RESEARCH ARTICLE

Under-use of Radiotherapy in Stage III Bronchioaveolar Lung Cancer and Socio-economic Disparities in Cause Specific Survival: a Population Study

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Abstract

<u>Background</u>: This study used the receiver operating characteristic curve (ROC) to analyze Surveillance, Epidemiology and End Results (SEER) bronchioaveolar carcinoma data to identify predictive models and potential disparity in outcomes. <u>Materials and Methods</u>: Socio-economic, staging and treatment factors were assessed. For the risk modeling, each factor was fitted by a Generalized Linear Model to predict cause specific survival. The area under the ROC was computed. Similar strata were combined to construct the most parsimonious models. A random sampling algorithm was used to estimate modeling errors. Risk of cause specific death was computed for the predictors for comparison. <u>Results:</u> There were 7,309 patients included in this study. The mean follow up time (S.D.) was 24.2 (20) months. Female patients outnumbered male ones 3:2. The mean (S.D.) age was 70.1 (10.6) years. Stage was the most predictive factor of outcome (ROC area of 0.76). After optimization, several strata were fused, with a comparable ROC area of 0.75. There was a 4% additional risk of death associated with lower county family income, African American race, rural residency and lower than 25% county college graduate. Radiotherapy had not been used in 2/3 of patients with stage III disease. <u>Conclusions:</u> There are socio-economic disparities in cause specific survival. Under-use of radiotherapy may have contributed to poor outcome. Improving education, access and rates of radiotherapy use may improve outcome.

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

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Introduction

Bronchioaveolar carcinoma is a relatively rare lung cancer, it is an aggressive form of adenocarcinoma (Raz and Jablons, 2006; Riquet et al., 2006; Garfield and Franklin, 2008; Varlotto et al., 2008). This study used the Surveillance Epidemiology and End Results (SEER) cancer registry data to analyze the biological and socioeconomic factors affecting the outcome of bronchioaveolar carcinoma. Surveillance Epidemiology and End Results (SEER) (http://seer.cancer.gov/) is a public use cancer registry of United States of America (US). SEER is funded by National Cancer Institute and Center for Disease Control to cover 28% of all oncology cases in US. SEER started collecting data in 1973 for 7 states and cosmopolitan registries. Its main purpose is through collecting and distributing data on cancer, it strives to decrease the burden of cancer. SEER data are used widely as a bench-mark data source for studying cancer outcomes in US and in other countries. The extensive ground coverage by the SEER data is ideal for identifying the disparity in oncology outcome and treatment in different geographical and cultural areas for cancers. In particular, SEER data have been used to study socio-economic factors associated with bronchioaveolar lung cancer (Hasan et al., 2004; Saeed et al., 2012). This study aimed to explore the potential barriers to good treatment outcome that may be discernable from a national database.

Materials and Methods

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, 2012) was used mine SEER data and construct accurate and efficient prediction models (Cheung et al., 2001a; 2001b). The data were obtained from SEER 18 database. SEER is a public use database that can be used for analysis with no internal review board approval needed. SEER*Stat (http://seer.cancer.gov/seerstat/) was used for listing the cases. The filter used was: Site and Morphology. ICD-O-3 Hist/behav, malignant='8250/3: Bronchiolo-alveolar adenocarcinoma' AND Race, Sex, Year Dx, Registry, County. Year of diagnosis='2004','2005','2006','2007','2008','2009'. This study explored a long list of socio-economic, staging and treatment factors that were available in the SEER database. Histologic type ICD-O-3 was 8250. The variable 'SEER cause-specific death classification' was used as the

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outcome.

The codes of SCOPE are posted on Matlab Central (www.mathworks.com). SCOPE has a number of utility programs that are adapted to handle the large SEER data pipeline. All statistics and programming were performed in Matlab (www.mathworks.com). Each risk factor was fitted by a Generalized Linear Model to predict the outcome ("SEER cause-specific death classification"). The areas under the receiver operating characteristic curve (ROC) were computed. Similar strata were fused to make more efficient models if the ROC performance did not degrade (Cheung et al., 2001a; 2001b). In addition, it also implemented binary fusion and optimization to streamline the risk stratification by combining risk strata when possible. SCOPE uses Monte Carlo sampling with replacement to estimate the modeling errors and allow t-testing of the areas under the ROC. SCOPE provides SEER-adapted programs for user friendly exploratory studies, univariate recoding and parsing.

