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Original Article

Underusage of radiotherapy and a lack of socio-economic disparity in treatment outcome: a population-based study on adenoid cystic carcinomas

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Abstract

This study used receiver operating characteristic curve to analyse a long list of biological, treatment and socio-economic predictors of adenoid cystic carcinoma treatment outcome. Anatomical staging was found to be the most predictive factor of outcome.

Purpose: This study used receiver operating characteristic curve (ROC) to analyse surveillance, epidemiology and end results (SEER) adenoid cystic carcinoma data to identify predictive models and potential disparity in outcome.

Materials and methods: For the risk modelling, each factor was fitted by a generalised linear model to predict the 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 the modelling errors. Risk of adenoid cystic carcinoma death was computed for the predictors for comparison.

Results: There were 5,947 patients diagnosed from 1973 to 2009 included in this study. The mean follow-up time (SD) was 93·8 (90·6) months. Three out of five patients were women. The mean (SD) age was 58·55 (16·01) years. SEER stage was the most predictive factor of outcome (ROC area of 0·68). Sex, radiotherapy and surgery had ROC areas of about 0·57. None of the socio-economic disparities was found for treatment outcome. Radiotherapy was underused in localised and regional stages when the intent was curative, especially in older patients.

Conclusion: Anatomical staging was predictive and useful in treatment selection. Understaging and underuse of radiotherapy may have contributed to poor outcomes.

Keywords: adenoid cystic carcinoma; cause specific survival; radiotherapy; SEER registry; under usage

INTRODUCTION

The surveillance epidemiology and end result (SEER) cancer registry data have been extensively used to model prognostic models for adenoid cystic carcinoma.[1–3] Adenoid cystic carcinomas are a heterogeneous group of carcinomas, mostly occurring in salivary gland tumours,[4–7] but it could occur in a large variety of anatomic sites.[2,8] SEER data are a particularly important source for identifying disparity in treatment.

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Table 1. *The risk models include the socio-demographic, tumour and treatment factors for adenoid cystic carcinoma*

Variables	Risk models	n	%	Model	ROC area	SD
Study population		5,947				
Age of diagnosis	Mean	59				
	SD	16				
	<20 years	36	0·61		0·5	0·000
	≥20 years old	5,911	99·39			
Follow-up (months)	Mean	94				
	SD	91				
Sex	Female	3,775	63·48		0·558	0·011
	Male	2,172	36·52			
SEER historic stage A	Localised, I	2,748	46·21	I, II, III, IV	0·68	0·007
	Regional, II	1,929	32·44	Optimised		
	Distant, III	583	9·80	(I, II), III, IV	0·662	0·008
	Unstaged/others, IV	687	11·55			
Site of disease	Salivary gland	2,005	33·71		0·51	0·000
	Others	3,842	64·60			
Grade	Well differentiated; grade I	377	6·34		0·522	0·004
	Moderately differentiated; grade II	538	9·05			
	Poorly differentiated; grade III	311	5·23			
	Undifferentiated; anaplastic; grade IV	138	2·32			
	Unknown	4,583	77·06			
Rural–urban continuum	Counties in metropolitan areas ≥1 million population	3,755	63·14		0·504	0·005
Code 2003	Counties in metropolitan areas of 250,000 to 1 million population	1,151	19·35			
	Counties in metropolitan areas of <250,000 population	418	7·03			
	Urban population of ≥20,000 adjacent to a metropolitan area	142	2·39			
	Urban population of ≥20,000 not adjacent to a metropolitan area	95	1·60			
	Urban population of 2,500 to 19,999, adjacent to a metro area	182	3·06			
	Urban population of 2,500 to 19,999, not adjacent to a metro area	138	2·32			
	Rural, <2,500 urban population, not adjacent to metro area	31	0·52			
	Rural, <2,500 urban population, adjacent to a metro area	33	0·55			
	Unknown/missing/no match (Alaska – Entire State)	1	0·02			
	Unknown/missing/no match	1	0·02			
County family income	≥$50,000	3,678	61·85		0·506	0·009
	<$50,000	2,269	38·15			
County % college graduate	≥25%	3,284	55·22		0·512	0·008
	<25%	2,663	44·78			
Race	White/others	5,345	89·88		0·508	0·008
	Black	602	10·12			
Radiation treatment given	Beam radiation	3,073	51·66		0·566	0·005
	None	2,542	42·74			
	Other radiation (1973–1987 cases only)	2	0·03			
	Combination of beam with implants or isotopes	68	1·14			
	Radiation, NOS method or source not specified	40	0·67			

