment, and outcome of oral cavity cancer: A national cancer data base report. *Head Neck-J Sci Spec Head Neck* 2002;24(2):165-80.
40. Khuri FR, Lippman SM, Spitz MR, et al. Molecular epidemiology and retinoid chemoprevention of head and neck cancer. *J Natl Cancer Inst* 1997;89(3):199-211.
41. What Is Nasopharyngeal Cancer? : American Cancer Society. (http://www.cancer.org/cancer/nasopharyngeal-cancer/about/what-is-nasopharyngeal-cancer.html). (Accessed 01/07/2017).

42. Dhooge IJ, De Vos M, Van Cauwenberge PB. Multiple primary malignant tumors in patients with head and neck cancer: Results of a prospective study and future perspectives. *Laryngoscope* 1998;108(2):250-6.
43. Shikhani AH, Matanoski GM, Jones MM, et al. MULTIPLE PRIMARY MALIGNANCIES IN HEAD AND NECK-CANCER. *Arch Otolaryngol Head Neck Surg* 1986;112(11):1172-9.
44. Hong WK, Lippman SM, Itri LM, et al. PREVENTION OF 2ND PRIMARY TUMORS WITH ISOTRETINOIN IN SQUAMOUS-CELL CARCINOMA OF THE HEAD AND NECK. *N Engl J Med* 1990;323(12):795-801.
45. Kubota K, Yokoyama J, Yamaguchi K, et al. FDG-PET delayed imaging for the detection of head and neck cancer recurrence after radio-chemotherapy: comparison with MRI/CT. *Eur J Nucl Med Mol Imaging* 2004;31(4):590-5.
46. Lowe VJ, Boyd JH, Dunphy FR, et al. Surveillance for recurrent head and neck cancer using positron emission tomography. *J Clin Oncol* 2000;18(3):651-8.
47. Cooney TR, Poulsen MG. Is routine follow-up useful after combined-modality therapy for advanced head and neck cancer? *Arch Otolaryngol Head Neck Surg* 1999;125(4):379-82.
48. Devisscher AVM, Manni JJ. ROUTINE LONG-TERM FOLLOW-UP IN PATIENTS TREATED WITH CURATIVE INTENT FOR SQUAMOUS-CELL CARCINOMA OF THE LARYNX, PHARYNX, AND ORAL CAVITY - DOES IT MAKE SENSE. *Arch Otolaryngol Head Neck Surg* 1994;120(9):934-9.
49. Joshi A, Calman F, O'Connell M, et al. Current Trends in the Follow-up of Head and Neck Cancer Patients in the UK. *Clin Oncol* 2010;22(2):114-8.
50. Ryan WR, Fee WE, Le QT, et al. Positron-emission tomography for surveillance of head and neck cancer. *Laryngoscope* 2005;115(4):645-50.
51. Manikantan K, Khode S, Dwivedi RC, et al. Making sense of post-treatment surveillance in head and neck cancer: when and what of follow-up. *Cancer Treat Rev* 2009;35(8):744-53.
52. Andrade RS, Heron DE, Degirmenci B, et al. Posttreatment assessment of response using FDG-PET/CT for patients treated with definitive radiation therapy for head and neck cancers. *Int J Radiat Oncol Biol Phys* 2006;65(5):1315-22.
53. Porceddu SV, Pryor DI, Burmeister E, et al. RESULTS OF A PROSPECTIVE STUDY OF POSITRON EMISSION TOMOGRAPHY-DIRECTED MANAGEMENT OF RESIDUAL NODAL ABNORMALITIES IN NODE-POSITIVE HEAD AND NECK CANCER AFTER DEFINITIVE RADIOTHERAPY WITH OR WITHOUT SYSTEMIC THERAPY. *Head Neck-J Sci Spec Head Neck* 2011;33(12):1675-82.
54. Yao M, Graham MM, Hoffman HT, et al. The role of post-radiation therapy FDG PET in prediction of necessity for post-radiation therapy neck dissection in locally advanced head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2004;59(4):1001-10.
55. Juliusson G, Lazarevic V, Horstedt AS, et al. Acute myeloid leukemia in the real world: why population-based registries are needed. *Blood* 2012;119(17):3890-9.
56. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;341(27):2061-7.
57. Warren JL, Klabunde CN, Schrag D, et al. Overview of the SEER-Medicare data - Content, research applications, and generalizability to the United States elderly population. *Med Care* 2002;40(8):3-18.
58. Number of Persons by Race and Hispanic Ethnicity for SEER Participants. National Cancer Institute. (https://seer.cancer.gov/registries/data.html). (Accessed 2016).
59. Overview of the SEER Program. National Cancer Institute. (https://seer.cancer.gov/about/overview.html). (Accessed 2017).

60. SEER-Medicare Linked Database. National Cancer Institute. (https://healthcaredelivery.cancer.gov/seermedicare/). (Accessed 2017).
61. Medicare Enrollment and Claims Data. National Cancer Institute. (https://healthcaredelivery.cancer.gov/seermedicare/medicare/). (Accessed 2017).
62. Warren JL, Klabunde CN, Schrag D, et al. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care* 2002;40(8 Suppl):IV-3-18.
63. Levesque LE, Hanley JA, Kezouh A, et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *Bmj* 2010;340:b5087.
64. Doubeni CA, Corley DA, Quinn VP, et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. *Gut* 2016.
65. Cohen EE, LaMonte SJ, Erb NL, et al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. *CA Cancer J Clin* 2016;66(3):203-39.