Results

There were 7309 bronchioalveolar lung cancer patients included in this study. The mean follow up time (S.D.) was 24.2 (20) months. Female patients outnumbered male ones 3:2. Female patients had a 19.8% risk of death compared with 25.7% for male patients. The mean (S.D.) age was 70.1 (10.64) years. There was 1 patient younger than 19 years old. The overall crude risk of death from bronchioaveolar carcinoma was about 20.1% but it varied

Table 1. The Risk Models Include the Socio-demographic, Tumor and Treatment Factors for Ewing Sarcoma

	Number	%	Model	ROC area	S.D.	ROC area of each run				
	7309									
Mean	70.01									
S.D.	10.64									
<20 years	1									
≥20 years old	7308									
Mean	24.16									
S.D.	20.04									
Female	4502	61.60								
Male	2807	38.40								
IA. I	2664	36.45	I, II, III, IV,V	0.76	0.01	0.75	0.76	0.77	0.76	0.77
IB, II	1275	17.44	VI, VII, VIII							
IIA, III	104	1.42	IX							
IIB, IV	163	2.23	Optimized							
IIIA, V	355	4.86	I, II, III	0.75	0.01	0.75	0.74	0.74	0.75	0.75
IIIB, VI	610	8.35								
IV, VII	1547	21.17								
OCCULT, VIII	201	2.75								
UNK Stage, IX	390	5.34								
Lung and bronchus										
Others										
Well differentiated; Grade I	2647	36.22								
Moderately differentiated; Grade II	1870	25.58								
Poorly differentiated; Grade III	429	5.87								
Undifferentiated; anaplastic; Grade IV	20	0.27								
Unknown	2343	32.06								
Counties in metropolitan areas ge 1 million pop	4794	65.59		0.50	0.01	0.51	0.51	0.5	0.5	0.5
Counties in metropolitan areas of 250,000 to 1 million pop	1229	16.81								
Urban pop of ge 20,000 adjacent to a metropolitan area	191	2.61								
Urban pop of ge 20,000 not adjacent to a metropolitan area	93	1.27								
Counties in metropolitan areas of lt 250 thousand pop	539	7.37								
Urban pop of 2,500 to 19,999, adjacent to a metro area	232	3.17								
Urban pop of 2,500 to 19,999, not adjacent to a metro area	142	1.94								
Comp rural lt 2,500 urban pop, adjacent to a metro area	40	0.55								
Comp rural lt 2,500 urban pop, not adjacent to metro area	43	0.59								
Unknown/missing/no match (Alaska - Entire State)	6	0.08								
≥$50000	4219	57.72		0.52	0.01	0.51	0.51	0.53	0.54	0.52
<$50000	3090	42.28								
≥25%	3524	48.21		0.52	0.01	0.534	0.521	0.525	0.52	0.52
<25%	3785	51.79								
White/others	6738	92.19		0.51	0.01	0.51	0.5	0.5	0.51	0.51
Black	571	7.81								
None	6281	85.94								
Beam radiation	837	11.45								
Refused	68	0.93								
Radioactive implants	10	0.14								
Radiation, NOS method or source not specified	28	0.38								
Recommended, unknown if administered	33	0.45								
Combination of beam with implants or isotopes	3	0.04								
Unknown	49	0.67								
Surgery performed	4727	64.67								
Not recommended	2121	29.02								
Not recommended, contraindicated due to other conditions	155	2.12								
Recommended but not performed, unknown reason	145	1.98								
Recommended but not performed, patient refused	74	1.01								
Unknown; death certificate or autopsy only case	63	0.86								
Recommended, unknown if performed	15	0.21								
Not performed, patient died prior to recommended surgery	9	0.12								
N/A not first tumor	2397	32.80								
Dead	1613	22.07								
Alive or dead of other cause	3299	45.14								

greatly with the stage of the disease and other factors (Table 1 and Table 2). 90% percent of patients did not receive radiation treatment (Table 1).

The AJCC (American Joint Committee on Cancer) stage was the most predictive factor of outcome (ROC area of 0.76). There were about 30% crude rate of cause specific death for stage III patients (Table 1). After optimization, 9-tiered initial risk levels model was slimmed down to 3 level (stage IA, Stage IB and the rest) with a comparable ROC area of 0.75. Radiotherapy has not been used in 2/3 of stage III patients (Figure 1). Of the about 11% patients treated with external beam radiotherapy, they had 37.6% risk of death versus 20% if they did not receive radiotherapy. Only 1/3 of patients with stage IIIA and 13.9% stage IIIB patients had radiotherapy. 64.6% patients had surgery. Patients had a 10.4% risk of death if they had surgery, and 43.3% risk of death if they did not. Poorly and undifferentiated bronchioaveolar carcinoma had a 28.7% and 20% risk of cause specific death respectively. 42% of patients did not have their tumor graded. Being un-graded carried a 32.4% risk of cause specific death (Table 1 and Table 2).

Among the socio-economic factors, African American patients had 26.3% risk of death compared with 21.7% for the others. County percent college graduate less than 25% was associated with a 19.97% risk of bronchioalveolar carcinoma specific death compared with 24.02% risk of death if county percent college graduate was more than 25%. County family income level less than $50,000 was associated with 24.2% risk of death versus 20.5% otherwise. Metropolitan and rural residence was associated with 21.7% and 26.3% of risk of cause specific death respectively. The ROC areas of these four socio-economic factors were calculated (Table 1).

