RESEARCH ARTICLE

Poor Treatment Outcome of Neuroblastoma and Other Peripheral Nerve Cell Tumors May be Related to Under Usage of Radiotherapy and Socio-Economic Disparity: A US SEER Data Analysis

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Abstract

Purpose: This study used receiver operating characteristic curve to analyze Surveillance, Epidemiology and End Results (SEER) neuroblastoma (NB) and other peripheral nerve cell tumors (PNCT) outcome data. This study found under usage of radiotherapy in these patients. Materials and methods: This study analyzed socio-economic, staging and treatment factors available in the SEER database for NB and other PNCT. For the risk modeling, each factor was fitted by a generalized linear model to predict the outcome (soft tissue specific death, yes/no). The area under the receiver operating characteristic curve (ROC) was computed. Similar strata were combined to construct the most parsimonious models. A random sampling algorithm was used to estimate the modeling errors. Risk of neuroendocrine (other endocrine including thymus as coded in SEER) death was computed for the predictors. Results: There were 5261 patients diagnosed from 1973 to 2009 were included in this study. The mean follow up time (S.D.) was 83.8 (97.6) months. The mean (SD) age was 18 (25) years. About 30.45% of patients were un-staged. The SEER staging has high ROC (SD) area of 0.58 (0.01) among the factors tested. We simplified the 4-layered risk levels (local, regional, distant, un-staged/others) to a simpler 3-tiered model with comparable ROC area of 0.59 (0.01). Less than 50% of PNCT patients received radiotherapy (RT) including the ones with localized disease. This avoidance of RT use occurred in adults and children. Conclusion: The high under-staging rate may have prevented patients from selecting definitive radiotherapy (RT) after surgery. Using RT for, especially, adult PNCT patients is a potential way to improve outcome.

Keywords: Peripheral nerve cell tumors - neuroblastoma - radiotherapy - SEER registry - under use

Asian Pacific J Cancer Prev, **13**, 4587-4592

Introduction

The Surveillance Epidemiology and End Results (SEER) cancer registry has been extensively used to modeling outcome prediction models peripheral nerve cell tumors (PNCT) including neuroblastoma (NB). Numerous studies have done to better characterize these rare tumors to identify socio-economic disparity in treatment outcome and to build models for selecting patients for clinical trials (Esiashvili et al., 2007; Benoit et al., 2008; Hsieh et al., 2009; Shapiro and Bhattacharyya, 2009; Friedman et al., 2010; Pan et al., 2010: 2011; Bhatia, 2011; Johnson et al., 2011; Navalkele et al., 2011; Platek et al., 2011; Pui et al., 2012). The cause specific survival rates for both childhood and adult with PNCT are about 80% ((2011) and this study). Thus there is still room for improvement. For the first time, this study used receiver operating characteristic curve (ROC) to analyze SEER PNCT outcome data. The aim of this study was to identify and optimize predictive PCNT models to aid treatment and patient selection.

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 PNCT outcomes in US and in other countries (Perme and Jereb, 2009; Lacour et al., 2010; Johnson et al., 2011). 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 (Bhatia, 2011; Johnson et al., 2011; Pui et al., 2012). In addition to the biological staging factors and the treatment factors, this database also contains a large number of county level socio-economic

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factors 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) (Cheung, 2012) was used mine SEER data and construct accurate and efficient prediction models (Cheung et al., 2001a, b). 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. ICCC site recode ICD-O-3} ='IV Neuroblastoma and other peripheral nervous cell tumors'. This study explored a long list of socio-economic, staging and treatment factors that were available in the SEER database.

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 (cause of death: other neuroendocrine including thymus as coded in SEER). 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, b). 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 and replacement to estimate the modeling errors and allows 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 5261 patients included in this study (Table 1). There were Neuroblastoma (n=3742, 71.11%), Other pediatric and embryonal tumors, NOS (n=743, 14.2%), and Paraganglioma and glomus tumors (n=776, 14.76%). The PNCT specific death is defined as 'other endocrine including thymus'. The follow up (S.D.) was 83.8 (97.6) months. 47% of the patients were female. The mean (S.D.) age was 18.04 (25) years. Children and young adults constituted two third of the PNCT patients listed from SEER data. About 34.45% of patients were grouped in the un-staged/other categories. For pretreatment factors, the SEER staging categories using localized, regional, metastatic and un-staged (Table 1) has the highest ROC (S.D.) area of 0.58 (0.01) among the factors tested in Table 1.