TABLES

Table 1. Distribution of Demographic and Cancer-specific variables by Imaging Status

		Overall N=14936	(%)	No Imaging N= 4469	(%)	Imaging N= 10467	(%)
Age Level	66-70	4766	31.9	1280	28.6	3486	33.3
	71-75	4897	32.8	1371	30.7	3526	33.7
	>75	5273	35.3	1818	40.7	3455	33.0
Charlson Comorbidity Index[a]	0	9329	62.5	3030	67.8	6299	60.2
	1	3469	23.2	887	19.8	2582	24.7
	2	2138	14.3	552	12.4	1586	15.2
Poverty Level[b]	0-5%	4305	28.8	1230	27.5	3075	29.4
	6%-20%	8043	53.8	2404	53.8	5639	53.9
	>21%	2588	17.3	835	18.7	1753	16.7
Race	Caucasian	13712	91.8	4077	91.2	9635	92.1
	Black	1224	8.2	392	8.8	832	7.9
Gender	Male	9640	64.5	2858	64.0	6782	64.8
	Female	5296	35.5	1611	36.0	3685	35.2
Marital Status	Married	8018	53.7	2232	49.9	5786	55.3
	Other	6918	46.3	2237	50.1	4681	44.7
Total		**14936**		**4469**		**10467**	

[a] Charlson Comorbidity Index scale quantifies comorbidities based on adjusted 10-year survival/mortality risk (weighted 0 to 2)

[b] Poverty Level covariate based on 2010 Census tract

Table 2. Cancer Specific Covariate Distribution by Imaging

		Overall N=14936	(%)	No Imaging N= 4469	(%)	Imaging N= 10467	(%)
Deaths		4555	30.5	1229	27.5	3326	31.8
Sequence of this Cancer[a]	0	12887	86.3	3833	85.8	9054	86.5
	1	2049	13.7	636	14.2	1413	13.5
Tumor Stage	Localized	7586	50.8	2528	56.6	5058	48.3
	Regional	7350	49.2	1941	43.4	5409	51.7
Tumor Grade	I, II	8312	55.7	2590	58.0	5722	54.7
	III, IV	3618	24.2	889	19.9	2729	26.1
	Unknown	3006	20.1	990	22.2	2016	19.3
Treatment included surgery	No	5685	38.1	2110	47.2	3575	34.2
	Yes	9251	61.9	2359	52.8	6892	65.8
Treatment included chemotherapy	No	11867	79.5	4046	90.5	7821	74.7
	Yes	3069	20.5	423	9.5	2646	25.3
Treatment included radiation	No	4036	27.0	1971	44.1	2065	19.7
	Yes	10900	73.0	2498	55.9	8402	80.3
Primary Site of HNC	Lip and Oral Cavity	5670	38.0	1856	41.5	3814	36.4
	Parotid and other salivary	1482	9.9	463	10.4	1019	9.7
	Tonsil, Oropharynx, Other and ill defined	1409	9.4	344	7.7	1065	10.2
	Nasopharynx	308	2.1	75	1.7	233	2.2
	Pyriform Sinus and Hypopharynx	765	5.1	172	3.8	593	5.7
	Larynx	5302	35.5	1559	34.9	3743	35.8
Total		**14936**		**4469**		**10467**	

[a] HNC was the first or only primary cancer

Table 3. Extended Cox Model Comparing Intervals with and without Imaging Stratified by Primary Site of HNC[a]

HNC Primary Site[b]	Hazard Ratio[c]	(95% CI)	P-Value
Lip and Oral Cavity	2.74	(2.44-3.07)	<.001
Parotid and other salivary	3.13	(2.44-4.02)	<.001
Tonsil, Oropharynx, Other and ill defined	1.60	(1.31-1.96)	<.001
Nasopharynx	1.97	(1.29-3.02)	0.002
Pyriform Sinus and Hypopharynx	1.85	(1.43-2.39)	<.001
Larynx	2.98	(2.58-3.44)	<.001

[a] Number of observations in the original data set = 25403. Number of observations used = 23684.
[b] The estimated stratified treatment effect was controlled by: Age levels, Charlson comorbidity index,Grade, If patient had chemotherapy, If patient had radiation, Marital status, Poverty level, Race, Stage
[c] Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: If patient had surgical treatment.

Table 4. Extended Cox Model Comparing Intervals with and without Imaging Stratified by HNC Stage[a]

HNC Stage[b]	Hazard Ratio[c]	(95% CI)	P-Value
Localized	3.62	(3.16-4.14)	<.001
Regional	2.18	(1.98-2.39)	<.001

[a] Number of observations in the original data set = 25403. Number of observations used = 23684.
[b] The estimated stratified treatment effect was controlled by: Age levels, Charlson comorbidity index, Grade, If patient had chemotherapy, If patient had radiation, Marital status, Poverty level, Primary site, Race
[c] Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: Gender.