Table 1. Continued

Variables	Risk models	n	%	Model	ROC area	SD
	Unknown	44	0·74			
	Refused	63	1·06			
	Recommended, unknown if administered	98	1·65			
	Radioactive implants	11	0·18			
	Radioisotopes	6	0·10			
Reason no cancer-directed surgery	Surgery performed	5,065	85·15		0·574	0·005
	Recommended but not performed, unknown reason	292	4·91			
	Not recommended	459	7·72			
	Not recommended, contraindicated due to other conditions	31	0·52			
	Unknown; death certificate or autopsy only case	58	0·98			
	Recommended but not performed, patient refused	29	0·49			
	Recommended, unknown if performed	13	0·22			
SEER cause-specific survival	Alive or dead of other cause	3,908	65·70			
	na not first tumour	664	11·16			
	Dead	1,375	23·12			

Abbreviations: ROC, receiver operating characteristic curve; SD, standard deviation; SEER, surveillance, epidemiology and end results.

The cause-specific survival rates for adenoid cystic carcinoma are about 75–80%[1,2,5–9] (this study). Thus, there is room for improvement. For the first time, this study used receiver operating characteristic curve (ROC) to analyse SEER adenoid cystic carcinoma outcome data. The aim of this study was to identify and optimise predictive adenoid cystic carcinoma models to aid treatment and patient selection. This study also examined socio-economic factors that were predictors of treatment outcome.

SEER (http://seer.cancer.gov/) is a public-use cancer registry of the United States. SEER is funded by National Cancer Institute and Center for Disease Control. It covers 28% of all oncology cases in the United States. SEER started collecting data in 1973 for seven states and cosmopolitan registries. Its main purpose is, through collecting and distributing data on cancer, to strive to decrease the burden of cancer. SEER data are used widely as a benchmark data source for studying cancer outcomes in the United States and in other countries.[10–16] 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.[17] In addition to the biological staging factors and the treatment factors, this database also contains a large number of county-level socio-economic factor data. This study aimed to identify 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)[18] was used to mine SEER data and construct accurate and efficient prediction models.[19,20] 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. The SEER website www.seer.gov has detailed information and data of SEER databases. SEER*Stat (http://seer.cancer.gov/seerstat/) was used for

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listing the cases. The filter used was: Site and Morphology.ICD-O-3 Hist/behav, malignant = '8200/3: Adenoid cystic carcinoma'. This study explored a long list of socio-economic, staging and treatment factors that were available in the SEER database. The outcome used was 'SEER cause-specific death classification'.

The codes of SCOPE are posted on Matlab Central (www.mathworks.com). SCOPE has a number of utility programmes 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 generalised linear model to predict the outcome (cause of death: brain and other nervous system as coded in SEER). The areas under the ROC were computed. Similar strata were fused to make more efficient models if the ROC performance did not degrade.[19,20] In addition, it also implemented binary fusion and optimisation to streamline the risk stratification by combining risk strata when possible. SCOPE uses Monte Carlo sampling with replacement to estimate the modelling errors and allows *t*-testing of the areas under the ROC. SCOPE provides SEER-adapted programmes for user-friendly exploratory studies, univariate recoding and parsing.