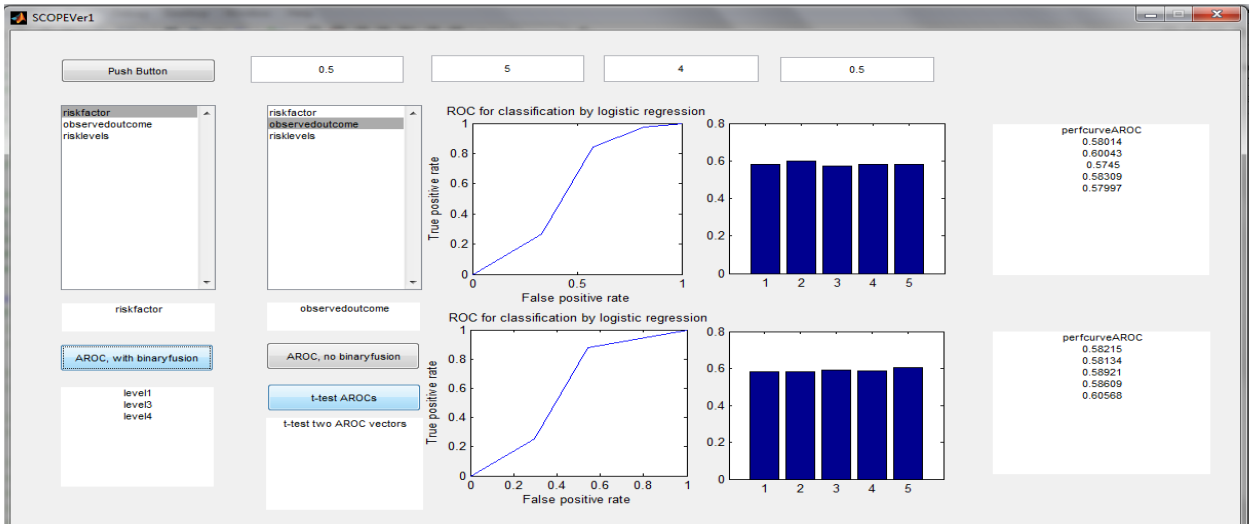

Figure 1. Measuring and Optimizing the ROC Areas of SEER Staging Model as a Predictor of Cause Specific Survival of PNCT (including NB) Patients

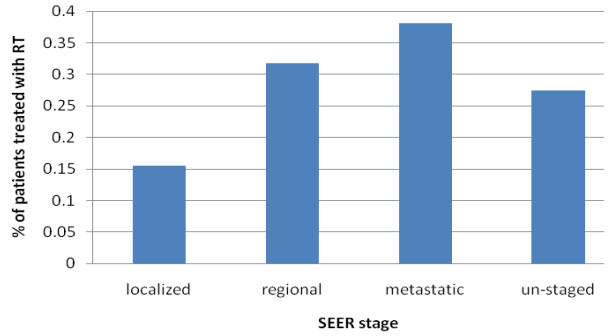

Figure 2. Fraction of Patients Received Radiotherapy at each SEER Stage

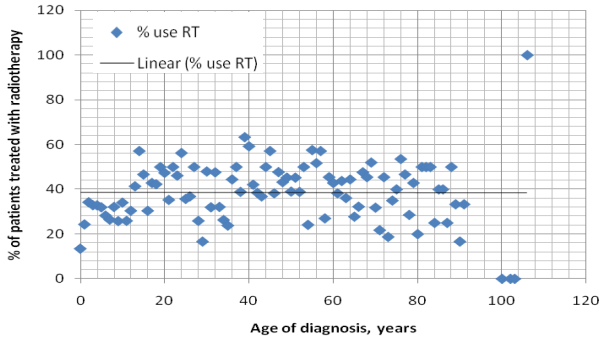

Figure 3. Fraction of Patients Received Radiotherapy as a Function of Age of Diagnosis