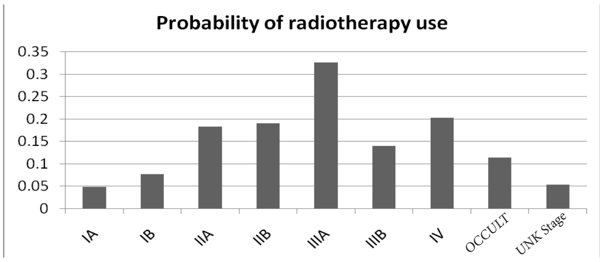

Figure 1. Probability of Being Treated with Radiotherapy by Stage

Table 2. Risk of Cause Specific Mortality Associated with Different Models

Initial univariate risk models		No. at risk	% mortality
Study population		1844	0.36
Age of diagnosis (years)	<20	1252	0.33
	≥20	592	0.43
Sex	Female	672	0.33
	Male	1172	0.38
Rural-Urban Continuum Code 2003	Metropolitan	1629	0.37
	Rural	215	0.34
County Family Income	≥50000	887	0.37
	<50000	957	0.36
County % college graduate	≥25%	1000	0.38
	<25%	844	0.34
Race	Others	1797	0.36
	Black	47	0.43
Radiation treatment given	Beam radiation	949	0.40
	None	895	0.32
Reason no cancer-directed surgery	Surgery performed	957	0.28
	Surgery not performed	887	0.45

Discussion

SEER data are useful in identifying the disparity in cancer outcome and treatment used because SEER has different socioeconomic and outcome data (Ognjanovic et al., 2009; Sultan et al., 2009; Cheung et al., 2010; McDowell et al., 2010; Pappo et al., 2010; Bhatia, 2011; Perez et al., 2011) (Harlan et al., 1995; Shavers et al., 2003; Wampler et al., 2005; Gross et al., 2008; Lund et al., 2008; Downing et al., 2010; Martinez et al., 2010; 2012; Schlichting et al., 2012; Yao et al., 2012). In particular, SEER data have outcome and socio-economic data associated with bronchioaveolar lung cancer (Hasan et al., 2004; Saeed et al., 2012). This study is interested in constructing models that will aid patient and treatment selection for bronchioaveolar carcinoma cancer patients. To that end, this study examined the ROC models (Hanley 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). For example, a clinical ROC model can be used to predict if a patient receiving the recommended treatment will die from the disease. AJCC stage was the most predictive of patient outcome (Table 1). AJCC stage has ROC of 0.69 that was the highest among the other factors tested. Thus complete staging is important for patient selection and council.

After binary fusion by SCOPE, the 9 tiered grade was reduced to a 3 tiered grade based on ROC area calculations (Table 1). Un-staged/others was associated with high risk of cause specific death (Table 2). Although in this study, the un-staged was fused with disease higher than stage IA and stage IB, there was no a priori reason to assume leaving un-staged patients in the modeling would not affect the optimization. The results of the optimization suggested that these un-staged patients were likely to have lymph node positive disease, and thus important to have their lymph nodes examined. The binary fusion was performed to demonstrate how a complex predictive model could be numerically optimized to a much simpler model that may also be useful. 90% of patients were not treated with radiotherapy (Table 1). Most troublesome was that more than 2/3 of stage III patients were not treated with radiotherapy when it is clearly indicated (Mantovani et al., 2012; Price, 2012). Thus radiation oncologists should be more attentive in recommending RT for these patients.

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 information theoretic under-pinning. For practical purposes, simpler models require fewer patients for a randomized trials because fewer risk strata need to be balanced. In the clinic, simpler models are easier to use. SCOPE streamlined ROC models by binary fusion (Table 1). Two adjacent strata were tested iteratively to see if they could be combined without sacrificing the higher predictive power usually belong to the more complex models. This study has shown that SCOPE can built efficient and accurate prediction models.

ROC areas of the socio-economic factors had modestly higher than 0.5 (Table 1 and 2). For a point of reference, using we computed the prostate risk model was 0.75 in its accuracy of predicting biochemical failure (Cheung et al., 2001a; 2001b). Low ROC areas imply the information content (e.g. the staging accuracy) of the models may be limited. The 4% difference in cause specific survival related to the socio-economic factors might not make them very reliable predictors of outcome as judged by their ROC areas.

In conclusion, this study has identified the staging models that are highly prognostic of treatment outcomes of bronchioaveolar cancer patients. The poor rates of radiotherapy (Figure 1) after surgery use may have contributed to the poor outcome in these patients with this aggressive disease. Ensuring proper education and access to cancer treatment may help to eliminate these socio-economic disparities.

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