Table 5. Multivariable Extended Cox Model[a]

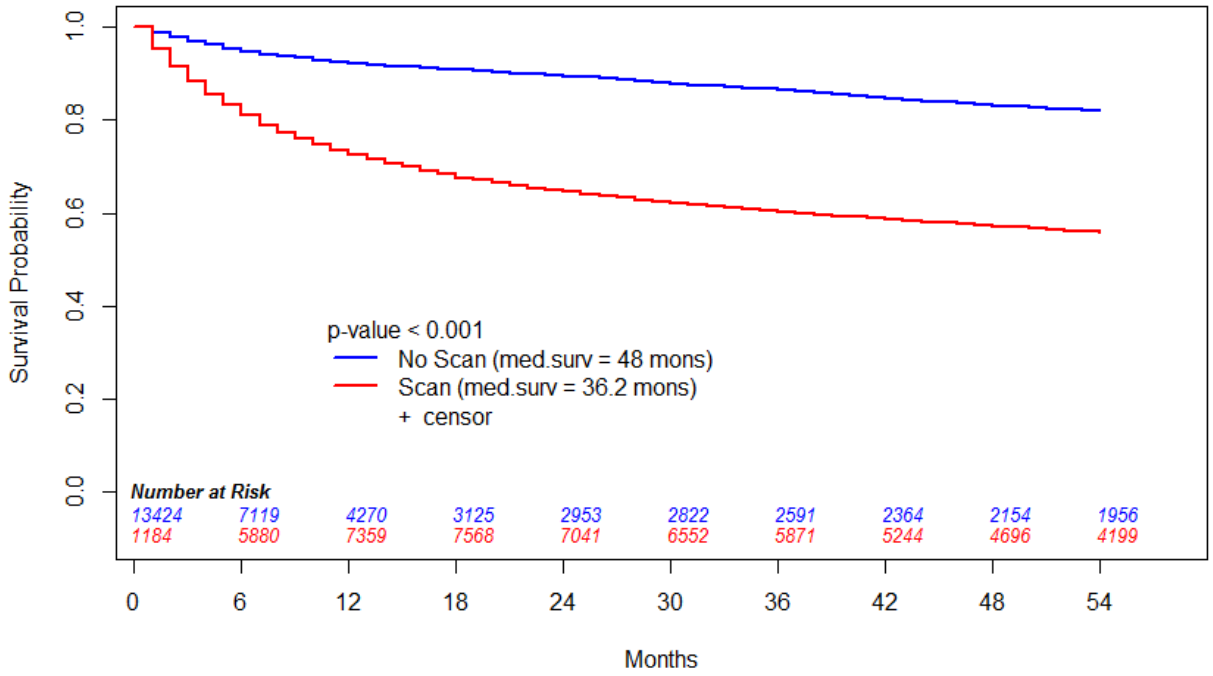
Parameter		Hazard Ratio[b]	(95% CI)	P-Value
Imaging	No Imaging	1.00		
	Imaging	2.58	(2.38 – 2.79)	<.001
Age Level	66-70	1.00		
	71-75	1.12	(1.03-1.21)	0.005
	>75	1.50	(1.39 – 1.62)	<.001
Charlson Comorbidity Index[a]	0	1.00		
	1	1.1	(1.02-1.18)	0.012
	2	1.27	(1.17-1.39)	<.001
Poverty Level[b]	0-5%	1.00		
	6%-20%	1.15	(1.07-1.24)	<.001
	>21%	1.21	(1.10-1.33)	<.001
Race	Caucasian	1.00		
	Black	1.25	(1.13-1.39)	<.001
Marital Status	Married	1.00		
	Other	1.33	(1.25-1.41)	<.001
Primary Site of Cancer				
	Larynx	1.00		
	Lip and Oral Cavity	1.37	(1.27-1.49)	<.001
	Parotid and other salivary and ill-defined	0.98	(0.86-1.11)	0.717
	Tonsil, Oropharynx, Other	1.06	(0.95-1.18)	0.307
	Nasopharynx	1.11	(0.91-1.35)	0.301
	Pyriform Sinus and Hypopharynx	1.53	(1.35-1.73)	<.001
Tumor Stage	Localized	1.00		
	Regional	2.29	(2.13-2.47)	<.001
Tumor Grade	I, II	1.00		
	III, IV, B-Cell	1.06	(0.98-1.14)	0.135
	Unknown	0.9	(0.82-0.98)	0.011
Treatment included chemotherapy	No	1.00		
	Yes	1.24	(1.15-1.34)	<.001
Treatment included radiation	No	1.00		
	Yes	1.33	(1.21-1.45)	<.001

[a] Number of observations in the original data set = 25403. Number of observations used = 23684. The estimated stratified treatment effect was controlled by: Age levels, Charlson comorbidity index, grade, If patient had chemotherapy, If patient had radiation, Marital status, Poverty level, Primary site, and Race.

[b]Backward selection with an alpha level of removal of .05 was used. The following variables were removed from the model: Gender, and If patient had surgical treatment

FIGURE

Figure 1: Extended Cox by Imaging



3. CHAPTER III: SUMMARY, PUBLIC HEALTH IMPLICATIONS, POSSIBLE FUTURE DIRECTIONS

Using SEER-Medicare linkage data, we observed that that imaging during follow-up was associated with lower HNC survival. This observation goes against our *a priori* expectation, but appears to be consistent in both the overall and the site-specific analyses, and does not differ by stage, and with or without adjustment for possible confounders. Perhaps the most notable feature of this study is the large and diverse population-based sample that was not affected by non-participation bias and allowed several multivariable and stratified analyses of sufficient statistical power. The main limitation of the current analysis is the inability to distinguish between imaging tests performed for surveillance and diagnostic purposes. A true surveillance imaging test has to be performed in the absence of any clinical symptoms or suspicion of recurrence.

