RESEARCH ARTICLE

Socio-economic Factors Affect the Outcome of Soft Tissue Sarcoma: an Analysis of SEER Data

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Abstract

   Background: This study analyzed whether socio-economic factors affect the cause specific survival of soft tissue sarcoma (STS). Methods: Surveillance, Epidemiology and End Results (SEER) soft tissue sarcoma (STS) data were used to identify potential socio-economic disparities in outcome. Time to cause specific death was computed with Kaplan-Meier analysis. Kolmogorov-Smirnov tests and Cox proportional hazard analysis were used for univariate and multivariate tests, respectively. The areas under the receiver operating curve were computed for predictors for comparison. Results: There were 42,016 patients diagnosed STS from 1973 to 2009. The mean follow up time (S.D.) was 66.6 (81.3) months. Stage, site, grade were significant predictors by univariate tests. Race and rural-urban residence were also important predictors of outcome. These five factors were all statistically significant with Cox analysis. Rural and African-American patients had a 3-4% disadvantage in cause specific survival. Conclusions: Socio-economic factors influence cause specific survival of soft tissue sarcoma. Ensuring access to cancer care may eliminate the outcome disparities.

Keywords: Soft tissue sarcoma - SEER data - socio-economic factors - survival

Introduction

   Soft tissue sarcoma is a challenging cancer to treat because of its heterogeneity and aggressiveness (Clark et al., 2005). An important advancement has been using less aggressive limb sparing surgery combined with post-operative radiotherapy (Yang et al., 1998) or chemotherapy. There is an important improvement in limb preservation (Yang et al., 1998), but so far little gain in overall survival with radiotherapy (Yang et al., 1998) or chemotherapy (Pervaiz et al., 2008). There is an active search for ways to improve the survival of soft tissue sarcoma patients.

   This study used Surveillance, Epidemiology and End Results (SEER) soft tissue sarcoma (STS) data to identify predictive models and potential socio-economic disparities in outcome. The Surveillance Epidemiology and End Results (SEER) cancer registry data have been used to build prognostic models for soft tissue sarcoma (Ferrari et al., 2011), however, the impact of socio-economic disparities used in this study has not been well studied. Soft tissue sarcomas (STS) are a heterogeneous group of sarcoma (Ferrari et al., 2011). SEER data have been a particularly important source for identifying disparities in treatment (Cheung, 2013a, b, c). However, the nature of the socio-economic barriers to good outcome for STS is not well characterized. Recently, a long-term 10-15 years research has shown that socio-economic factors affected the development of obesity of individuals (Ludwig et al.,

2011). In particular, living in low income neighborhoods adversely affected the well-being of individuals and moving these individuals to a better neighbor improved their health status (Ludwig et al., 2011) (Ludwig et al., 2012). This approach has not been proven in oncology, but it is certainly thought provoking. In view of these, this study sought to investigate the effects of socio-economic factors on STS treatment outcome with the hope to formulate hypothesis for future testing

Materials and Methods

   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 et al., 2001a, b). 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 with Kaposi and mesothelioma = ' Soft Tissue including Heart'. This study explored a long list of socio-economic, staging and treatment factors that were available in the SEER database. The variable 'SEER cause-specific death classification' was used as the outcome.

   Kaplan-Meier curves were used to plot time to cause specific death data, Kolmogorov-Smirnov 2-sample tests were used to test the significance of differences of two

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Kaplan-Meier curves. Cox proportional hazard analysis was used to study the multivariate analysis. Socio-economic factors with p<0.25on univariate analyses were chosen to be used in Cox analysis. For Kolmogorov-Smirnov and Cox proportional hazards analyses the categorical variables were coded as follows: Stage (0=localized and regional, 1=un-staged and metastatic); Site (0=extremities, 1=others); Grade (0=grade 1 and 2, 1= grade 3-4 and ungraded); Rural-urban status of county of residence (0=urban, 1 =rural); Race (0=not African American, 1=African American). All statistics and programming were performed in Matlab (www. mathworks.com). 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).

Results

There were 42, 016 patients included in this study. The follow up duration (S.D.) was 66.6 (81.3) months. 55% of the patients were female. The mean (S.D.) age was 53.5 (23.4) years. The overall risk of death from soft tissue sarcoma was 27.7%. About 10% of the STS patents younger than 20 years old were diagnosed with

Figure 1. Kaplan-Meier Survival Curve for STS Patients. '+' indicates censoring

soft tissue sarcoma. The risk of cause specific death was 25.4% for patients younger than 20 years old and 27.9% for older patients. Lower extremities STS account for about 1/3 of all cases. About 15% of STS occurred in the lower extremities. Each section of head and neck, thorax, abdomen and pelvis has about 10% cases. Autonomic nervous tissue tumors account for the remaining few percent. Extremity STS carries a 22.6% risk of cause specific death compared with 32.2% for the others (mostly head and neck and trunk STS). 44% of STS patients were not graded. Being un-graded has a 30.8% risk of cause specific death. This was close to the 32.9% for poorly differentiated and 35.2% for undifferentiated STS. SEER stage was predictive of overall risk of cause specific death. There was a 16% 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 36% risk of death. Living in a cosmopolitan area was associated with 27% risk of STS specific death compared with 30% risk living in a rural area. African American has 31% risk of STS specific death compared with 27% for the others. County education attainment and family income were not associated with treatment outcome. Pre-operative radiotherapy was given to 4.3% of patients and was associated with 30% risk of STS death. Post-operative radiotherapy was given to 26.3% of patients and was associated with 26% risk of death. Surgery was associated with 22% risk of STS death while 50% risk of death was associated with no surgery performed.

