Title

Older age impacts radiotherapy-related outcomes in soft tissue sarcoma

Journal

Journal of Surgical Research, 199(2)

ISSN

0022-4804

Authors

Yuen, Noah K
Li, Chin-Shang
Monjazeb, Arta M
et al.

Publication Date

2015-12-01

DOI

10.1016/j.jss.2015.06.020

Peer reviewed

HHS Public Access

Author manuscript

J Surg Res. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

J Surg Res. 2015 December ; 199(2): 494–504. doi:10.1016/j.jss.2015.06.020.

Older age impacts radiotherapy-related outcomes in soft tissue sarcoma

Noah K. Yuen, MD[a], **Chin-Shang Li, PhD**[b], **Arta M. Monjazeb, MD, PhD**[c], **Dariusz Borys, MD**[d], **Richard J. Bold, MD**[a], and **Robert J. Canter, MD**[a,*]

[a]Division of Surgical Oncology, Department of Surgery, UC Davis School of Medicine, Sacramento, California

[b]Division of Biostatistics, Department of Public Health Sciences, UC Davis, Sacramento, California

[c]Department of Radiation Oncology, UC Davis School of Medicine, Sacramento, California

[d]Department of Pathology, Stritch School of Medicine, Loyola University, Chicago, Illinois

Abstract

Background—Radiation therapy (RT) is a standard component in the multimodality management of localized soft tissue sarcoma (STS). Increasing studies are focusing on biological modifiers that may influence the host's response to RT, including immunologic mechanisms known to change with the aging process. We hypothesized that the effects of RT would be influenced by age, contributing to differences in treatment outcome.

Methods—Using Surveillance, Epidemiology, and End Results (1990–2011), we identified 30,898 adult patients (>18 y) with nonmetastatic STS undergoing initial surgery. We compared patient demographics, tumor characteristics, and treatments by age. Multivariable analyses were used to analyze overall survival (OS) and disease-specific survival (DSS). Hazard ratios (HRs) were calculated based on multivariable Cox proportional hazards models.

Results—Mean age at diagnosis was 56.6 ± 16.8 y, and 33.6% of patients were ≥65 y. Of the total, 52.1% of patients were male and 67% were white; 59.9% of patients underwent surgery alone, 33.3% received adjuvant RT, and 6.8% neoadjuvant RT. On multivariable analysis, age, sex, year of diagnosis, histology, grade, size, marital status, and RT predicted OS, whereas age, year of diagnosis, ethnicity, histology, site, grade, RT, size, and marital status predicted DSS. In all patients, RT was associated with improved OS and DSS compared to surgery alone (median OS 136 ± 13 mo with RT *versus* 118 ± 9 mo without RT and 5-y OS 63.2 ± 1.4% with RT *versus*

[*]*Corresponding author*. Division of Surgical Oncology, Department of Surgery, UC Davis Cancer Center, UC Davis School of Medicine, Suite 3010, 4501 X Street, Sacramento, CA 95817. Tel.: + 1 916 734 7044; fax: + 1 916 703 5267. robert.canter@ucdmc.ucdavis.edu (R.J. Canter).

This article was presented in part at the Academic Surgical Congress 10th Annual Meeting, February 2–4, 2015, Las Vegas, Nevada.

Author's contributions: N.K.Y. and R.J.C. contributed to the study conception and design. N.K.Y., C.S.L., A.M.M., R.J.B., and R.J.C. did the analysis and interpretation of data. N.K.Y. and R.J.C. wrote the article. C.S.L., A.M.M., R.J.B., and R.J.C. did the critical revision of the article.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in the article.

60.5 ± 1.2% without, $P < 0.01$). Patients ≥65 y derived greater improvements in OS and DSS compared with patients <65 y. These benefits were most notable after neoadjuvant RT with patients ≥65 y having significantly better OS (HR = 0.63; 95% confidence interval = 0.53–0.75), whereas patients <65 y did not (HR = 0.96; 95% confidence interval = 0.83–1.10). In addition, interaction testing demonstrated a significant modifier effect between RT and age ($P < 0.05$).

Conclusions—RT is associated with improved survival in patients with STS undergoing surgical treatment, but improvements in oncologic outcome with RT were greatest among older patients. Further studies into the mechanism of these age-related effects are needed.

Keywords

Soft tissue sarcoma; Radiotherapy; Surgery; Age

1. Introduction

Soft tissue sarcomas (STSs) are rare mesenchymal malignancies, accounting for 1% of cancer cases diagnosed in the United States annually [1]. There are at least 50 recognized histologic subtypes, and these can occur across diverse primary sites in the body. Given the wide variation in clinical behavior and response to therapy that has been observed, multimodality treatment guidelines for specific STS subtypes are evolving [2–5].

Although surgery remains the mainstay of treatment for the vast majority of localized STS, chemotherapy and/or radiation therapy (RT) are frequently used as adjuncts [3,5,6]. Historically, combined chemoradiation has been used more frequently in younger patients, despite the lack of definitive data supporting this treatment approach [2,7]. Although clinical trials have shown no benefit of RT on survival in the setting of complete surgical excision [3,8,9], numerous population-based observational studies have demonstrated a statistically significant association between receipt of RT and survival in patients with STS undergoing surgical resection [10,11]. It is not clear whether these disparate results are related to selection bias in observational studies or inadequate statistical power in relatively small clinical trials or both. These inconsistent results also raise the question of whether and how individual patient and tumor characteristics may impact the efficacy of RT [12].