A proper analysis of the association between surveillance imaging and disease prognosis requires more detailed information about indications for testing among asymptomatic patients. Imaging in the current analysis is probably a surrogate for disease severity and/or recurrence. It appears that in the absence of randomized trials, the only way of establishing the effect of surveillance imaging on HNC prognosis is through identification and exclusion of patients whose follow-up testing was carried out in response to clinical signs or symptoms. In a retrospective study this can be achieved through detailed review and abstraction of medical records. While detailed record abstraction of all eligible cohort members may not be feasible due to unrealistic time requirements and prohibitively high costs, a more efficient design alternative is a case-control study nested within an established cohort with access to electronic medical records including clinical notes.

4. APPENDICES

SAS Code

```
*****************************************************************;
* Program: H:\My Documents\_Thesis\Data\orgnize.sas               *;
* Date Created: Feb. 2012/Yuan Liu                               *;
* Date Accessed: 12/01/2016                                      *;
* Programmer: Priti Shah                                         *;
* Source: SEER and Medicare                                      *;
*                                                                *;
* Purpose: This program is a dataset created from SEER & Medicare *;
* dataset used to study the relationship between imaging efforts and
recurrence of head & neck cancers.                               *;
/* Purpose:  To create counting process for extended cox (SAS --> R -->
SAS)                                                        */    *;
*****************************************************************;

libname thesis "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder";

*Create formats;

proc format;
value age               0 = '66-70'       1 = '71-75'       2='>75';
value cci               0 = 'CCI=0 '      1 = '0<CCI<=1'    2 =
'CCI>1';
value poverty           0 = '0%-5%'       1 = '6%-20%'      2 = '>20%';
value race              0 = 'Caucasian' 1 = 'Black';
value gender            0 = 'Male'        1 = 'Female';
value married           0 = 'Married'     1 = 'Other';
value stage             1 = 'In Situ  ' 2 = 'Localized' 3 = 'Regional';
value grade             1 = 'I, II          '   2 = 'III, IV, B-cell'
3 = 'Unknown';
value yesno             0 = 'No'  1 = 'Yes';
value psite             1 = 'Lip and Oral Cavity
        '
                              2 = 'Parotid and other salivary'
                              3 = 'Tonsil, Oropharynx, Other and ill
defined'
                              4 = 'Nasopharynx'
                              5 = 'Pyriform Sinus and Hypopharynx'
                              6 = 'Larynx';
value css               0 = 'Censored          '      1 = 'Cause
Specific Death';
value group             1= "Scan"         2= "No Scan";
run;

*****************************************************************;
* COUNTING PROCESS                                               *;
*****************************************************************;

*** Prepare data into counting process data format for Extended Cox
Model;
proc contents data=THESIS.ORGNIZE;
run;
```

```
DATA ONE;
      SET THESIS.ORGNIZE;

      *drop in-situ cancer types;
      if stage_status=1 then delete;

      if SCAN=1 THEN COHORT=SCAN;

      IF SCAN=0 THEN COHORT2=1;
      ELSE COHORT2=0;

      time1=0;
      time2 = fupstrttoscan;
      time3=.;
      S1 = 2;
      S2 = cohort;
      SS1 = 2;
      SS2 = cohort2;
      ARRAY t(*) time1-time3;
      ARRAY s(*) s1-s2;
      ARRAY ss(*) ss1-ss2;
      dead=0;
      DO j=1 TO 2 WHILE (t(j) NE .);
      start=t(j);
      group = s(j);
      group2 = ss(j);
      stop=t(j+1);
      IF t(j+1)=. THEN DO;
      stop=survm5yrfrmfupstrt;
      dead=caussurv5yr;
      END;
      OUTPUT;
      END;
      LABEL group = "Scan of Primary Site" group2 = "NO Scan at Primary
Site";

      FORMAT group group. psiten psite. AGE_LEVELN AGE. RACE_N RACE.
POVERTY poverty. MARITAL MARRIED. STAGE_STATUS STAGE. GRADE GRADE.
SURGERY YESNO. CHEMO YESNO. RAD YESNO. SCAN YESNO. caussurv5yr css.
diag_date MMDDYYS10. claim_date MMDDYYS10. sex gender.;
RUN;



*****************************************************************;
* Univariate Survival Analysis                                  *;
*****************************************************************;

%include "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\MACROS\UNI_PHREG
V26.sas";

TITLE "UNIVARIATE SURVIVAL ANALYSIS";
%UNI_PHREG(DATASET=ONE, event=survm5yrfrmfupstrt, CENSOR=caussurv5yr,
      CLIST = scan age_leveln comorb poverty race_n sex marital
stage_status grade surgery chemo rad psiten,
```

```
      NLIST=survm5yr  mondiff2 fupstrttoscan , DOC=T,
      LOGRANK=T,   ORIENTATION=PORTRAIT,
      OUTPATH=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\02.11.2017 - Univariate
Analyses\,
      FNAME=Univariate Survival Analysis);
   TITLE;



*************************************************************************;
* * METHOD 1: PHREG_SEL MACRO WITHOUT R*                                 *;
*************************************************************************;

%let dir = \\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\;

%include "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\MACROS\MULTIPLE_PHREG
V21.sas";