Table 1. The Risk Models Include the Socio-Demographic, Tumor and Treatment Factors for NB and PNCT

Initial univariate risk models		Number	%	Model	ROC Area	S.D.
Study population		5261				
Age of diagnosis	Mean	18.04				
	S.D.	25				
	<20 years	3623	68.87		0.572	0.01
	≥20 years old	1638	31.13			
Follow up (months)	Mean	83.87				
	S.D.	97.58				
Sex	Female	2472	46.99		0.506	0.01
	Male	2789	53.01			
SEER historic stage A	Localized, I	818	15.55	I, II, III, IV	0.582	0.01
	Regional, II	1180	22.43	optimized		
	Distant, III	1661	31.57	(I, II), III, IV	0.59	0.01
	Unstaged/others, IV	1602	30.45			
Site of disease	Other Endocrine including Thymus	2051	38.98			
	Others	3210	61.02			
Rural-Urban Continuum Code 2003	Counties in metropolitan areas ge 1 million pop	3211	61.02	Metopolitan	0.512	0.01
	Counties in metropolitan areas of 250,000 to 1 million pop	1137	21.60	vs. rural		
	Urban pop of ge 20,000 adjacent to a metropolitan area	128	2.43			
	Urban pop of ge 20,000 not adjacent to a metropolitan area	78	1.48			
	Counties in metropolitan areas of lt 250 thousand pop	385	7.32			
	Urban pop of 2,500 to 19,999, adjacent to a metro area	146	2.77			
	Comp rural lt 2,500 urban pop, adjacent to a metro area	37	0.70			
	Urban pop of 2,500 to 19,999, not adjacent to a metro area	108	2.05			
	Comp rural lt 2,500 urban pop, not adjacent to metro area	28	0.53			
	Unknown/missing/no match (Alaska - Entire State)	3	0.06			
County Family Income	≥$50000	3275	62.25		0.504	0.01
	< $50000	1986	37.75			
County % college graduate	≥25	2906	55.24		0.512	0.00
	<25	2355	44.76			
Race	White/others	4628	87.97		0.512	0.01
	Black	633	12.03			
Radiation treatment given	None	3524	66.97	Beam vs Not	0.546	0.01
	Beam radiation	1573	29.89			
	Unknown	39	0.74			
	Recommended, unknown if administered	69	1.31			
	Refused	8	0.15			
	Radioactive implants	4	0.08			
	Radiation, NOS method or source not specified	21	0.40			
	Other radiation (1973-1987 cases only)	1	0.02			
	Combination of beam with implants or isotopes	10	0.19			
	Radioisotopes	12	0.23			
Reason no cancer-directed surgery	Surgery performed	3726	70.81	Surgery vs Not	0.624	0.01
	Recommended but not performed, unknown reason	509	9.67			
	Unknown; death certificate or autopsy only case	119	2.26			
	Not recommended, contraindicated due to other conditions	68	1.29			
	Not recommended	810	15.39			
	Recommended but not performed, patient refused	8	0.15			
	Recommended, unknown if performed	19	0.36			
	Not performed, patient died prior to recommended surgery	2	0.04			
COD to site rec KM	Alive	3274	62.22			
	Other Endocrine including Thymus	1123	21.34			
	Others	864	16.44			

Graphically driven SEER Clinical Outcome Prediction Expert (SCOPE) was used to perform ROC curve and area under the curve calculations (Figure 1). In this example, the ROC area of the 4-tiered SEER staging model as computed for 5 random samples (Figure 1 upper panels and Table 1). In the lower panels, SCOPE simplified the 4-layered SEER risk levels (local, regional, distant, un-staged) to a simpler non-metastatic (I and II) versus metastatic (III) and un-staged (IV) model. The ROC area (S.D.) of the 3-tiered model was 0.59 (0.01) based on 5 random samples with replacement from the SEER data. Whether the patient received surgical treatment was the most predictive factor among treatment factors and overall predictors. The risk of cause specific death for rural versus metropolitan residence was 20.8% versus 25.9% (Table 1 and 2). African American PNCT patients had 36% risk of cause specific death compared with 15% for other race/ethnicity groups Tables 1 and 2). The level of differences for these two factors did have make the socio-economic factors very predictive of outcome. They had a ROC area of around 0.5 that is expected for a random variable with no predictive power. County's family income level and county's education attainment did not contribute to poor outcome.