We studied the utility of predictors of absolute cause specific survival by measuring the ROC areas. For the SEER stage model, the staging of STS was defined as localized, regional, distant or incompletely staged/others. The stage status was highly predictive of STS specific survival (ROC area or 0.70). 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 0.69.
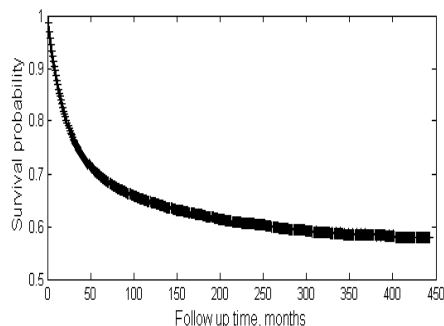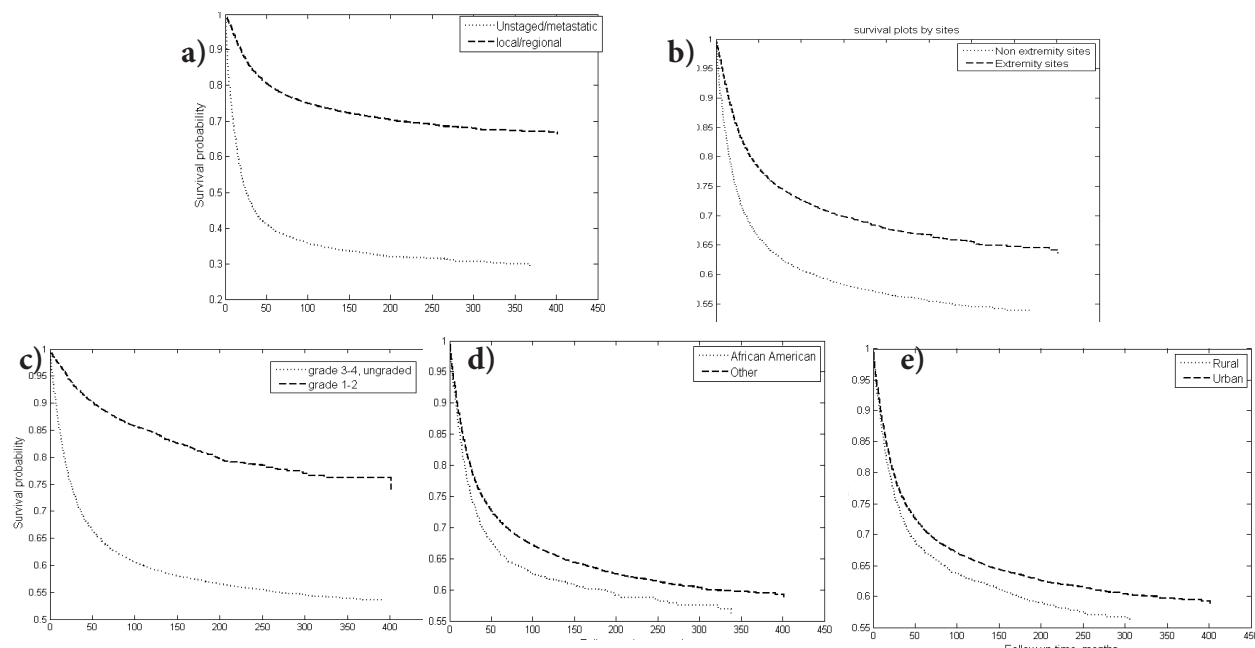

Figure 2. Probability of STS Specific Death by a) Stage, b) Site, c) Grade, d) Race and e) Rural-urban Residence

Table 1. Univariate (Kolomogov-Smirnov Test) and Multivariate (Cox Proportional Hazard Regression) Comparison of Survival Probabilities

	Kolmogorov-Smirnov Test			Cox Proportional Hazard Model		
	h	p	k	beta	s.e.	p x 1.0^{-05}
Stage (0=localized/regional, 1=un-staged/metastatic)	1	1.902E-79	9.321E-01	1.29280	0.01930	0.00000
Site (0=extremities, 1=others)	1	8.890E-50	7.100E-01	0.34610	0.01930	0.00000
Grade (0=grade 1/ 2, 1= grade 3-4/ungraded)	1	1.644E-77	9.012E-01	0.99000	0.03140	0.00000
Status of county of residence (0=urban, 1 =rural)	0	1.612E-01	1.136E-01	0.15680	0.02800	0.00200
Race (0=not African American, 1=African American)	0	6.672E-01	7.690E-02	0.13500	0.02860	0.22780