%include "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\MACROS\PHREG_SEL
V23.sas";

*interactions by sex;
TITLE 'Extended Cox_Multivariable - interaction by grade';
%phreg_sel(dsn=one,
      censor=dead,start=start, stop=stop,
      VAR=  group|grade comorb sex race_n poverty age_leveln
stage_status age_leveln  marital   surgery chemo rad psiten ,
      cvar=       group(DESC)*sex* age_leveln* comorb* poverty* race_n*
marital* stage_status* grade* surgery* chemo *rad *psiten,
    slstay=.05,
      EFFECT =  group,
      SLICEBY = grade,
    report=T,type3=T,clnum=F,ORIENTATION = portrait,
    outpath=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      filename=Extended_Cox_Multivariable - interaction by grade);
title;

*interactions by site;
TITLE 'Extended_Cox -  interaction by site';
%phreg_sel(dsn=one,
      censor=dead,start=start, stop=stop,
      VAR=  group|psiten stage_status age_leveln comorb poverty race_n
sex marital  grade surgery chemo rad ,
      cvar=       group(DESC)* age_leveln* comorb* poverty* race_n*
sex* marital* stage_status* grade* surgery* chemo *rad *psiten,
    slstay=.05,
      EFFECT =  group,
      SLICEBY = psiten,
    report=T,type3=T,clnum=F,ORIENTATION = portrait,
```

```
    outpath=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      filename=Extended_Cox -  interaction by site);
title;

*interactions by grade;
TITLE 'Extended_Cox -  interaction by grade';
%phreg_sel(dsn=one,
      censor=dead,start=start, stop=stop,
      VAR=  group|grade sex psiten stage_status age_leveln comorb
poverty race_n  marital   surgery chemo rad ,
      cvar=       group(DESC)* age_leveln* comorb* poverty* race_n*
sex* marital* stage_status* grade* surgery* chemo *rad *psiten,
    slstay=.05,
      EFFECT =  group,
      SLICEBY = grade,
    report=T,type3=T,clnum=F,ORIENTATION = portrait,
    outpath=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      filename=Extended_Cox -  interaction by grade);
title;

***SURVIVAL GRAPHS;

*Overall;
proc phreg data=one PLOTS(overlay=row)=s;
class group/order=internal param=glm;
model (start,stop)*dead(0) = group/rl;
strata group;
run;


/*KM PLOTS*/
%include "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\MACROS\KM_PLOT
V22.sas";

TITLE "Extended_COX_KM";
   %km_plot(dsn=one ,censors=dead,events=survm5yrfrmfupstrt,
      grplist= group, title= "Extended Cox: SURVIVAL CURVES BY IMAGING"
,entrytitle="extended Kaplan-Meier Plot",xlab= TIME (MONTHS), ylab=
SURVIVAL,pairwise=F,
    timelist=12,unit=MO,join=T,plot=T,table=T, atrisk=T,
      OUTPATH=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      fname=Extended_COX_KM);

*****************************************************************;
* METHOD 2: EXPORT TO EXCEL-->R*                                 *;
*****************************************************************;

Data TWO;set ONE;
if start < stop;
run;
```

```
/*Export to Excel to plot extended KM in R*/

PROC EXPORT DATA= WORK.TWO
            OUTFILE= "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\HNC_counting.csv"
            DBMS=CSV REPLACE;
     PUTNAMES=YES;
RUN;


*****************************************************************;

* Program: H:\My Documents\_Thesis\Data\orgnize.sas               *;
* Date Created: Feb. 2012/Yuan Liu                               *;
* Date Accessed: 12/01/2016                                      *;
* Programmer: Priti Shah                                         *;
* Source: SEER and Medicare                                      *;
*                                                                *;
* Purpose: This program is a dataset created from SEER & Medicare *;
* dataset used to study the relationship between imaging efforts and
recurrence of head & neck cancers.                               *;
/* Purpose:  To create counting process for extended cox (SAS --> R -->
SAS)                                          */                 *;
*****************************************************************;


libname thesis "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder";

*Create formats;

proc format;
value age               0 = '66-70'       1 = '71-75'       2='>75';
value cci               0 = 'CCI=0 '      1 = '0<CCI<=1'    2 =
'CCI>1';
value poverty           0 = '0%-5%'       1 = '6%-20%'      2 = '>20%';
value race              0 = 'Caucasian' 1 = 'Black';
value gender            0 = 'Male'        1 = 'Female';
value married           0 = 'Married'     1 = 'Other';
value stage             1 = 'In Situ  ' 2 = 'Localized' 3 = 'Regional';
value grade             1 = 'I, II          '   2 = 'III, IV, B-cell'
3 = 'Unknown';
value yesno             0 = 'No'  1 = 'Yes';
value psite             1 = 'Lip and Oral Cavity
        '
                              2 = 'Parotid and other salivary'
                              3 = 'Tonsil, Oropharynx, Other and ill
defined'
                              4 = 'Nasopharynx'
                              5 = 'Pyriform Sinus and Hypopharynx'
                              6 = 'Larynx';
value css               0 = 'Censored          '      1 = 'Cause
Specific Death';
```

```
value group              1= "Scan"          2= "No Scan";
run;

*****************************************************************;
* COUNTING PROCESS                                              *;
*****************************************************************;

*** Prepare data into counting process data format for Extended Cox
Model;
proc contents data=THESIS.ORGNIZE;
run;

DATA ONE;
      SET THESIS.ORGNIZE;

      *drop in-situ cancer types;