70% patients did not receive RT (Table 1). Figure 2 shows that even in the localized and regional stages when RT could be used for curative intent (Platek et al., 2011), very low percentage of patients under went RT. Fig. 3 shows that this under usage of RT is most evident among the adult patients when the radiation side effects

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

Initial univariate risk models		No. at risk	Risk of cause specific death (%)
Age of diagnosis			
	<20 years	3623	0.25
	≥20 years old	1638	0.14
Sex	Female	2472	0.20
	Male	2789	0.23
SEER historic stage A			
	Localized, I	818	0.16
	Regional, II	1180	0.32
	Distant, III	1661	0.38
	Unstaged/others, IV	1602	0.27
Site of disease	Other Endocrine including Thymus		
		3210	0.16
	Others	2051	0.30
Rural-Urban Continuum Code 2003			
	Counties in metropolitan areas ge 1 million pop		
		4733	0.21
	Counties in metropolitan areas of 250,000 to 1 million pop/Urban pop of ge 20,000 adjacent to a metropolitan area versus		
	Others	528	0.26
County Family Income			
	≥$50000	3275	0.21
	<$50000	1986	0.22
County % college graduate			
	≥25 college graduate	2906	0.21
	< 25 % college graduate	2355	0.22
Race	White/others	3726	0.15
	Black	1535	0.36
Radiation treatment given			
	Beam radiation	1573	0.27
	Others	3688	0.19
Reason no cancer-directed			
	Surgery performed	3726	0.15
	Surgery Others	1535	0.36

are expected to be less severe compared with younger patients (Miralbell et al., 2002; Cohen et al., 2005; Herzog, 2005).

Discussion

This study is interested in constructing models that will aid patient and treatment selection for PNCT 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. The SEER anatomic staging is most predictive pretreatment model of patient outcome (Figure 1 and Table 1). Therefore it is useful in guiding treatment selection. After binary fusion, it reduced to non-metastatic versus metastatic versus un-staged classification of the PNCT patients (Figure 1 and Table 1). Such efficient model may aid in reducing patients needed for clinical trials because it has much fewer risk groups than the current PNCT grouping to balance (Platek et al., 2011; Pui et al., 2012).

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.

For radiotherapy, the ROC areas were modest (0.5). Low ROC areas imply the information content (i.e. the staging accuracy) of the models may be limited. It is consistent with the fact that only 70% patients had complete SEER staging (Table 2). In addition, the outcome of the completely staged patients was much more superior when compared with the entire cohort (Figure 2). It may be a consequence of having a better guidance model in treatment and patient selection. PNCT cancers have good treatment outcomes, there is a 4-10% risk of PNCT death (Table 2) at a localized/regional stage, however, the under-staged patients were disadvantaged and had double this risk likely due to the lack of guidance in treatment selection. There was only 15%-35% use of RT in the localized and regional PNCT patients. These data suggest an under treatment of the adult PNCT patients (Figure 3) with RT. And outcome could be further improved in these patients, especially when they are adult patients. Thus radiation oncologists should be more attentive in recommending RT for these patients. For the pediatric populations, proton use is expected to improve the outcome of these patients by primarily decreasing the rate of secondary cancers (Bassal et al., 2006; Schultz et al., 2007; Friedman et al., 2010; Kuhlthau et al., 2012).

In conclusion, this study has identified the staging models are the most prognostic pre-treatment model of treatment outcomes of PNCT cancer patients. The high under-staging rates may have prevented patients from selecting definitive local therapy. The poor rates of radiotherapy after surgery use may have contributed to the poor outcome in these patients with this disease. Furthermore, education and access to appropriate cancer treatment may eliminate the potential socio-economic barriers to good outcome.

References

Bassal M, Mertens AC, Taylor L, et al. (2006). Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol*, **24**, 476-83.

Benoit MM, Bhattacharyya N, Faquin W, Cunningham M (2008). Cancer of the nasal cavity in the pediatric population. *Pediatrics*, **121**, e141-5.

