RESEARCH ARTICLE

Low Income and Rural County of Residence Increase Mortality from Bone and Joint Sarcomas

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Abstract

Background: This is a part of a larger effort to characterize the effects on socio-economic factors (SEFs) on cancer outcome. Surveillance, Epidemiology and End Result (SEER) bone and joint sarcoma (BJS) data were used to identify potential disparities in cause specific survival (CSS). Materials and Methods: This study analyzed SEFs in conjunction with biologic and treatment factors. Absolute BJS specific risks were calculated and the areas under the receiver operating characteristic (ROC) curve were computed for predictors. Actuarial survival analysis was performed with Kaplan-Meier method. Kolmogorov-Smirnov's 2-sample test was used to for comparing two survival curves. Cox proportional hazard model was used for multivariate analysis. Results: There were 13501 patients diagnosed BJS from 1973 to 2009. The mean follow up time (SD) was 75.6 (90.1) months. Staging was the highest predictive factor of outcome (ROC area of 0.68). SEER stage, histology, primary site and sex were highly significant pre-treatment predictors of CSS. Under multivariate analysis, patients living in low income neighborhoods and rural areas had a 2% and 5% disadvantage in cause specific survival respectively. Conclusions: This study has found 2-5% decrement of CSS of BJS due to SEFs. These data may be used to generate testable hypothesis for future clinical trials to eliminate BJS outcome disparities.

Keywords: Bone and joint sarcoma - radiotherapy - SEER registry - socio-economic factors - cause specific survival

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Introduction

This study is a part of a comprehensive effort to survey Surveillance Epidemiology and End Result (SEER) (Cheung, 2012) for socio-economic factors (SEFs) impacting on the cause specific survival (CSS) of bone and joint sarcomas (BJS). SEER cancer registry data have been used to study the biologic and racial prognostic factors for the large number of sub-types of bone and joint sarcoma (Giuffrida et al., 2009; Nathan and Healey, 2012). To improve the power of this analysis, the SEER designation of BJS was used as opposed to using the sub-types. The nature of the socio-economic barriers to good CSS for BJS as a whole has not been well characterized. In addition to constructing the best predictors of cause specific survival, this study also aimed to identify barriers to good treatment outcome that may be discernable only from a national database. To this end, this study investigated the impact of rural urban residence status, county level family income and county level percent college graduate on CSS of BJS.

Materials and Methods

SEER registers public use data. These data can be used for analysis with no internal review board approval needed. SEER registry has massive amount of data available for analysis, however, manipulating the data could be challenging. SEER Clinical Outcome Prediction Expert (SCOPE) (Cheung, 2012) was used to mine SEER data and construct accurate and efficient prediction models (Cheung, 2012). The data were obtained from SEER 18 database. SEER*Stat (http://seer.cancer.gov/seerstat/) was used for listing the cases. The filter used was: Site and Morphology. Site rec B with Kaposi and mesothelioma='Bones and Joints'. All of the statistics and programming of this study were performed in Matlab (www.mathworks.com). The variable 'SEER cause-specific death' was used as the CSS outcome variable. The areas under the receiver operating characteristic (ROC) curve were computed. Similar strata were fused to make more efficient models if the ROC performance did not degrade (Cheung et al., 2001a; 2001b). Kaplan-Meier method was used for time to event data analysis. Kolmogorov-Smirnov's 2-sample test and Cox proportional hazard model were used respectively univariate and multivariate analyses. Probability $p<0.05$ was considered significant.