      if stage_status=1 then delete;

      if SCAN=1 THEN COHORT=SCAN;

      IF SCAN=0 THEN COHORT2=1;
      ELSE COHORT2=0;

      time1=0;
      time2 = fupstrttoscan;
      time3=.;
      S1 = 2;
      S2 = cohort;
      SS1 = 2;
      SS2 = cohort2;
      ARRAY t(*) time1-time3;
      ARRAY s(*) s1-s2;
      ARRAY ss(*) ss1-ss2;
      dead=0;
      DO j=1 TO 2 WHILE (t(j) NE .);
      start=t(j);
      group = s(j);
      group2 = ss(j);
      stop=t(j+1);
      IF t(j+1)=. THEN DO;
      stop=survm5yrfrmfupstrt;
      dead=caussurv5yr;
      END;
      OUTPUT;
      END;
      LABEL group = "Scan of Primary Site" group2 = "NO Scan at Primary
Site";

      FORMAT group group. psiten psite. AGE_LEVELN AGE. RACE_N RACE.
POVERTY poverty. MARITAL MARRIED. STAGE_STATUS STAGE. GRADE GRADE.
SURGERY YESNO. CHEMO YESNO. RAD YESNO. SCAN YESNO. caussurv5yr css.
diag_date MMDDYYS10. claim_date MMDDYYS10. sex gender.;
RUN;

***LIP & ORAL CANCERS;
DATA LIP_ORAL;
      SET THESIS.ORGNIZE;
```

```
      *restrict to lip_oral cancer types;
      if psiten  ne 1 then delete;

      *drop in-situ cancer types;
      if stage_status=1 then delete;

      if SCAN=1 THEN COHORT=SCAN;

      IF SCAN=0 THEN COHORT2=1;
      ELSE COHORT2=0;

      time1=0;
      time2 = fupstrttoscan;
      time3=.;
      S1 = 2;
      S2 = cohort;
      SS1 = 2;
      SS2 = cohort2;
      ARRAY t(*) time1-time3;
      ARRAY s(*) s1-s2;
      ARRAY ss(*) ss1-ss2;
      dead=0;
      DO j=1 TO 2 WHILE (t(j) NE .);
      start=t(j);
      group = s(j);
      group2 = ss(j);
      stop=t(j+1);
      IF t(j+1)=. THEN DO;
      stop=survm5yrfrmfupstrt;
      dead=caussurv5yr;
      END;
      OUTPUT;
      END;
      LABEL group = "Scan of Primary Site" group2 = "NO Scan at Primary
Site";

      FORMAT group group. psiten psite. AGE_LEVELN AGE. RACE_N RACE.
POVERTY poverty. MARITAL MARRIED. STAGE_STATUS STAGE. GRADE GRADE.
SURGERY YESNO. CHEMO YESNO. RAD YESNO. SCAN YESNO. caussurv5yr css.
diag_date MMDDYYS10. claim_date MMDDYYS10. sex gender.;
RUN;



***LARYNX;
DATA LARYNX;
      SET THESIS.ORGNIZE;

      *restrict to LARYNX cancer types;
      if psiten  ne 6 then delete;

      *drop in-situ cancer types;
      if stage_status=1 then delete;

      if SCAN=1 THEN COHORT=SCAN;
```

```
      IF SCAN=0 THEN COHORT2=1;
      ELSE COHORT2=0;

      time1=0;
      time2 = fupstrttoscan;
      time3=.;
      S1 = 2;
      S2 = cohort;
      SS1 = 2;
      SS2 = cohort2;
      ARRAY t(*) time1-time3;
      ARRAY s(*) s1-s2;
      ARRAY ss(*) ss1-ss2;
      dead=0;
      DO j=1 TO 2 WHILE (t(j) NE .);
      start=t(j);
      group = s(j);
      group2 = ss(j);
      stop=t(j+1);
      IF t(j+1)=. THEN DO;
      stop=survm5yrfrmfupstrt;
      dead=caussurv5yr;
      END;
      OUTPUT;
      END;
      LABEL group = "Scan of Primary Site" group2 = "NO Scan at Primary
Site";

      FORMAT group group. psiten psite. AGE_LEVELN AGE. RACE_N RACE.
POVERTY poverty. MARITAL MARRIED. STAGE_STATUS STAGE. GRADE GRADE.
SURGERY YESNO. CHEMO YESNO. RAD YESNO. SCAN YESNO. caussurv5yr css.
diag_date MMDDYYS10. claim_date MMDDYYS10. sex gender.;
RUN;



***Partoid_Salivary;
DATA Partoid_Salivary;
      SET THESIS.ORGNIZE;

      *restrict to Partoid_Salivary cancer types;
      if psiten  ne 5 then delete;

      *drop in-situ cancer types;
      if stage_status=1 then delete;

      if SCAN=1 THEN COHORT=SCAN;

      IF SCAN=0 THEN COHORT2=1;
      ELSE COHORT2=0;

      time1=0;
      time2 = fupstrttoscan;
      time3=.;
      S1 = 2;
      S2 = cohort;
      SS1 = 2;
```

```
      SS2 = cohort2;
      ARRAY t(*) time1-time3;
      ARRAY s(*) s1-s2;
      ARRAY ss(*) ss1-ss2;
      dead=0;
      DO j=1 TO 2 WHILE (t(j) NE .);
      start=t(j);
      group = s(j);
      group2 = ss(j);
      stop=t(j+1);
      IF t(j+1)=. THEN DO;
      stop=survm5yrfrmfupstrt;
      dead=caussurv5yr;
      END;
      OUTPUT;
      END;
      LABEL group = "Scan of Primary Site" group2 = "NO Scan at Primary
Site";

      FORMAT group group. psiten psite. AGE_LEVELN AGE. RACE_N RACE.
POVERTY poverty. MARITAL MARRIED. STAGE_STATUS STAGE. GRADE GRADE.
SURGERY YESNO. CHEMO YESNO. RAD YESNO. SCAN YESNO. caussurv5yr css.
diag_date MMDDYYS10. claim_date MMDDYYS10. sex gender.;
RUN;


***REGIONAL;
DATA REGIONAL;
      SET THESIS.ORGNIZE;

      *restrict to Partoid_Salivary cancer types;
      if stage_status  ne 3 then delete;

      if SCAN=1 THEN COHORT=SCAN;

      IF SCAN=0 THEN COHORT2=1;
      ELSE COHORT2=0;

      time1=0;
      time2 = fupstrttoscan;
      time3=.;
      S1 = 2;
      S2 = cohort;
      SS1 = 2;
      SS2 = cohort2;
      ARRAY t(*) time1-time3;
      ARRAY s(*) s1-s2;
      ARRAY ss(*) ss1-ss2;
      dead=0;
      DO j=1 TO 2 WHILE (t(j) NE .);
      start=t(j);
      group = s(j);
      group2 = ss(j);
      stop=t(j+1);
      IF t(j+1)=. THEN DO;
      stop=survm5yrfrmfupstrt;
      dead=caussurv5yr;
```

```
      END;
      OUTPUT;
      END;
      LABEL group = "Scan of Primary Site" group2 = "NO Scan at Primary
Site";

      FORMAT group group. psiten psite. AGE_LEVELN AGE. RACE_N RACE.
POVERTY poverty. MARITAL MARRIED. STAGE_STATUS STAGE. GRADE GRADE.
SURGERY YESNO. CHEMO YESNO. RAD YESNO. SCAN YESNO. caussurv5yr css.
diag_date MMDDYYS10. claim_date MMDDYYS10. sex gender.;
RUN;


***LOCALIZED;
DATA LOCALIZED;
      SET THESIS.ORGNIZE;

      *restrict to Partoid_Salivary cancer types;
      if stage_status  ne 2 then delete;

      if SCAN=1 THEN COHORT=SCAN;

      IF SCAN=0 THEN COHORT2=1;
      ELSE COHORT2=0;

      time1=0;