It is increasingly recognized that RT has potent immunomodulatory effects [13–17]. The various immunologic effects of RT have been well described, including but not limited to its stimulatory effect on tumor antigen presentation and antitumor T-lymphocyte proliferation [15,18]. However, as the human body ages, the immunologic system undergoes various phenotypic and functional changes in both the innate and adaptive immune system, commonly referred to as “immunosenescence.” [19] Whether these age-related immunologic changes affect response to RT remains unanswered. We hypothesized that the effects of RT would be influenced by age, contributing to differences in treatment outcome. Therefore, we sought to evaluate the effect of age on survival in patients undergoing surgery and RT in a national database of STS patients.

2. Materials and methods

2.1. Data source

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute collects data from 17 population-based cancer registries and comprises 28% of the US patient population. The database is the only of the few sources of comprehensive information on patient demographics, tumor morphology, and survival. Well-recognized limitations of SEER include lack of data on resection margin status and adjuvant systemic chemotherapy treatment, and therefore, these variables could not be included in our analyses.

2.2. Case selection

Using the SEER database, we identified 73,951 patients with STS using standard published *International Classification of Diseases, Third Revision* codes [10,11,20,21]. We excluded patients <18 y old (n = 4159) because of the differences in treatment between pediatric and adult patients, especially as pertains to chemotherapy and RT [3,20]. We also excluded tumors with primary site in bone, brain, spinal cord, and/or meninges (n = 457). Patients with incomplete or missing tumor information–including unknown grade (n = 12,758), site (n = 306), or size (n = 7160)– were also excluded from analysis to minimize the potential for missing data to bias our results. We limited our analysis to diagnoses after 1990 because of the advances in diagnostic imaging and pathologic evaluation that became more widely available around that time.

Patient demographic data included age, sex, race and/or ethnicity, marital status, and year of diagnosis. We also abstracted data on tumor-related factors such as tumor site, grade, size, and histologic subtype. We assessed treatment-related data including use of surgery and adjuvant or neoadjuvant RT. Survival was reported in months, with cause of death listed as due to cancer (disease-specific survival [DSS]) or any cause (overall survival [OS]).

Patients were stratified by age, using multiple cutoffs to define younger and older populations. Although the data were overall similar regardless of specific age cutoff used (data not shown), we found an age cutoff of 65 y old to most effectively illustrate the differences in survival. Because SEER patient information is deidentified, this study qualified as exempt from UC Davis Institutional Review Board approval.

2.3. Statistical analysis

To compare age-stratified patient populations, we used Pearson chi-square tests to determine statistical significance. Multivariable Cox proportional hazards (PH) regression analyses were used to examine the effect of the study variables on OS and DSS [39]. Hazard ratios (HRs) were calculated based on multivariable Cox PH models adjusting for age, sex, year of diagnosis, marital status, tumor size, grade, site, histologic subtype, and modality of RT. Adjusted survival function estimates using Kaplane–Meier (KM) methods were generated based on a fitted Cox PH model including treatment. Median and 5-y survival rates were calculated from the life tables in our KM analysis. Analyses were conducted using Stata

(StataCorp LP, College Station, TX) and SAS (SAS Institute Inc, Cary, NC) data analysis and statistical software packages. Statistical significance was set at $P < 0.05$.

3. Results

A total of 15,380 patients met our inclusion criteria. Baseline patient and tumor characteristics are listed in Table 1. The mean age was 56.6 ± 16.8, 52.1% were male, and 67% were white. The number of cases reported per year steadily increased from 1990–1996 (15.1%) to 2007–2011 (33.7%).

Tumors occurred most frequently in the extremities (41.1%), were predominantly high grade (56%), and were mostly 5–10 cm in size (30.7%), although there was a wide range. Most patients were married at the time of diagnosis (59.3%). Of the total, 59.9% of patients were treated with surgery alone. Of those patients, 29.4% had low grade, 22.3% had intermediate grade, and 47.8% had high-grade tumors. Of all patients, 33.3% were treated with adjuvant RT, and 6.8% received neoadjuvant RT; 68.3% of patients treated with either adjuvant or neoadjuvant RT had high-grade tumors.

3.1. Stratification by age group

A comparison of patients stratified by age group is listed in Table 2. Although there were a greater number of patients <65 y old ($n = 10,210$ *versus* $n = 5170$), there were no significant differences in sex among the two groups. Patients <65 y were more likely to be single (22.0% *versus* 10.0%, $P < 0.01$), and less likely to be divorced, separated, or widowed (13.6% *versus* 29.8%, $P < 0.01$). A smaller percentage of patients <65 y were white (63.3% *versus* 74.3%, $P < 0.01$), whereas a greater proportion were black (12.6% *versus* 7.4%, $P < 0.01$) and Hispanic (15.4% *versus* 9.2%, $P < 0.01$). genitourinary (GU) and/or gynecologic (GYN) tumors occurred more frequently in patients <65 y (17.3% versus 11.8%, $P < 0.01$). There were also fewer high-grade tumors among patients <65 y (54.0% versus 60.0%, $P < 0.01$). Tumor size and histologic subtype varied between the two groups, with older patients having a higher percentage of tumors >15 cm ($P < 0.01$). Patients ≥65 y were also more frequently treated with surgery alone (61.4% versus 59.1%, $P < 0.02$), and had lower rates of both neoadjuvant (6.2% versus 7%, $P < 0.02$) and adjuvant (32.4% versus 33.8%, $P < 0.02$) RT compared to patients <65 y.