Results

There were 13501 patients included in this study (Table 1). The follow up duration (SD) was 75.6 (90.1) months. 56% of the patients were male. The mean (SD) age was 40.1 (24.2) years. The absolute overall risk of death from

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

Initial univariate risk models		No	%	Model	ROC Area	S.D.
Study population	13501					
Age of diagnosis	Mean±SD					
	< 20 years	3976		0.29	0.50	0.01
	≥20 years old	9525		0.71		
Follow up (months)	Mean±SD					
Sex	Female	5960		0.44	0.53	0.00
	Male	7541		0.56		
Site	Extremities	6676		0.49	0.52	0.00
	Others	6825		0.51		
SEER historic stage A	Localized=I*	4762		0.35	0.68	0.01
	Regional=II**	4895		36.25		
	Distant=III***	2283		16.91	0.67	0.01
	Unstaged=IV	1561		11.56		
Histology	9180-9249: osseous and chondromatous neoplasms	8380		62.07	0.55	0.01
	Others	5121		37.93		
Grade	Unknown	6426		47.59	0.61	0.00
	Moderately differentiated; Grade II	1714		12.69		
	Well differentiated; Grade I	1578		11.69		
	Poorly differentiated; Grade III	1399		10.36		
	Undifferentiated; anaplastic; Grade IV	2384		17.66		
Rural-Urban Continuum	Counties in metropolitan areas ge 1 million pop	8120		60.14	0.51	0.00
Code 2003	Counties in metropolitan areas of 250,000 to 1 million pop	2870		21.26		
	Urban pop of ge 20,000 adjacent to a metropolitan area	379		2.81		
	Unknown/missing/no match	5		0.04		
	Urban pop of ge 20,000 not adjacent to a metropolitan area	217		1.61		
	Counties in metropolitan areas of lt 250 thousand pop	985		7.30		
	Urban pop of 2,500 to 19,999, not adjacent to a metro area	307		2.27		
	Comp rural lt 2,500 urban pop, not adjacent to metro area	91		0.67		
	Urban pop of 2,500 to 19,999, adjacent to a metro area	411		3.04		
	Comp rural lt 2,500 urban pop, adjacent to a metro area	100		0.74		
	Unknown/missing/no match (Alaska - Entire State)	16		0.12		
County Family Income	≥$50000	8141		0.60	0.51	0.00
	<$50000	5360		0.40		
County % college graduate	≥25%	7213		0.53	0.50	0.01
	< 25%	6288		0.47		
Race	White/others	12259		0.91	0.50	0.00
	Black	1242		0.09		
Radiation treatment given	No radiation and/or cancer-directed surgery	11697		86.63	0.52	0.00
	Radiation after surgery	1522		11.27		
	Radiation prior to surgery	216		1.60		
	Radiation before and after surgery	35		0.26		
	Intraoperative radiation	8		0.06		
	Sequence unknown, but both were given	20		0.15		
	Intraoperative rad with other rad before/after surgery	3		0.02		
Reason no cancer-directed	Surgery performed	9813		72.68	0.60	0.01
surgery	Recommended but not performed, unknown reason	1222		9.05		
	Recommended, unknown if performed	93		0.69		
	Not recommended	1753		12.98		
	Unknown; death certificate or autopsy only case	444		3.29		
	Recommended but not performed, patient refused	97		0.72		
	Not recommended, contraindicated due to other conditions	76		0.56		
	Not performed, patient died prior to recommended surgery	3		0.02		
SEER cause specific Survival	Alive or dead of other cause	7980		59.10		
	Dead	4211		31.19		
	N/A not first tumor	1310		9.70		

Model: *I,II,III,IV; **Optimized; and ***I,(II,III),IV

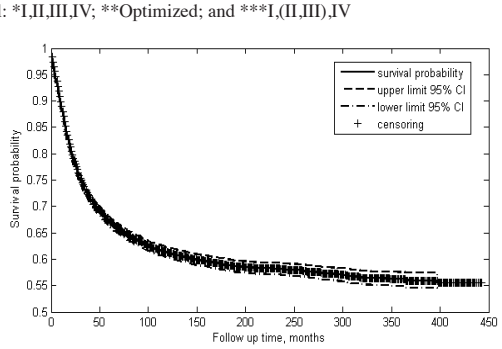

Figure 1. Kaplan-Meier Product Limit Estimate of BJS Cause Specific Survival. The '+' marker indicates when censoring occurred

