Analysis of SEER Adenosquamous Carcinoma Data to Identify Cause Specific Survival Predictors and Socioeconomic Disparities

Rex Cheung

Abstract

Background: This study used receiver operating characteristic curve to analyze Surveillance, Epidemiology and End Results (SEER) adenosquamous carcinoma data to identify predictive models and potential disparities in outcome. Materials and Methods: This study analyzed socio-economic, staging and treatment factors available in the SEER database for adenosquamous carcinoma. For the risk modeling, each factor was fitted by a generalized linear model to predict the cause specific survival. An area under the receiver operating characteristic curve (ROC) was computed. Similar strata were combined to construct the most parsimonious models. Results: A total of 20,712 patients diagnosed from 1973 to 2009 were included in this study. The mean follow up time (S.D.) was 54.2 (78.4) months. Some 2/3 of the patients were female. The mean (S.D.) age was 63 (13.8) years. SEER stage was the most predictive factor of outcome (ROC area of 0.71). 13.9% of the patients were un-staged and had risk of cause specific death of 61.3% that was higher than the 45.3% risk for the regional disease and lower than the 70.3% for metastatic disease. Sex, site, radiotherapy, and surgery had ROC areas of about 0.55-0.65. Rural residence and race contributed to socioeconomic disparity for treatment outcome. Radiotherapy was underused even with localized and regional stages when the intent was curative. This under use was most pronounced in older patients. Conclusions: Anatomic stage was predictive and useful in treatment selection. Under-staging may have contributed to poor outcome.

Keywords: Adenosquamous carcinoma - radiotherapy - SEER registry - under usage - cause specific survival

Introduction

SEER registry has massive amount of data available for analysis, however, manipulating this data pipeline could be challenging. SEER Clinical Outcome Prediction Expert (SCOPE) (Cheung, 2014c; Cheung, 2014a; Cheung, 2014d; Cheung, 2014b) was used mine SEER data and construct accurate and efficient prediction models (Cheung et al., 2001a; Cheung et al., 2001b). The areas under the receiver operating characteristic curve (ROC) were computed (Cheung, 2014a; 2014b; 2014c; 2014b; 2014e; Cheung, 2015a; 2015b; Cheung, 2015 (In press)). Similar strata were fused to make more efficient models if the ROC performance did not degrade (Cheung et al., 2001a; Cheung et al., 2001b). In addition, it also implemented binary fusion and optimization to streamline the risk stratification by combining risk strata when possible (Cheung, 2014a; 2014b; 2014c; 2014b; 2014e; Cheung, 2015a; 2015b; Cheung, 2015 (In press)). Similar strata were fused to make more efficient models if the ROC performance did not degrade (Cheung et al., 2001a; Cheung et al., 2001b). In addition, it also implemented binary fusion and optimization to streamline the risk stratification by combining risk strata when possible (Cheung, 2014a; 2014b; 2014c; 2014b; 2014e; Cheung, 2015a; 2015b; Cheung, 2015 (In press)). SCOPE provides SEER-adapted programs for user friendly exploratory studies, univariate recoding and parsing (Cheung, 2014a; 2014b; 2014c; 2014b; 2014e; Cheung, 2015a; 2015b; Cheung, 2015 (In press)).
Table 1. The Risk Models Include the Socio-demographic, Tumor and Treatment Factors for Adenosquamous Carcinoma

| Number | %            |
|--------|--------------|
| Mean   | 63           |
| S.D.   | 14           |
| < 20 years old | 7.03 |
| ≥ 20 years old | 99.97 |
| Female | 13109 63.29  |
| Male   | 5603 36.71   |
| Localized, I | 9001 32.84 |
| Regional, II | 6196 29.92 |
| Distant, III | 4957 23.35 |
| Untreated/other, IV | 2079 13.80 |
| Lung and bronchus | 1497 45.73 |
| Others | 11240 54.27  |
| Well differentiated, Grade I | 790 3.81 |
| Moderately differentiated, Grade II | 4017 19.39 |
| Poorly differentiated, Grade III | 8793 42.45 |
| Undifferentiated, anaplastic, Grade IV | 786 3.77 |
| Unknown | 6332 30.57 |
| Counties in metropolitan areas 0.01 million pop/Counties in metropolitan areas of 250,000 to 1 million pop/Urban pop of ge 20,000 adjacent to a metropolitan area | 18446 89.06 |
| versus | 2266 10.94 |
| Others | 11052 57.71 |
| ≤ 50000 | 8760 42.29 |
| ≥ 50000 | 10557 50.97 |
| < 25% | 10555 49.03 |
| ≥ 25% | 10634 49.57 |
| Black | 2078 10.03 |
| None | 11291 54.51 |
| Beam radiation | 6275 32.47 |
| Combination of beam with implants or isotopes | 1491 7.20 |
| Refused | 172 0.83 |
| Other radiation (1973-1987 cases only) | 264 1.27 |
| Recommended, unknown if administered | 293 1.41 |
| Radioisotopes | 17 0.08 |
| Radioactive implants | 192 0.93 |
| Radiation, NOS method or source not specified | 149 0.72 |
| Unknown | 118 0.57 |
| Surgery performed | 13639 65.45 |
| Recommended but not performed, unknown reason | 992 4.62 |
| Not recommended | 4227 20.41 |
| Recommended but not performed, patient refused | 100 0.48 |
| Not recommended, contraindicated due to other conditions | 389 1.88 |
| Recommended, unknown if performed | 66 0.32 |
| Unknown, death certificate or autopsy only case | 7 0.03 |
| Death | 5285 15.86 |
| Alive or dead of other cause | 8163 39.41 |