3.2. Predictors of OS and DSS

As listed in Table 3, multivariate analysis of all patients revealed that age at diagnosis (HR = 1.02; 95% confidence interval [CI] = 1.016–1.020), male sex (HR = 1.21; 95% CI = 1.14–1.27), earlier year of diagnosis, African American race (HR = 1.15; 95% CI = 1.06–1.24), and divorced or widowed marital status (HR = 1.50; 95% CI = 1.41–1.60) predicted worse OS ($P < 0.0001$). Thoracic tumor site (HR = 2.53; 95% CI = 2.15–2.98), high-tumor grade (HR = 3.04; 95% CI = 2.74–3.34), and tumor size >15 cm (HR = 3.44; 95% CI = 3.16–3.74) were also associated with worse OS ($P < 0.0001$). Importantly, both neoadjuvant (HR = 0.81; 95% CI = 0.72–0.90) and adjuvant (HR = 0.79; 95% CI = 0.74–0.84) RT were associated with improved survival ($P < 0.0001$) compared to surgery alone when analyzing all patients. When combining both radiation modalities into a single RT group for analysis,

we observed a median OS of 136 ± 13 mo compared to 118 ± 9 mo for patients undergoing surgery alone ($P < 0.001$). Similarly, 5-y survival rates for patients receiving RT (63.2% ± 1.4%) were statistically greater ($P < 0.01$) than for surgery alone (60.5% ± 1.2%).

Similarly, we observed that age (HR = 1.01; 95% CI = 1.01–1.02), male sex (HR = 1.14; 95% CI = 1.07–1.21), African American race (HR = 1.15; 95% CI = 1.05–1.26), earlier year of diagnosis, and divorced or widowed marital status (HR = 1.33; 95% CI = 1.24–1.43) predicted worse DSS ($P < 0.0001$). Thoracic tumor site (HR = 2.92; 95% CI = 2.45–3.49), high-tumor grade (HR = 4.09; 95% CI = 3.59–4.68), and tumor size >15 cm (HR = 4.64; 95% CI = 4.19–5.14) also predicted statistically worse DSS ($P < 0.0001$). Again, importantly, both neoadjuvant (HR = 0.86; 95% CI = 0.76–0.97) and adjuvant (HR = 0.83; 95% CI =0.78–0.89) RT were associated with improved DSS ($P < 0.0001$) when analyzing predictors of DSS among all patients.

Overall, OS and DSS varied with histologic subtype, with patients with well-differentiated liposarcoma experiencing the best survival, whereas patients with malignant peripheral nerve sheath tumor had the poorest survival (OS HR = 4.15, 95% CI = 2.47–6.98; DSS HR = 6.51, 95% CI = 3.71–11.41).

3.3. Predictors of overall survival by age group

A comparison of predictors of OS stratified by age 65 y is listed in Table 4. Male sex, divorced or widowed marital status, thoracic tumor site, high grade, and tumor size >15 cm predicted worse OS in both age groups. In patients <65 y, African American race (HR = 1.12; 95% CI = 1.01–1.23), and year of diagnosis predicted worse OS. In patients >65 y, however, ethnicity did not predict OS ($P = 0.182$), and patients diagnosed between 1990 and 2006 experienced statistically equivalent survival.

Patients ≥65 y receiving RT rather than surgery alone had markedly improved survival (median OS, 70 ± 9.4 *versus* 60 ± 5.4 mo; $P < 0.001$) compared to patients <65 y (median OS, 192 ± 20.4 *versus* 180 ± 20.8; $P = 0.02$).

3.4. Predictors of DSS by age group

As summarized in Table 5, worse DSS was predicted by male sex, thoracic tumor site, high grade, and tumor size >15 cm. Patients >65 y again experienced equivalent survival between the years of 1990–2006, whereas patients <65 y showed improved DSS over that same time frame. American Indian and Alaskan Natives (HR = 1.46, 95% CI = 1.01–2.12) had poorer DSS in patients <65 y. In contrast, ethnicity failed to predict DSS in patients >65 y.

Similar to OS, patients ≥65 y receiving RT compared to surgery alone experienced improved median DSS (RT: not reached; No RT: 154 mo, CI not calculable, $P < 0.05$). For patients <65 y, there was no statistical difference in median DSS between the RT and non-RT cohorts (RT = not reached; No RT = not reached; $P = 0.12$).

3.5. Kaplan-Meier survival analysis

As noted above, for KM survival analysis, patients who received either neoadjuvant or adjuvant RT were combined into a single radiation group. This allowed us to analyze the

overall effects of RT, regardless of timing, compared to those patients undergoing surgery alone.

Figure 1 demonstrates the improvement in OS for patients of all ages receiving RT ($P < 0.001$). As shown in Figure 2, patients <65 y receiving RT had a statistically significant improvement in OS compared to surgery alone ($P = 0.02$), although the magnitude of the treatment effect was markedly smaller than that observed for patients ≥65 y. Interaction testing revealed a statistically significant modification effect between RT and patient age ($P < 0.05$). Figure 3 illustrates the difference in OS in patients >65 y, showing a significant survival benefit for those patients receiving RT compared with those that underwent surgery alone ($P < 0.001$). We observed a 6.7% improvement in median OS for patients <65 y treated with RT ($P < 0.01$) compared to a 16.7% OS benefit in patients ≥65 y ($P < 0.01$). This improvement in survival in younger patients may be statistically, however not clinically, significant, whereas the benefit from RT in OS for older patients achieves both statistical and clinical significance.

4. Discussion

We abstracted a large national database of STS patients to evaluate the effect of age on oncologic outcomes after RT. We observed a statistically significant improvement in OS and DSS in all patients receiving neoadjuvant or adjuvant RT compared to surgery alone. This positive effect was significantly amplified in patients aged >65 y.

As depicted in Figure 1, when compared to the patients who did not receive RT, administration of RT resulted in improved OS. When stratified by age, both younger and older patient groups demonstrated a statistically significant improved survival. However, we appreciated a greater magnitude of improved survival in patients aged >65 y, as evidenced by the notable difference in median survival. These data suggest that the survival benefit imparted by RT is more likely to achieve clinical significance in older patients.