bone and joint sarcoma was 31.2% (Table 2). Figure 1 shows the actuarial survival probability of BJS patients from SEER database. About 29.4% of the BJS patents younger than 20 years old were diagnosed with bone and joint sarcoma. The absolute risk of cause specific death was 29.4% for patients younger than 20 years old and similarly for older patients (Table 2). Extremities BJS account for about 55% of all cases (Table 3). Extremity BJS carries a 28.9% risk of cause specific death compared with 33.4% for the others (Table 2). Grade was predictive of BJS survival. The risk of cause specific death was 10.3% for grade I, 16.6% for grade II, 34.3% for grade III and 37.2% for grade IV. Being un-graded has the same

risk of cause specific death as patients with a grade IV disease. SEER stage was predictive of absolute risk of cause specific death. There was a 17.1% risk of death for localized disease. This risk increased to more than 30% when there was lymph node metastasis. When the staging was not complete, it was associated with 58.4% risk of death (Table 2) that is higher than the 38.2% risk of death of patients with metastatic disease. Living in a cosmopolitan area was associated with 30.6% risk of BJS specific death compared with 35.5% risk living in a rural area (Table 2). Race, county education attainment and family income were not predictive of treatment outcome. Pre-operative radiotherapy was given to 4.3% of patients and was associated with 30% risk of BJS death. Pre-operative radiotherapy was given to 1.6% of patients and 11.3% of patients had post-operative radiotherapy (Table 1). Surgery was associated with 25.3% risk of BJS death while 56.7% risk of death was associated with no surgery performed.

For the SEER stage model, the staging of BJS was defined as localized, regional, distant or incompletely staged/others. The stage status was highly predictive of BJS specific survival (ROC area or 0.68). This 4-tiered staging model was optimized to a 3-tiered model consisted of localized versus regional or distant versus un-staged/others with a ROC area of 0.67 (Table 1). Based on absolute risk of death from BJS, rural residents had a 5% additional risk of BJS specific death. This translated into marginally elevated ROC areas (Table 1). Other pre-treatment factors grade, site and histology had respectively 0.61, 0.55 and 0.52 ROC areas. Radiotherapy had a ROC

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

Variables: risk models		No. at risk	expected risk of death
Age of diagnosis	<20	3976	0.32
	≥20	9525	0.31
Sex	Female	5960	0.28
	Male	7541	0.33
Primary site			
C40.2-Long bones of lower limb and associated joints/C40.0-Long bones: upper limb, scapula, and associated joints		6676	0.29
Others		6825	0.33
Histology			
9180-9249: osseous and chondromatous neoplasms		8380	0.28
Others		5121	0.36
Grade Well differentiated; Grade I		1578	0.10
Moderately differentiated; Grade II		1714	0.17
Poorly differentiated; Grade III		1399	0.34
Undifferentiated; anaplastic; Grade IV		2384	0.37
Unknown		6426	0.37
Rural-Urban Continuum			
Counties in metropolitan areas ge 1 million pop/Code 2003/Counties in metropolitan areas of 250,000 to 1 million pop/Urban pop of ge 20,000 adjacent to a metropolitan area versus		11975	0.31
Others		1526	0.36
County Family Income	≥$50000	8141	0.30
	<$50000	5360	0.32
County % college graduate	≥25	7213	0.31
	<25	6288	0.31
Race	White/others	12259	0.31
	Black	1242	0.31
Radiation treatment given			
Preoperative Radiotherapy		216	0.42
Postoperative Radiotherapy		1522	0.37
Others		11763	0.30
Reason no cancer-directed surgery			
Surgery performed		9813	0.25
Others		3688	0.47
SEER Staging	Localized	4762	0.17
	Regional	4895	0.30
	Un-staged/others	1561	0.38
	Distant	2283	0.58