      time2 = fupstrttoscan;
      time3=.;
      S1 = 2;
      S2 = cohort;
      SS1 = 2;
      SS2 = cohort2;
      ARRAY t(*) time1-time3;
      ARRAY s(*) s1-s2;
      ARRAY ss(*) ss1-ss2;
      dead=0;
      DO j=1 TO 2 WHILE (t(j) NE .);
      start=t(j);
      group = s(j);
      group2 = ss(j);
      stop=t(j+1);
      IF t(j+1)=. THEN DO;
      stop=survm5yrfrmfupstrt;
      dead=caussurv5yr;
      END;
      OUTPUT;
      END;
      LABEL group = "Scan of Primary Site" group2 = "NO Scan at Primary
Site";

      FORMAT group group. psiten psite. AGE_LEVELN AGE. RACE_N RACE.
POVERTY poverty. MARITAL MARRIED. STAGE_STATUS STAGE. GRADE GRADE.
SURGERY YESNO. CHEMO YESNO. RAD YESNO. SCAN YESNO. caussurv5yr css.
diag_date MMDDYYS10. claim_date MMDDYYS10. sex gender.;
RUN;

*****************************************************************;
```

```
* * METHOD 1: PHREG_SEL MACRO WITHOUT R*                              *;
*********************************************************************;

%let dir = \\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\;

%include "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\MACROS\MULTIPLE_PHREG
V21.sas";
%include "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\MACROS\PHREG_SEL
V23.sas";

*interactions by stage;
TITLE 'Extended_Cox_Multivariable - interaction by stage';
%phreg_sel(dsn=one,
      censor=dead,start=start, stop=stop,
      VAR=  group|stage_status age_leveln comorb poverty race_n sex
marital  grade surgery chemo rad psiten ,
      cvar=       group(DESC)* age_leveln* comorb* poverty* race_n*
sex* marital* stage_status* grade* surgery* chemo *rad *psiten,
    slstay=.05,
      EFFECT =  group,
      SLICEBY = stage_status,
    report=T,type3=T,clnum=F,ORIENTATION = portrait,
    outpath=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      filename=Extended_Cox_Multivariable - interaction by stage);
title;

*interactions by site;
TITLE 'Extended_Cox -  interaction by site';
%phreg_sel(dsn=one,
      censor=dead,start=start, stop=stop,
      VAR=  group|psiten stage_status age_leveln comorb poverty race_n
sex marital  grade surgery chemo rad ,
      cvar=       group(DESC)* age_leveln* comorb* poverty* race_n*
sex* marital* stage_status* grade* surgery* chemo *rad *psiten,
    slstay=.05,
      EFFECT =  group,
      SLICEBY = psiten,
    report=T,type3=T,clnum=F,ORIENTATION = portrait,
    outpath=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      filename=Extended_Cox -  interaction by site);
title;

*multivariable all vars;
TITLE 'Extended_Cox_Multivariable_all_predictors';
%phreg_sel(dsn=one,
      censor=dead,start=start, stop=stop,
      VAR=  group age_leveln comorb poverty race_n sex marital psiten
stage_status  grade surgery chemo rad ,
```

```
      cvar=       group * age_leveln(desc)* comorb(desc)*
poverty(desc)* race_n(desc)* sex(desc)* marital(desc)*
stage_status(desc)* grade(desc)* surgery(desc)* chemo(desc)* rad(desc)*
psiten,
    slstay=.05,
    report=T,type3=T,clnum=F, ORIENTATION = portrait,
    outpath=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      filename=Extended_Cox_Multivariable_all_predictors );
title;

*multivariable selected vars;
TITLE 'Extended_Cox_Multivariable_limited_predictors';
%phreg_sel(dsn=one,
      censor=dead,start=start, stop=stop,
      VAR=  group age_leveln comorb poverty race_n sex marital psiten
stage_status  surgery ,
      cvar=       group * age_leveln(desc)* comorb(desc)*
poverty(desc)* race_n(desc)* sex(desc)* marital(desc)*
stage_status(desc)* surgery(desc)* psiten,
    slstay=.05,
    report=T,type3=T,clnum=F, ORIENTATION = portrait,
    outpath=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      filename=Extended_Cox_Multivariable_limited_predictors );
title;



*interactions by grade;
TITLE 'Extended_Cox -  interaction by grade';
%phreg_sel(dsn=one,
      censor=dead,start=start, stop=stop,
      VAR=  group|grade sex psiten stage_status age_leveln comorb
poverty race_n  marital   surgery chemo rad ,
      cvar=       group(DESC)* age_leveln* comorb* poverty* race_n*
sex* marital* stage_status* grade* surgery* chemo *rad *psiten,
    slstay=.05,
      EFFECT =  group,
      SLICEBY = grade,
    report=T,type3=T,clnum=F,ORIENTATION = portrait,
    outpath=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      filename=Extended_Cox -  interaction by grade);
title;

***SURVIVAL GRAPHS;

*Overall;
proc phreg data=one PLOTS(overlay=row)=s;
class group/order=internal param=glm;
model (start,stop)*dead(0) = group/rl;
strata group;
run;
```

```
/*KM PLOTS*/
%include "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\MACROS\KM_PLOT
V22.sas";

TITLE "Extended_COX_KM";
   %km_plot(dsn=one ,censors=dead,events=survm5yrfrmfupstrt,
      grplist= group, title= "Extended Cox: SURVIVAL CURVES BY SCAN"
,entrytitle="Kaplan-Meier Plot",xlab= TIME (MONTHS), ylab=
SURVIVAL,pairwise=F,
    timelist=12,unit=MO,join=T,plot=T,table=T, atrisk=T,
      OUTPATH=\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\,
      fname=Extended_COX_KM);

*****************************************************************;
* METHOD 2: EXPORT TO EXCEL-->R*                                 *;
*****************************************************************;

Data TWO;set ONE;
if start < stop;
run;


/*Export to Excel to plot extended KM in R*/

PROC EXPORT DATA= WORK.TWO
            OUTFILE= "\\nasn2acts.cc.emory.edu\gccsresearch-
ts\medicare\Chen\SharedFolder\HNC Data Analysis\03.12.2017-
Extended_Cox\HNC_counting.csv"
            DBMS=CSV REPLACE;
     PUTNAMES=YES;
RUN;
```