Although previous studies have evaluated the impact of RT on OS and DSS in the multimodality management of various STS, the results have been equivocal [3,6,8–11,22,23]. Although there is clear benefit of RT on improved local control, some studies have demonstrated improved survival with RT, whereas randomized prospective trials by Yang *et al*. and Beane *et al*. have failed to demonstrate any improvement in OS among patients receiving adjuvant RT [8,9].

One of the notable strengths of our study relates to the large number of STS patients included in our analysis from a population-based database. Although certain data points are not abstracted by SEER (most notably margin status and administration of chemotherapy), the SEER registry is one of the most comprehensive sources of information on tumor morphology, patient demographics, and survival time. In addition, the SEER registry is highly representative of the overall US population, increasing the generalizability of our data, which is often lacking in single-institution studies or even randomized trials. Less than 5% of the US population participates in registered clinical trials, and elderly patients are heavily underrepresented, often because of exclusion criteria related to comorbidities or

functional status [24–26]. These factors highlight the importance of retrospective data from population-based sources such as SEER that allow a more thorough investigation into the oncologic outcome of patients aged >65 y.

The characteristics of the patients in our analysis are comparable to other observational and single-institution studies, taking into account our inclusion of all tumor sites rather than extremities only. For example, Koshy *et al*. [10] studied a cohort consisting of 48% women and 52% men in whom 47% of patients received RT. They observed an improvement in 3-y survival for patients with high-grade tumors receiving RT compared with those not receiving RT (73% versus 63%, $P < 0.001$). Not surprisingly, given the overlap in study patients, our results reinforce the findings of previous studies such as those of Koshy *et al*., specifically the positive effects of RT, as well as female sex, married marital status, and later years of diagnosis on improved oncologic outcome [10,22]. Furthermore, similar to prior studies, we identified tumor size and grade to be strong predictors of worse oncologic outcome [5,6,20]. We also found histologic subtype to predict survival, consistent with the previously published findings of Canter *et al*. [20,21] among others.

The observed differences in survival were even more apparent for patients receiving RT in a neoadjuvant setting. Young patients did not experience any survival benefit from neoadjuvant RT *versus* surgery alone, whereas patients >65 y of age had improved OS and DSS with neoadjuvant RT. These data suggest the highest impact of age-related effect of RT may be in those patients receiving RT before surgery. This may be an important consideration in our investigation into the immunologic mechanisms responsible for these findings.

To our knowledge, analysis of the effect of advancing age on the response to RT and oncologic outcome has not yet been rigorously investigated, although several clinical trials across multiple solid malignancies–such as breast, lung, prostate, and head and neck tumors–have attempted to address this association [27–29]. In breast cancers, for example, omission of RT in elderly patients has not been observed to translate to inferior oncologic outcome among patients receiving breast conservation therapy [30]. Although some investigators suggest this may be due to an underlying indolent tumor biology in older patients, these patients are nevertheless receiving alternative cancer-directed therapy in the form of endocrine therapy [28,30]. In the field of head and neck cancer, three studies directly comparing outcomes across age groups in patients-receiving RT demonstrated equivalent, but not improved, survival in older compared with younger patients-receiving RT [29,31,32]. One of those studies showed a small detriment to survival when age was addressed as a continuous variable [32]. Numerous randomized trials assessing the role of RT in the treatment of lung cancer have met with similarly inconclusive results analyzing age as predictive of survival [27,33,34]. Therefore, we maintain that more investigation into the association between age and response to RT is needed.

Multiple studies have demonstrated the array of immunologic changes associated with the administration of RT, including increasing tumor antigen expression, dendritic cell antigen presentation, stimulation of T lymphocytes, and an immunosuppressive upregulation of CD25+ T regulatory (Treg) cells [15,35]. Whether this stimulation of the immune

microenvironment sensitizes the tumor to various immunotherapies is an area of ongoing and exciting investigation [16,17]. The effects of age-related immunosenescence are also well described and include a general decrease in lymphocyte cytotoxic activity, although a change in the constellation of the lymphocyte population and an upregulation of Tregs has also been appreciated [19,36]. Tregs may be a key component of these age-related phenomena because they are upregulated by both RT and age. Although much is unknown regarding these associations, the interplay between the changes in the immune system that occur with RT and the aging process may help to explain the improvement in survival in older STS patients-receiving RT, which we have observed.

Admittedly, there are limitations to our study. First, the SEER database lacks important data on chemotherapy and surgical margin status. Chemotherapy also has a significant impact on the antitumor immune response [17], and these data are not available for our analysis. The retrospective nature of our study design has its inherent limitations, and with no predefined treatment algorithms, there is likely to be selection bias in terms of which patients receive or do not receive RT. Although it may be reasonable to assume that older patients were preferentially selected for RT based on better functional status and lower comorbidities, this same logic would apply to selection for younger patients, which may alleviate the effect of this potential bias. Furthermore, older patients had statistically significant higher incidence of adverse tumor features–such as large and high-grade tumors–which only strengthens our findings of improved survival in the older patient cohort–receiving RT. We also realize there are no categorical changes that occur in the immune system specifically at the age of 65 y, but the differences in survival were most notable when using 65 y as the age cutoff to stratify younger and older patient groups. We observed the same association of age and RT treatment–related effects when using different age cutoffs between 60 and 80 y (data not shown). There was also a significant portion of patients with incomplete tumor morphology data, specifically missing tumor site, size, or grade. Given the possibility that the exclusion of these patients would impact our results, we included these patients in a separate analysis, also with largely unchanged results.

Margin status has been repeatedly associated with OS and DSS in STS patients and was unfortunately unavailable to incorporate in our analysis because of database restrictions. However, other factors–such as size, grade, depth, and, more recently, histologic subtype–are stronger independent predictors of survival [37,38]. Furthermore, although margin status may help guide adjuvant dosing of RT, it is rarely the sole factor to the overall decision to implement RT in treatment algorithms. Therefore, we do not believe these missing data contribute more bias than are usual for a SEER study.