Table 3. The Distribution of Sites that BJS Occurred

Factor	Count	Percent
Primary Site - labeled	13501	
C40.2-Long bones of lower limb and associated joints	5167	38.26840468
C41.0-Bones of skull and face and associated joints	1163	8.613538735
C40.0-Long bones: upper limb, scapula, and associated joints	1509	11.17612206
C41.2-Vertebral column	942	6.976744186
C41.3-Rib, sternum, clavicle and associated joints	1007	7.458154348
C41.4-Pelvic bones, sacrum, coccyx and associated joints	2140	15.84950378
C41.1-Mandible	615	4.554880758
C41.9-Bone, NOS	434	3.214338617
C40.1-Short bones of upper limb and associated joints	160	1.185009628
C40.3-Short bones of lower limb and associated joints	304	2.251518294
C40.9-Bone of limb, NOS	39	0.288846097
C41.8-Overlap bones, joints, and art. cartilage	15	0.111094653
C40.8-Overlap of bones, joints, and art. cartilage of limbs	6	0.044437861

Table 4. Univariate and Multivariate Tests Performed on the Predictors*

		Kolmogorov-Smirnov 2-sample test			Cox proportional hazard model		
		l	p	k	beta	s.e.	p
SEER stage	0=local/regional 1=metastatic/unstaged	1	4.15E-53	0.8641	1.0073	0.0318	0
Sex	0=female 1=male	1	4.13E-23	0.5596	0.1352	0.0315	0
Primary site	0=long bones (Table 2) 1=others	1	9.79E-20	0.5157	0.2612	0.034	0.0001
Histology	0=bone/cartilage 1=others	1	4.70E-18	0.4898	-0.1355	0.0523	0
Grade	0=grade 1-2 1=grade 3-4, ungraded	1	9.84E-54	0.8737	1.1049	0.0523	0
Rural Urban residence	0=urban 1=rural	0	0.1081	0.1446	0.1584	0.0492	0.0013
County level family income	0=more than $50k/year 1=less or equal to $50k/yr	0	0.8287	0.0695	0.1173	0.0335	0.0005

*For Kolmogorov-Smirnov's test, l=1 if the two survival curves were statistically different as measure by k. Beta and s.e. were respectively Cox proportional hazard coefficients and the standard errors. Probability p<0.05 was considered significant

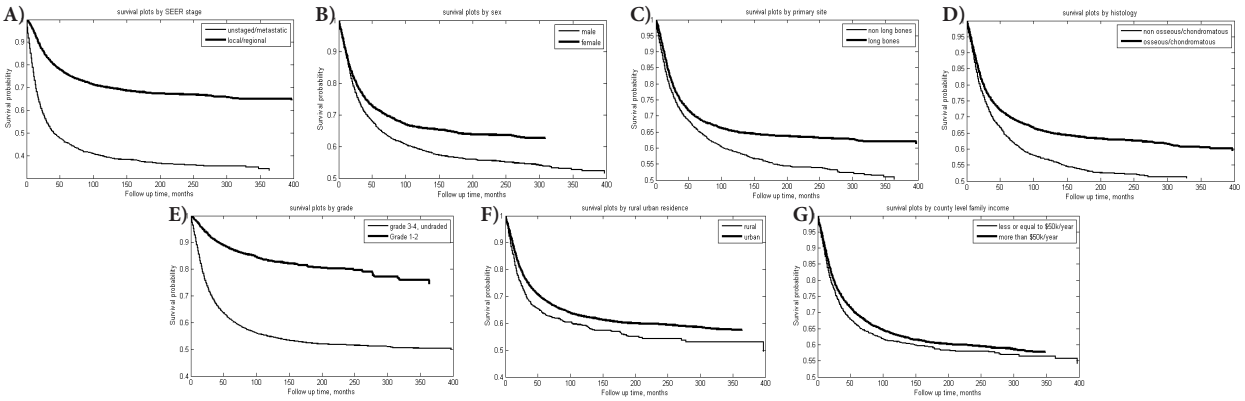

Figure 2. The Survival Curves Plotted. A) SEER stage; **B)** Sex; **C)** Primary site; **D)** Histology; **E)** Grade; **F)** Rural urban residence status; and **G)** County level family income. In each case, the two curves were compared with a 2-sample Kolmogorov-Smirnov's test. The results were reported in Table 4