Bhatia S (2011). Disparities in cancer outcomes: lessons learned from children with cancer. *Pediatr Blood Cancer* **56,** 994-1002.

Cheung R (2012). Using SEER Clinical Outcome Prediction Expert (SCOPE) to mine massive data and construct efficient prognostic models: predicting breast cancer specific survival in Georgia USA. Submitted.

Cheung R, Altschuler MD, D'Amico AV, et al (2001a). ROC-optimization may improve risk stratification of prostate cancer patients. *Urology*, **57**, 286-90.

Cheung R, Altschuler MD, D'Amico AV, et al (2001b). Using the receiver operator characteristic curve to select pretreatment and pathologic predictors for early and late post-prostatectomy PSA failure. *Urology*, **58**, 400-5.

Cohen RJ, Curtis RE, Inskip PD, Fraumeni JF (2005). The risk of developing second cancers among survivors of childhood soft tissue sarcoma. *Cancer,* **103**, 2391-6.

D'Amico AV, Desjardin A, Chung A, et al. (1998). Assessment of outcome prediction models for patients with localized prostate carcinoma managed with radical prostatectomy or external beam radiation therapy. *Cancer,* **82**, 1887-96.

Esiashvili N, Goodman M, Ward K, et al (2007). Neuroblastoma in adults: incidence and survival analysis based on SEER data. *Pediatr Blood Cancer,* **49**, 41-6.

Friedman DL, Whitton J, Leisenring W, et al (2010). Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*, **102**, 1083-95.

Hanley JA, McNeil BJ (1982). The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* **143**, 29-36.

Herzog CE (2005). Overview of sarcomas in the adolescent and young adult population. *J Pediatr Hematol Oncol,* **27**, 215-8.

Hsieh MH, Meng MV, Walsh TJ, Matthay KK, Baskin LS (2009). Increasing incidence of neuroblastoma and potentially higher associated mortality of children from nonmetropolitan areas: analysis of the surveillance, epidemiology, and end results database. *J Pediatr Hematol Oncol*, **31**, 942-6.

Johnson KA, Aplenc R, Bagatell R (2011). Survival by race among children with extracranial solid tumors in the United States between 1985 and 2005. *Pediatr Blood Cancer,* **56**, 425-31.

Kuhlthau KA, Pulsifer MB, Yeap BY, et al (2012). Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy. *J Clin Oncol,* **30**, 2079-86.

Lacour B, Guyot-Goubin A, Guissou S, et al (2010). Incidence of childhood cancer in France: National Children Cancer Registries, 2000-2004. *Eur J Cancer Prev*, **19**, 173-81.

Miralbell R, Lomax A, Cella L, Schneider U (2002). Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. *Int J Radiat Oncol Biol Phys*, **54**, 824-9.

Navalkele P, O'Dorisio MS, O'Dorisio TM, et al (2011). Incidence, survival, and prevalence of neuroendocrine tumors versus neuroblastoma in children and young adults: nine standard SEER registries, 1975-2006. *Pediatr Blood Cancer*, **56**, 50-7.

Pan IJ, Daniels JL, Zhu K (2010). Poverty and childhood cancer incidence in the United States. *Cancer Causes Control,* **21**, 1139-45.

Perme M.P, Jereb B (2009). Trends in survival after childhood cancer in Slovenia between 1957 and 2007. *Pediatr Hematol Oncol,* **26,** 240-51.

Platek ME, Merzianu M, Mashtare TL, et al (2011). Improved survival following surgery and radiation therapy for olfactory neuroblastoma: analysis of the SEER database. *Radiat Oncol,* **6**, 41.

Pui CH, Pei D, Pappo AS, et al (2012). Treatment outcomes in black and white children with cancer: results from the SEER database and St Jude Children's Research Hospital, 1992 through 2007. *J Clin Oncol,* **30**, 2005-12.

Schultz KA, Ness KK, Whitton J, et al (2007). Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol*, **25**, 3649-56.

Shapiro NL, Bhattacharyya N (2009). Staging and survival for sinus cancer in the pediatric population. *Int J Pediatr Otorhinolaryngol*, **73**, 1568-71.

StatBite (2011). Neuroblastoma: five-year survival. *J Natl Cancer Inst* **103**, 1220.