Despite these limitations, this is the first population-based comprehensive analysis of the age-related impact of RT on survival in STS, and the large sample size of our study may help counteract the limitations of confounding in this retrospective study. In addition, these population-based data are complementary to single-institutional studies, which may be limited by selection bias and limited generalizability inherent to single-institution studies. Because of the relative rarity of STS, it is unlikely that a randomized trial that stratifies patients by age and receipt of RT will be performed given the number of patients needed to treat to reach statistical significance and the time needed to recruit the necessary sample

size. Therefore, outcomes data such as these serve an important function in helping to guide further hypothesis-driven research and multidisciplinary clinical decision-making.

The toxicities of RT have been well described [23], not only in STS but also in numerous solid malignancies, and may occur with greater frequency or severity in elderly patients undergoing RT [39,40]. Clinically, this may be deterrent to the administration of RT as adjuvant treatment in elderly patients. Our data, however, suggest that the concern for potential toxicity should be weighed carefully against the possible benefit in overall and disease-specific outcome in determining the best course of treatment for each individual patient.

In summary, RT was associated with improved survival in patients with STS undergoing surgical treatment. These improvements in oncologic outcome were most notable in older patients-receiving RT. Further studies into the mechanisms underlying this association are needed, and we suspect these may be of an immunologic nature. These data support the use of RT in the multimodality treatment of STS and further encourage the use of this modality in older patients that may derive greatest survival benefit.

Acknowledgments

This work was supported by funding from the National Institutes of Health (R.J.C., UC Davis Paul Calabresi K12 Career Development Award NIH 1K12CA138464-01A2) and the National Center for Advancing Translational Sciences (UL1 TR000002, C.-S.L.).

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015; 65:5. [PubMed: 25559415]
2. Sherman KL, Wayne JD, Chung J, et al. Assessment of multimodality therapy use for extremity sarcoma in the United States. J Surg Oncol. 2014; 109:395. [PubMed: 24375444]
3. Katz SC, Brennan MF. Randomized clinical trials in soft tissue sarcoma. Surg Oncol Clin N Am. 2010; 19:1. [PubMed: 19914557]
4. Wasif N, Smith CA, Tamurian RM, et al. Influence of physician specialty on treatment recommendations in the multidisciplinary management of soft tissue sarcoma of the extremities. JAMA Surg. 2013; 148:632. [PubMed: 23552630]
5. Singer S, Demetri GD, Baldini EH, Fletcher CD. Management of soft-tissue sarcomas: an overview and update. Lancet Oncol. 2000; 1:75. [PubMed: 11905672]
6. Curtis KK, Ashman JB, Beauchamp CP, et al. Neoadjuvant chemoradiation compared to neoadjuvant radiation alone and surgery alone for stage II and III soft tissue sarcoma of the extremities. Radiat Oncol. 2011; 6:91. [PubMed: 21827676]
7. Al-Refaie WB, Habermann EB, Dudeja V, et al. Extremity soft tissue sarcoma care in the elderly: insights into the generalizability of NCI Cancer Trials. Ann Surg Oncol. 2010; 17:1732. [PubMed: 20354801]
8. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol. 1998; 16:197. [PubMed: 9440743]
9. Beane JD, Yang JC, White D, Steinberg SM, Rosenberg SA, Rudloff U. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. Ann Surg Oncol. 2014; 21:2484. [PubMed: 24756814]

10. Koshy M, Rich SE, Mohiuddin MM. Improved survival with radiation therapy in high-grade soft tissue sarcomas of the extremities: a SEER analysis. Int J Radiat Oncol Biol Phys. 2010; 77:203. [PubMed: 19679403]
11. Schreiber D, Rineer J, Katsoulakis E, et al. Impact of postoperative radiation on survival for high-grade soft tissue sarcoma of the extremities after limb sparing radical resection. Am J Clin Oncol. 2012; 35:13. [PubMed: 21278563]
12. Sharma A, Bode B, Studer G, et al. Radiotherapy of human sarcoma promotes an intratumoral immune effector signature. Clin Cancer Res. 2013; 19:4843. [PubMed: 23861514]
13. Demaria S, Formenti SC. Radiotherapy effects on anti-tumor immunity: implications for cancer treatment. Front Oncol. 2013; 3:128. [PubMed: 23734344]
14. Demaria S, Pilones KA, Formenti SC, Dustin ML. Exploiting the stress response to radiation to sensitize poorly immunogenic tumors to anti-CTLA-4 treatment. Oncoimmunology. 2013; 2:e23127. [PubMed: 23802063]
15. Kachikwu EL, Iwamoto KS, Liao YP, et al. Radiation enhances regulatory T cell representation. Int J Radiat Oncol Biol Phys. 2011; 81:1128. [PubMed: 21093169]
16. Shahabi V, Postow MA, Tuck D, Wolchok JD. Immune-priming of the tumor microenvironment by radiotherapy: rationale for combination with immunotherapy to improve anticancer efficacy. Am J Clin Oncol. 2015; 38:90. [PubMed: 25616204]
17. Zheng Y, Dou Y, Duan L, et al. Using chemo-drugs or irradiation to break immune tolerance and facilitate immunotherapy in solid cancer. Cell Immunol. 2015; 294:54. [PubMed: 25687508]
18. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst. 2013; 105:256. [PubMed: 23291374]
19. Jagger A, Shimojima Y, Goronzy JJ, Weyand CM. Regulatory T cells and the immune aging process: a mini-review. Gerontology. 2014; 60:130. [PubMed: 24296590]
20. Canter RJ, Beal S, Borys D, Martinez SR, Bold RJ, Robbins AS. Interaction of histologic subtype and histologic grade in predicting survival for soft-tissue sarcomas. J Am Coll Surg. 2010; 210:191. e2. [PubMed: 20113939]
21. Tseng W, Martinez SR, Tamurian RM, Borys D, Canter RJ. Histologic type predicts survival in patients with retroperitoneal soft tissue sarcoma. J Surg Res. 2012; 172:123. [PubMed: 20869082]
22. Naing KW, Monjazeb AM, Li CS, et al. Perioperative radiotherapy is associated with improved survival among patients with synovial sarcoma: a SEER analysis. J Surg Oncol. 2015; 111:158. [PubMed: 25176165]
23. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002; 359:2235. [PubMed: 12103287]
24. Lara PN Jr, Higdon R, Lim N, et al. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. J Clin Oncol. 2001; 19:1728. [PubMed: 11251003]
25. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol. 2003; 21:1383. [PubMed: 12663731]
26. Tournoux C, Katsahian S, Chevret S, Levy V. Factors influencing inclusion of patients with malignancies in clinical trials. Cancer. 2006; 106:258. [PubMed: 16397866]
27. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009; 374:379. [PubMed: 19632716]
28. Albert JM, Liu DD, Shen Y, et al. Nomogram to predict the benefit of radiation for older patients with breast cancer treated with conservative surgery. J Clin Oncol. 2012; 30:2837. [PubMed: 22734034]
29. Allal AS, Maire D, Becker M, Dulguerov P. Feasibility and early results of accelerated radiotherapy for head and neck carcinoma in the elderly. Cancer. 2000; 88:648. [PubMed: 10649260]
30. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013; 31:2382. [PubMed: 23690420]
31. Pignon T, Horiot JC, Van den Bogaert W, Van Glabbeke M, Scalliet P. No age limit for radical radiotherapy in head and neck tumours. Eur J Cancer. 1996; 32A:2075. [PubMed: 9014748]