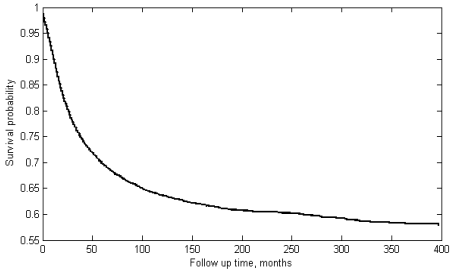

Figure 3. Cox Proportional Model Plotted with the Fitted Parameters in Table 4

area of 0.52 while surgery had a ROC area of 0.60. For lymph node positive patients, the use of radiotherapy was 17.2%.

Figure 2 shows the results of comparing the CSS separated by A) SEER stage; B) sex; C) primary site; D) histology; E) grade; F) rural urban residence status; and G) county level family income. SEER stage, sex, primary site, histology and grade were highly significant univariate predictors of CSS (Table 4). The rural urban residence status and county level family income were not significant under univariate analyses. Under multivariate analysis, these two SEFs became statistically independent CSS predictors. Figure 3 shows the Cox proportional model closely resembling the Kaplan-Meier survival estimate.

Discussion

This study investigated the impact of SEFs on CSS (Figure 1 and Table 1-3) of BJS using SEER data. Recently, an important 10-15 years long-term study demonstrated that moving patients from low income neighborhoods to higher ones improved their obesity and diabetes (Ludwig et al., 2011; 2012). In this study examined three SEFs: *i*) whether the patients lived in a rural as opposed to urban counties; *ii*) whether the patients lived in a county with a family income equal or lower than $50000 per year as opposed to a higher one; and *iii*) whether the patients lived in a low college education attainment county were examined. These SEFs were examined in conjunction with other pretreatment factors to detect if they were independent predictors of CSS of BJS.

In order to be consistent over decades, SEER historical stage abstracts the staging into simple but important stages for cancer progression: localized, regional and distant. SEER stage was highly predictive of patient outcome (Table 1). The model has a ROC area of 0.68. Thus complete staging is important in this disease since it will aid patient selection and council. After binary fusion by SCOPE, the 4-tiered stage model was reduced to a 3-tiered model based on ROC area calculations (Table 1). Being un-staged was associated with a risk of cause specific death similar to those with regional disease (Table 2).

Regional BJS is an aggressive disease, there was a 30% risk of cause specific (Table 2). These are patients most likely to benefit from radiotherapy (Horton et al., 2011; Schreiber et al., 2012). Thus radiation oncologist 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 (Miralbell et al., 2002; Cohen et al., 2005; DeLaney, 2007; Kuhlthau et al., 2012).

This study found the pretreatment factors (Figure 2A-2E) SEER stage, sex, primary site, histology, and grade were highly statistically significant predictors of CSS. While rural urban residence status (Figure 2F) and county level family income (Figure 2G) impacted on the CSS, but they were not significant on statistical tests (Table 4). This was probability due to the highly significant biologic factors (Table 4). Under multivariate analysis using Cox proportional hazard method (Table 4 and Figure 3), when the biologic factors were accounted for, these two SEFs become significant predictors. This study has found 2-5% decrement of CSS of BJS due to rural and low income county residence. These data may be used to generate testable hypothesis for future clinical trials to eliminate BJS outcome disparities. Further studies investigating the socio-economic disparities of subtypes of BJS is under way.

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