R Code

```
setwd("Y:\\medicare\\Chen\\SharedFolder\\HNC Data Analysis\\03.12.2017- Extended_Cox\\")

install.packages("KMsurv")
install.packages("survival")
install.packages("OIsurv")
install.packages("reshape")
install.packages("ggplot2")
install.packages("gridExtra")

library(survival)
library(KMsurv)
library(OIsurv)

Data<-read.table("HNC_counting.csv", header=T, sep=",")
colnames(Data)
```

```
png(file = "Figure 1 Extended KM curves for Imaging.png",
    bg = "transparent",width = 1200,height = 1200,pointsize = 30)

##work below;

sfit<-survfit(Surv(start, stop, dead)~ group, data=Data)
phfit<-coxph(Surv(start, stop, dead)~ group, data=Data)
p.val<-summary(phfit)$coefficients[5]
HR<-summary(phfit)$coefficients[2]
if (p.val < 0.001) pvalue<-"p-value < 0.001" else pvalue <-paste("p-value = ", round(p.val,3))

times <- seq(0, 54, by =6)
times[1]<-0.000001
strata = factor(summary(sfit,times = times,extend = TRUE)$strata)
time = summary(sfit,times = times,extend = TRUE)$time
n.risk = summary(sfit,times = times,extend = TRUE)$n.risk
med.surv = round(summary(sfit,times = times,extend = TRUE)$table[,5],1)
at.risk <- T


  plot(sfit, lty =c(1,1), col=c(4,2),lwd=2,xlim=c(-1,60), ylim=c(-0.1, 1),xlab= "Months since
Follow-Up Start", ylab="Survival Probability", xaxt="n")
  axis(1,at=round(times,0))
  legend(10,0.35,c(paste("No Imaging (med.surv = ", med.surv[1]," mons)",
sep=""),paste("Imaging (med.surv = ", med.surv[2]," mons)", sep=""), "+  censor"),lty =c(1,1,
0),lwd=2, col=c(4,2),bty = "n")
  text(10,0.35, label=pvalue, pos=4)
  text(0,0, label="Number at Risk",cex=0.8, pos=4,offset=-0.1,font=4)
  text(times, -0.05, n.risk[1:10],cex=0.8, pos=4,offset=-0.1, col="blue",font=3)
  text(times, -0.095, n.risk[11:22],cex=0.8, pos=4,offset=-0.1, col="red",font=3)


dev.off()
```