32. Huang SH, O'Sullivan B, Waldron J, et al. Patterns of carein elderly head-and-neck cancer radiation oncology patients: a single-center cohort study. Int J Radiat Oncol Biol Phys. 2011; 79:46. [PubMed: 20395066]

33. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst. 2007; 99:442. [PubMed: 17374834]

34. Cox JD. Are the results of RTOG 0617 mysterious? Int J Radiat Oncol Biol Phys. 2012; 82:1042. [PubMed: 22284026]

35. Qu Y, Jin S, Zhang A, et al. Gamma-ray resistance of regulatory CD4+CD25+Foxp3+ T cells in mice. Radiat Res. 2010; 173:148. [PubMed: 20095846]

36. Adeegbe DO, Nishikawa H. Natural and induced T regulatory cells in cancer. Front Immunol. 2013; 4:190. [PubMed: 23874336]

37. Gronchi A, Lo Vullo S, Colombo C, et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. Ann Surg. 2010; 251:506. [PubMed: 20130465]

38. Lewis JJ, Leung D, Espat J, Woodruff JM, Brennan MF. Effect of reresection in extremity soft tissue sarcoma. Ann Surg. 2000; 231:655. [PubMed: 10767786]

39. Yuen AR, Zou G, Turrisi AT, et al. Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. Cancer. 2000; 89:1953. [PubMed: 11064352]

40. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med. 1999; 340:265. [PubMed: 9920950]