RESULTS

There were 5,937 patients included in this study (Table 1). The follow-up (SD) was 93·8 (90·6) months. Of the patients, 64% were women. The mean (SD) age was 58·55 (16·01) years. Patients younger than 20 years old had 16·7% risk for cause-specific death compared with 22·3% for older patients (Table 2). Complete staging was done nearly for all these patients. There is a significant female to male difference in the risk

Table 2. *Risk of SEER cause-specific mortality (%) associated with different models*

Variables	Risk models	No. at risk	Expected risk of death
Age of diagnosis	<20 years	36	0·17
	≥20 years old	5,911	0·23
Sex	Female	3,775	0·20
	Male	2,172	0·28
Grade	Well differentiated; grade I	377	0·09
	Moderately differentiated; grade II	538	0·14
	Poorly differentiated; grade III	311	0·40
	Undifferentiated; anaplastic; grade IV	138	0·37
	Unknown	4,583	0·24
SEER staging	Localised	2,748	0·11
	Regional	1,929	0·30
	Distant	583	0·48
	Unstaged/others	687	0·33
Rural–Urban continuum Code 2003	Counties in metropolitan areas ≥1 million population/ Counties in metropolitan areas of 250,000 to 1 million population/versus	5,324	0·23
	Others	623	0·26
County family income	≥$50,000	3,678	0·23
	<$50,000	2,269	0·23
County % college graduate	≥25 college graduate	3,284	0·23
	<25% college graduate	2,663	0·23
Race	White/others	5,345	0·23
	Black	602	0·26
Radiation treatment given	Beam radiation	3,073	0·27
	Others	2,874	0·18
Reason no cancer-directed surgery	Surgery performed	5,065	0·20
	Others	882	0·41

Abbreviation: SEER, surveillance, epidemiology and end results.

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Table 3. The distribution of adenoid cystic carcinoma by anatomical sites

Site	n	%
Salivary gland	2,005	33·71
Gum and other mouth	846	14·22
Breast	773	13·00
Nose, nasal cavity and middle ear	572	9·62
Other non-epithelial skin	312	5·25
Tongue	236	3·97
Lung and bronchus	226	3·80
Trachea, mediastinum and other respiratory organs	146	2·45
Nasopharynx	119	2·00
Eye and orbit	116	1·95
Floor of mouth	103	1·73
Lip	96	1·61
Cervix uteri	77	1·29
Miscellaneous	66	1·11
Larynx	65	1·09
Vulva	56	0·94
Tonsil	24	0·40
Other oral cavity and Pharynx	22	0·37
Prostate	18	0·30
Oesophagus	17	0·29
Hypopharynx	12	0·20
Oropharynx	8	0·13
Soft tissue including heart	7	0·12
Vagina	6	0·10
Anus, anal canal and anorectum	6	0·10
Corpus uteri	3	0·05
Other urinary organs	2	0·03
Other male genital Organs	2	0·03
Ovary	2	0·03
Thyroid	1	0·02
Kidney and renal pelvis	1	0·02
Other endocrine including thymus	1	0·02
Pancreas	1	0·02

for cause-specific death (Table 2). Gender has a ROC (SD) of 0·56 (0·011). Radiation treatment has a ROC (SD) of 0·566 (0·005). Surgical resection has a ROC (SD) 0·574 (0·005). There were 66% ungraded adenoid cystic carcinoma cases (Table 1). Histological grade has a ROC (SD) of 0·52 (0·004) (Table 1). Unknown grade has a 24% risk for cause-specific death compared with 9% for grade I, 14% for grade II, 40% for grade III and 37 for grade IV (Figure 2). With respect to the socio-economic factors, African American patients had 26% risk for death compared with 23% for non-African Americans. Urban patients had a 23% risk for death compared with a 26% risk for rural patients (Table 2). However, these differences were not significantly associated with high ROC areas (Table 1). County-level family income and county education attainment were found not to be predictors of poor outcome (Tables 1 and 2). A third of the patients had salivary gland adenoid cystic carcinoma. But they could also occur in many other anatomic sites (Table 3). The distribution of other sites included: gum and other mouth sites 14·2%, breast 13%, nose, nasal cavity and middle ear 9·6%, other non-epithelial skin 5·3%, tongue 4%, lung and bronchus 3·8%, trachea, mediastinum and other respiratory organs 2·5% and nasopharynx 2%.

A four-tiered staging model (with a ROC area 0·68) was optimised to a three-tiered model (with a ROC area of 0·66) by SCOPE (Figure 1). ROC areas were used to optimise the risk models. For example, the SEER staging could be slimmed down to three-tiered risk model, while not maintaining the strong ROC prediction performance (Table 1). There was only 50% use of RT (Table 1). There were about 60% adult patients younger than 40 years old received RT compared with 40% older patients received RT (Figure 3). There was a decreasing rate of RT use with increasing age (Figure 3).