Results

There were 20712 patients included in this study (Table 1). The follow up (S.D.) was 54 (72.4) months. 64% of the patients were female. The mean (S.D.) age was 63 (13.8) years. There were 60% adenosquamous carcinoma patients listed from SEER database were adults. There were 7 patients younger than 20 years old in the SEER data, and it was a poor prognostic factor (Table 1 and Table 2). There is a significant female to male difference in risk of cause specific death (Table 2) favoring the female sex. 46% of the patients had lung cancers. Uterus and uterine cervix were also the common anatomic sites (Table 3). 30.6% of the tumors were not graded. Unknown grade has the highest risk of cause specific death at 51.8%. SEER stage model (localized, regional, distant, un-staged/others) was the most predictive model (ROC area or 0.71). A 4-tiered staging model was optimized to a 3-tiered model (with a ROC area of 0.67) by SCOPE (Table 1). ROC areas were used to optimize the risk models. For example, the SEER staging could be abstracted down to 3-tiered structure while not abandoning the poor (Table 1, 2, and 3). Among the socioeconomic factors studies, African American patients had 53.8% risk of death compared with 43.7% of others. However, this level of difference increased the ROC area mildly to 0.52 (Table 1). Actual residence and living a cosmopolitan area have respectively 48.7% and 42.4% risk of cause specific death (Table 1, 2 and 3).

There is about 44.7% overall risk of adenosquamous carcinoma death for patients listed in SEER. The risks were 19.1% and 45.3% for localized and regional adenosquamous carcinoma respectively (Table 2). Age older than 20 years old did correlate with higher percentage mortality during this study period from 1973 to 2009 (Table 1 and Table 2). RT with external beam was associated with 54.5% risk of death, and 32.5% risk of death (Table 3). RT with external beam had surgery had respectively 48.7% and 44.2% risk of cause specific death compared with 43.7% of others. However, this

Discussion

This study is interested in constructing models that will aid patient and treatment selection for adenosquamous carcinoma patients. To that end, this study examined the ROC models (Rex and McNeil, 1982) of a long list of potential explanatory factors (Table 1). ROC models take into account both sensitivity and specificity of the prediction. Ideal model would have a ROC area of 1 and a random model is expected to have an area of 0.5 (Hanley and McNeil, 1982; Rex, 2014c; Rex, 2014a; Rex, 2014d; Rex, 2014b; Rex, 2014e; Rex, 2015b; Rex, 2015c; Cheung, 2015 (In press)). For example, a clinical ROC model can be used to predict if a patient receiving the recommended treatment will die from the disease. SEER stage in order to be consistent over decades, it abstracts the staging into simple but important stages for cancer progression: localized, regional and distant. Stage was the most predictive of patient outcome (Table 1 and Table 2). There is a significant female to male difference in risk of cause specific death (Table 2) favoring the female sex. 46% of the patients had lung cancers. Uterus and uterine cervix were also the common anatomic sites (Table 3). 30.6% of the tumors were not graded. Unknown grade has the highest risk of cause specific death at 51.8%. SEER stage model (localized, regional, distant, un-staged/others) was the most predictive model (ROC area or 0.71). A 4-tiered staging model was optimized to a 3-tiered model (with a ROC area of 0.67) by SCOPE (Table 1). ROC areas were used to optimize the risk models. For example, the SEER staging could be abstracted down to 3-tiered structure while not abandoning the poor (Table 1, 2, and 3). Among the socioeconomic factors studies, African American patients had 53.8% risk of death compared with 43.7% of others. However, this level of difference increased the ROC area mildly to 0.52 (Table 1). Actual residence and living a cosmopolitan area have respectively 48.7% and 42.4% risk of cause specific death (Table 1, 2 and 3).

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| Factor                                      | Number | %     |
|---------------------------------------------|--------|-------|
| Alive or dead of other cause                | 8163   | 39.41 |
| N/A not first tumor                         | 3285   | 15.86 |
| Dead                                        | 9264   | 44.73 |
| Not recommended, contraindicated due to other causes | 100    | 0.48  |
| Recommended but not performed, patient refused | 4227   | 20.41 |
| Recommended but not performed, unknown reason | 1992   | 9.62  |
| Surgery performed                           | 13639  | 65.85 |
| Unknown                                     | 6332   | 30.57 |
| Counties in metropolitan areas of 250,000 to 1 million pop/Urban pop of ge 20,000 adjacent to a metropolitan area versus | 18466  | 89.06 |
| Others                                      | 2266   | 10.94 |
| < 50000                                     | 10557  | 50.97 |
| ≥ 25                                         | 10155  | 49.03 |
| White/others                                | 10634  | 99.97 |
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Results

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When there are competing prediction or prognostic models, the most efficient (i.e. the simplest) model is thought to prevail (D’Amico et al., 1998). This has an improvement. It may be a consequence of having a better guidance model in treatment and patient selection. Adenosquamous carcinoma is an aggressive disease, there was a 19% of adenosquamous carcinoma death (Table 2) despite treatments even for early stage cancer. In conclusion, this study has identified the staging models are the most prognostic of treatment outcomes of adenosquamous cancer patients. The high under-staging rates may have prevented patients from selecting definitive local therapy and may have contributed to the poor outcome in these patients with this aggressive disease.

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Adenosquamous carcinoma is an aggressive disease, there was a 19% relative reduction in adenosquamous carcinoma death (Table 2) despite treatments even for early stage cancer. In conclusion, this study has identified the staging models are the most prognostic of treatment outcomes of adenosquamous cancer patients. The high under-staging rates may have prevented patients from selecting definitive local therapy and may have contributed to the poor outcome in these patients with this aggressive disease.
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