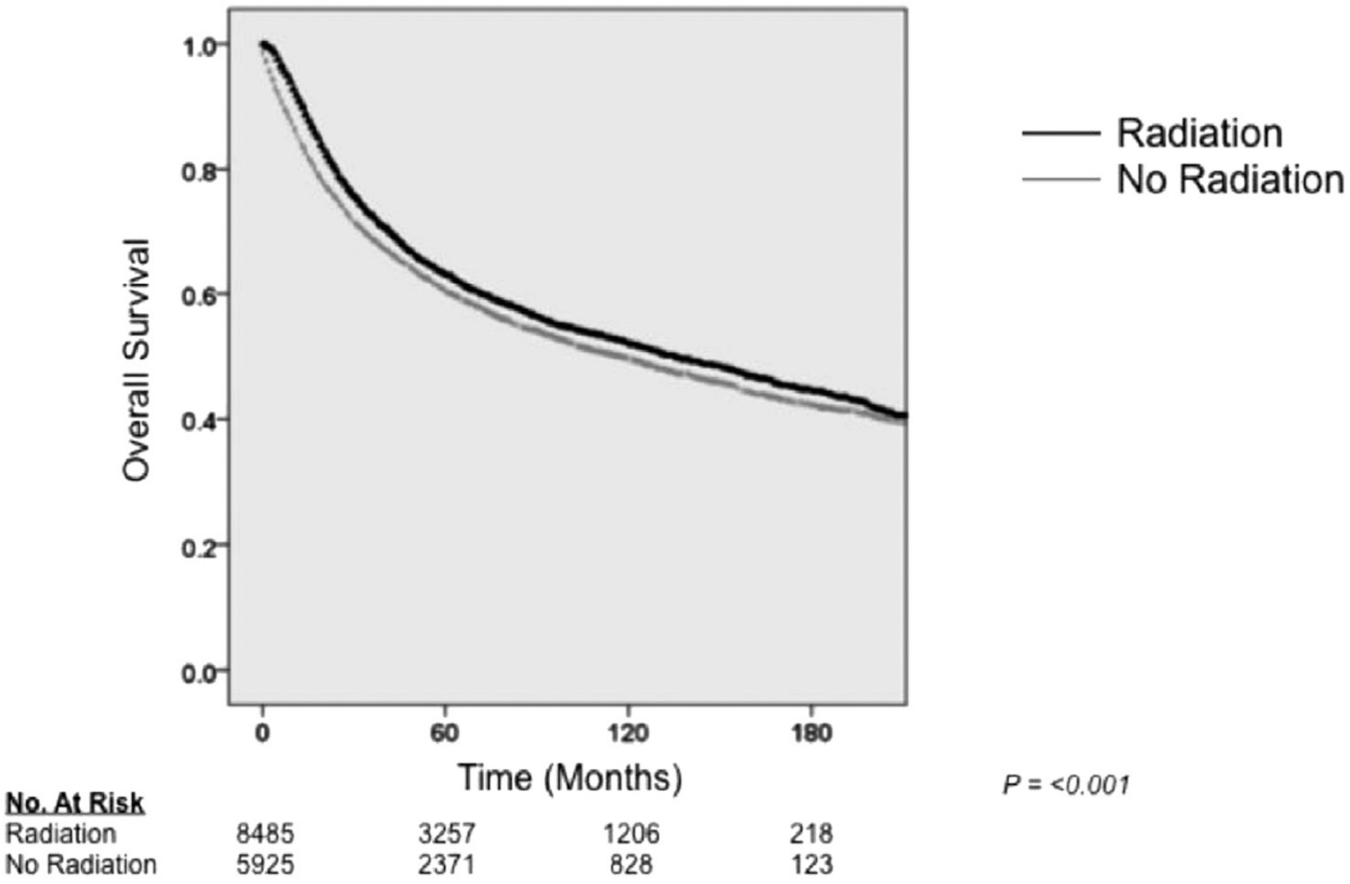

Fig. 1.

Kaplan–Meier curve depicting overall survival among patients with STS (*n* = 14,410) undergoing surgical resection stratified by receipt of radiation therapy.

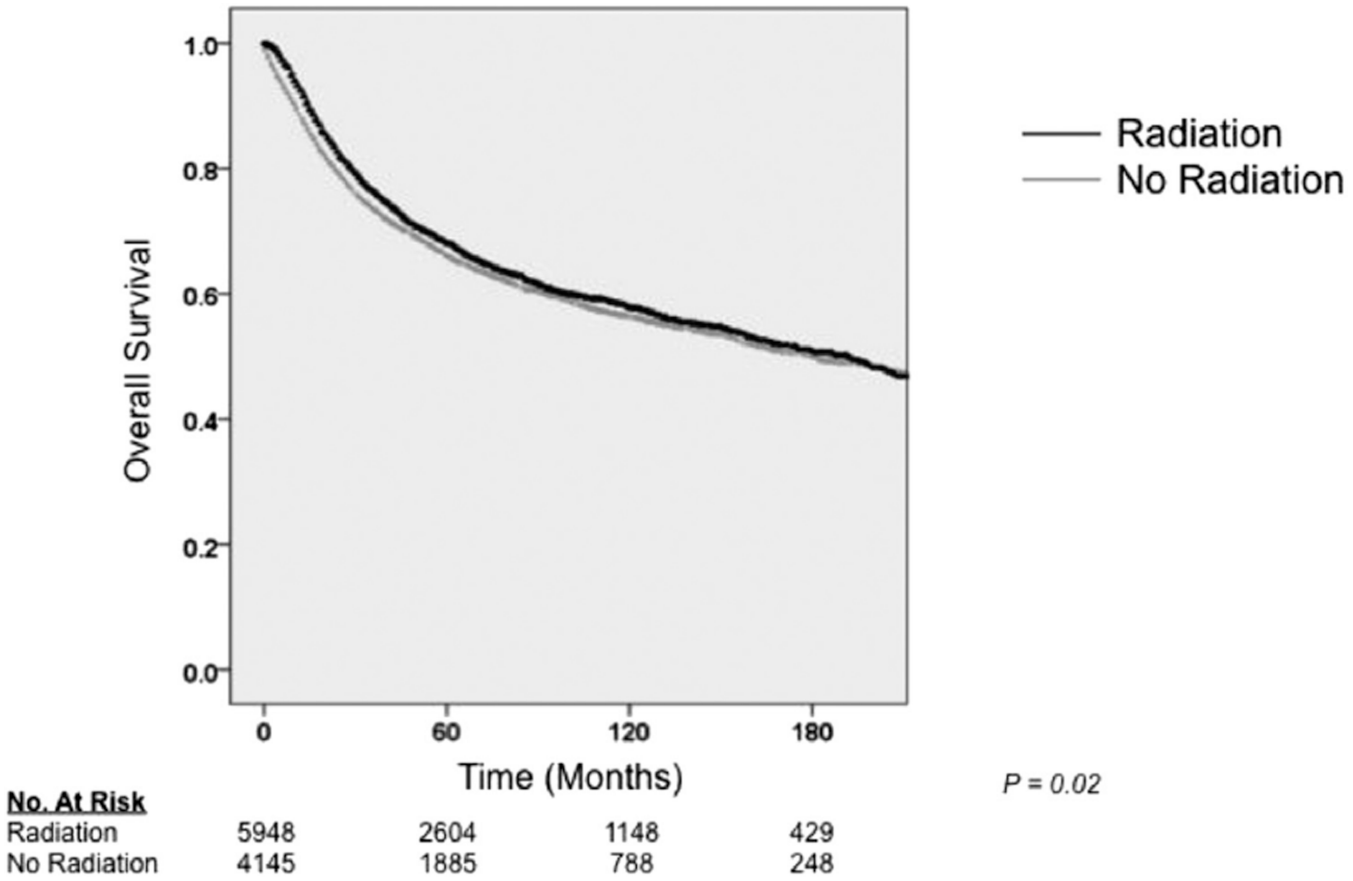

Fig. 2.

Kaplan–Meier curve depicting overall survival among patients <65 y old with STS undergoing surgical resection stratified by receipt of radiation therapy (*n* = 10,093).