DISCUSSION

This study is interested in constructing models that will aid patient and treatment selection for adenoid cystic carcinoma cancer patients. To that end, this study examined the ROC models[21] 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 a ROC area of 0·5.[21] For example, a clinical ROC model can be used to predict whether a patient receiving the recommended treatment will die from the disease.

SEER staging model (localised, regional, metastatic and unstaged/others) has a ROC of 0·68 that is the highest among all the factors tested. For this study, these stages were risk-labelled as level I, II, III and IV. The unstaged/other patients had outcome better than those with metastatic models (Table 2). However, for

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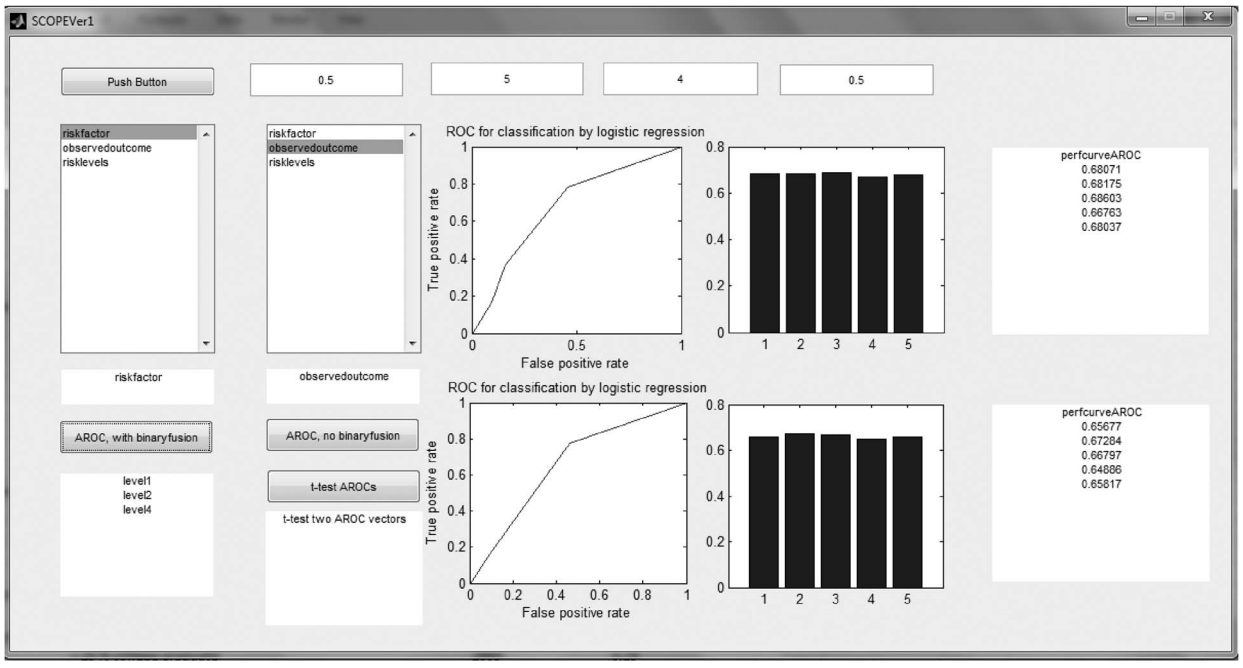

Figure 1. Interactive graphical interface of SCOPE. The ROC areas of SEER Stage of adenoid cystic carcinomas were calculated without (upper right-hand side panels) and with (the corresponding lower panels) optimisation.
Abbreviations: SCOPE, SEER Clinical Outcome Prediction Expert; ROC, receiver operating characteristic curve; SEER, surveillance, epidemiology and end results.