Test probability p < 0.05 was statistically significant. k is the test statistics. The result h of Kolomogov-Smirnov test was 1 if the test rejected the null hypothesis at the 5% significance level; 0 otherwise. s.e. is the standard errors of Cox proportional hazards coefficients. or significant Kolmogorov-Smirnov Statistics k, l =1. Beta and s.e. were respectively Cox proportional hazard coefficients and standard errors. probability p < 0.05 was considered significant
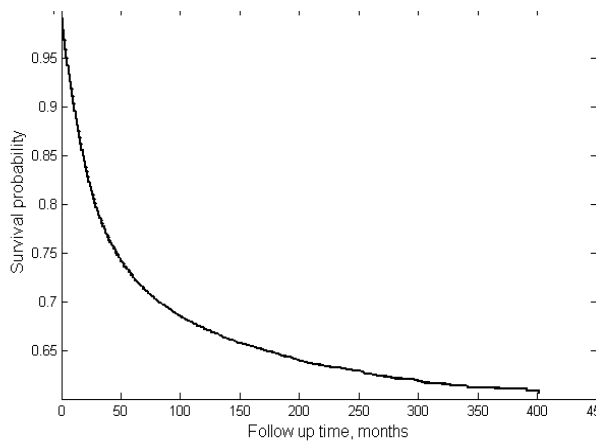
Figure 3. The Cox Model Fit of the STS Patient Cause Specific Survival Data

Figure 1 shows the Kaplan-Meier's curve for STS. Figure 2 a-e show the Kaplan-Meier's plots separated by prognostic factors. Table 4 shows that stage, site and grade were statistically significant univariables. Of the four tested socio-economic factors, rural-urban residence and race were most significant (Table 1). These five prognostic factors were used in the Cox multivariate analysis. Table 1 shows the Cox proportional hazards coefficients (standard errors) beta for were, respectively: 1.2928 (0.0193) for stage; 0.3461 (0.0193) for site; 0.9900 (0.0314) for grade; 0.1568 (0.0280) for rural-urban residence status and 0.1350 (0.0286) for race. These were all statistically significant (Table 1). Figure 3 shows the fitted Cox proportional hazard curve using the parameters in Table 4. The absolute and actuarial risks of mortality for socioeconomic factors were about 4% for rural-urban residence and race (Table 1 and Figure 2).

Discussion

SEER (http://seer.cancer.gov/) is a public use cancer registry of United States (U.S.). National Cancer Institute and Center for Disease Control fund SEER monitor the cancer epidemiology of US. SEER registers about 28% of all oncology cases in US. SEER started collecting data in 1973 for 7 state and cosmopolitan registries. SEER data have been used widely as a benchmark for studying cancer outcomes in US and in other countries (http://seer.cancer.gov/). The vastness of SEER data is ideal for identifying potential disparity in oncology outcome. In addition to constructing the best predictors of cause specific survival, this study also aimed to identify barriers

to good care when outcome may be discernable only from a survival difference. This study employed the ROC models (Hanley and McNeil, 1982) and a long list of potential prognostic factors in order to be consistent over decades of SEER history. We merge the staging into simple but important stage or cancer progression: localized, regional and distant. SEER stage was highly predictive of patient outcome (Fig. 2a and Table 1). The model had a ROC area of 0.73. For a random variable, its ROC area is 0.5, and for a perfect variable. Thus 0.70 is relatively high ROC area. Supporting complete staging as an important cancer disease variable to aid patient selection and counseling. After binary fusion by SCOPE, the 4-tiered stage model was reduced to a 3-tiered model based on ROC area calculations. Being un-staged was associated with a risk of cause specific death similar to those with regional disease.

Although this study focused on pretreatment predictors, for completeness, we also looked at treatment effects. Soft tissue sarcoma patients who receive chemotherapy or radiotherapy have worse prognostic factors based on pattern of care studies (Lawrence et al., 1987). Radiotherapy has long been used as a part of limb preservation therapy (Yang et al., 1998) (Harrison et al., 1993). Regional STS is an aggressive disease; there was a 30% risk of cause specific. These are patients most likely to benefit from radiotherapy (Horton et al., 2011; Schreiber et al., 2012). 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 (Miralbell et al., 2002; Cohen et al., 2005; DeLaney, 2007; Kuhlthau et al., 2012). In these patients lymph node positivity with or without positive surgical margin are required to receive radiotherapy on protocol(Donaldson et al., 2001). Although not shown in this data, preoperative radiotherapy has shown to slightly improve the survival of soft tissue sarcoma (O'Sullivan et al., 2002) at the price of higher wound complications.

Chemotherapy and radiotherapy have improved local recurrence after surgery and distant metastasis rates but not overall survival (Yang et al., 1998; Pervaiz et al., 2008). Therefore the 4% effects of socio-economic factors on overall survival detected (Table 1, Figures 1-3) here are small but remarkable. Especially these patients' residence is modifiable. Future studies will further investigate the effects of socio-economic factors on outcome of STS patients treated with radiotherapy. Ensuring access to

cancer care may eliminate the socioeconomic disparities in STS treatment outcome.

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