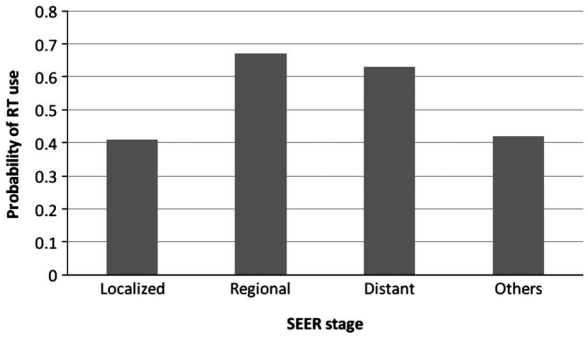

Figure 2. The outcome of adenoid cystic carcinoma patients by SEER stage.
Abbreviations: SEER, surveillance, epidemiology and end results; RT, radiotherapy.

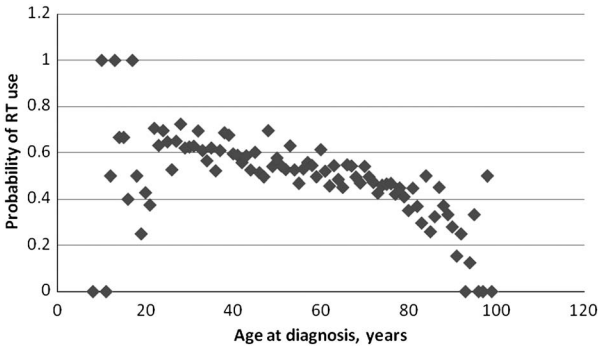

Figure 3. Fraction of patients received radiotherapy as a function of age of diagnosis.

this study, it is assigned level IV as there was no a priori reason to assume that unstaged patients had good outcomes. SCOPE optimised the four-tiered risk model to a three-tiered risk model (I and II), III and IV. In this case, the reported ROC area is marginally lower than the original risk. However, on the basis of tested variables of other sites (data not shown), SCOPE in general simplifies the model without sacrificing the ROC area. Second, a Monte Carlo simulation estimated the ROC areas. The estimates are expected to have random fluctuations.

When there are competing prediction or prognostic models, the most efficient (i.e., the simplest) model is thought to prevail.[22] This has an information theoretic underpinning. For practical purposes, simpler models require

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fewer patients for randomised 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 determine whether they could be combined without sacrificing the higher predictive power, usually belonging to the more complex models. This study has shown that SCOPE can build efficient and accurate prediction models.

For radiotherapy, the ROC area of 0·57 was modestly more than 0·5. For a point of reference, using we computed the prostate risk model was 0·75 in its accuracy of predicting biochemical failure.[19,20] Low ROC areas imply that the information content (i.e., the staging accuracy) of the models may be limited. Another variable Grade (Tables 1 and 2) may be a potential source for improvement. When divided into grade I/I versus grade III/IV, grading model separated patients with a low risk for cause-specific death from the high-risk ones (Table 2). However, the ROC areas were lower than expected. This was probably owing to the fact that more than 70% tumours were not graded. It is consistent with the fact that most patients did not have complete grading or staging (Table 2). This is an area of improvement. It may be a consequence of having a better guidance model in treatment and patient selection.

Adenoid cystic carcinoma is a heterogeneous (Table 3) and aggressive disease. There was a 23% risk for adenoid cystic carcinoma death (Table 1) despite treatments. There was only 50% use of RT (Table 1) even when the indication for RT was clear as for the localised and regional adenoid cystic carcinoma (Figure 2). Furthermore, more adult patients than paediatric patients did not get RT (Figure 3) and therefore did not get the benefit of RT. Thus, radiation oncologists should be more attentive in recommending RT for these patients. For the paediatric populations, proton use is expected to improve the outcome of these patients by primarily decreasing the rate of secondary cancers.[23–26] Among the socio-economic factors, race/ethnicity and urban rural residence status were associated with an increase in cause-specific death (Table 2) but were not significantly associated with high ROC areas (Table 1). This may be associated with relatively small numbers of the higher risk groups (African American patients and rural residents), but this may be further investigated.

In conclusion, this study has identified that the staging models are the most prognostic factors of treatment outcomes of adenoid cystic cancer patients. The relatively high understaging rates may have prevented patients from selecting definitive local therapy. The poor rates of radiotherapy after surgery may have contributed to the poor outcomes in these patients with this aggressive disease. Improving the completing rate of grading is another way to improve the modelling. This study did not identify any socio-economic disparity in the outcome of this disease.

Conflicts of Interest

None.

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