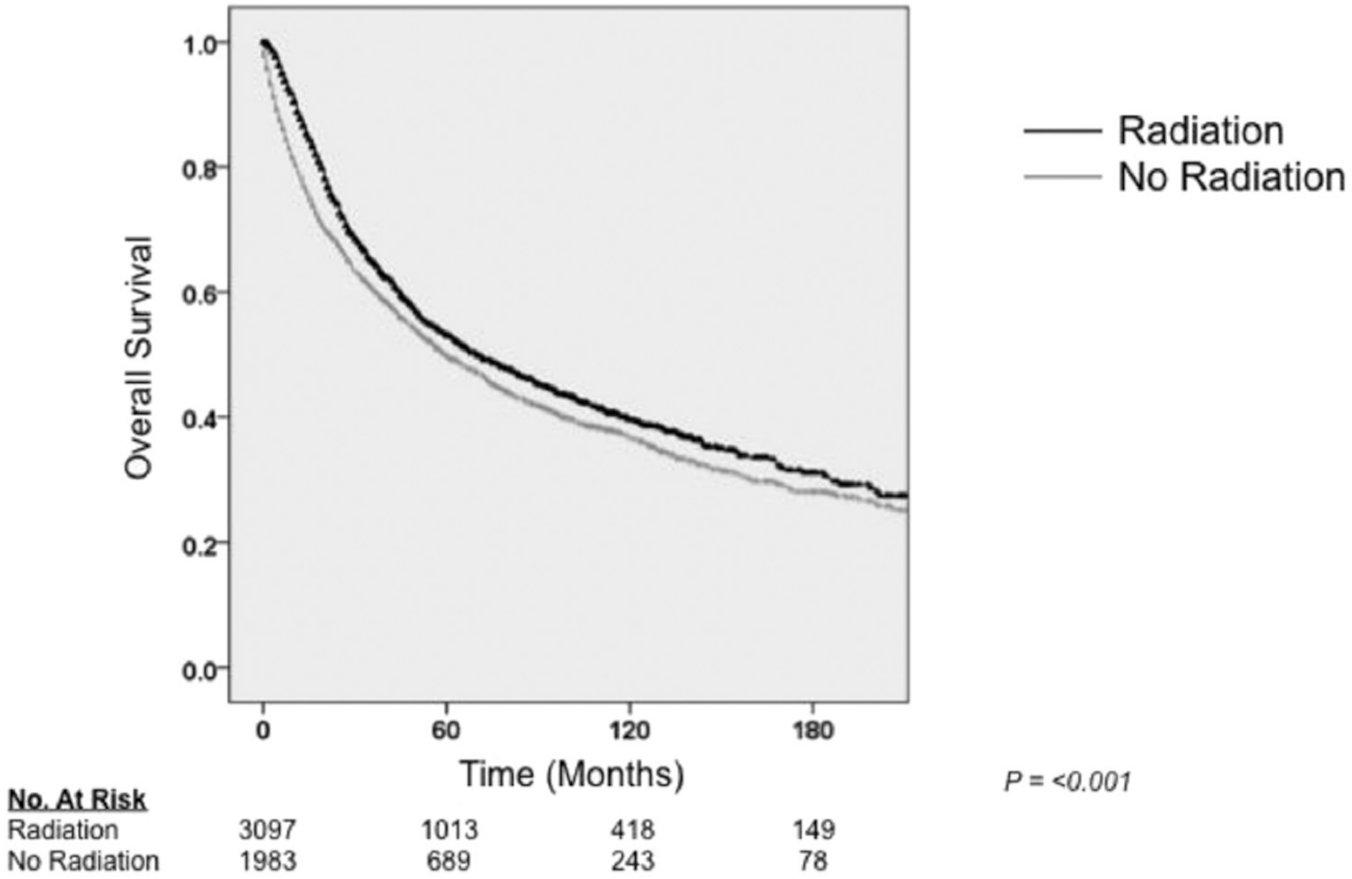

Fig. 3.

Kaplan–Meier curve depicting overall survival among patients ≥65 y old with STS undergoing surgical resection stratified by receipt of radiation therapy (n = 5080).

Table 1

Patient demographics and tumor characteristics.

Factor	All patients, *n* (%)
Total	
Patients	15,380 (100)
Sex	
Male	8018 (52.1)
Female	7362 (47.9)
Year of diagnosis	
1990–1996	2316 (15.1)
1997–2001	3119 (20.3)
2002–2006	4768 (31)
2007–2011	5177 (33.7)
Race	
White	10,310 (67)
Black	1679 (10.9)
Spanish-Hispanic-Latino	2041 (13.3)
Other*	1350 (8.8)
Histology	
Liposarcoma, well differentiated	1563 (10.2)
Dedifferentiated liposarcoma	692 (4.5)
Epithelioid	155 (1)
Leiomyosarcoma	4632 (30.1)
Liposarcoma	1308 (8.5)
Malignant fibrous histiocytoma	2581 (16.8)
Malignant peripheral nerve sheath tumor	25 (0.2)
Myxoid liposarcoma	1020 (6.6)
Rhabdomyosarcoma	241 (1.6)
Sarcoma	1661 (10.8)
Synovial sarcoma	635 (4.1)
Other†	867 (5.6)
Site	
Extremities	6324 (41.1)
GU and/or GYN	2380 (15.5)
Head and/or neck	662 (4.3)
Thoracic	262 (1.7)
Trunk	2367 (15.4)
Visceral	3385 (22)
Grade	
Low	3494 (22.7)
Intermediate	3272 (21.3)
High	8614 (56)

Factor	All patients, *n* (%)
Size (cm)	
<5	3917 (25.5)
5–10	4723 (30.7)
>10–15	3010 (19.6)
>15	3730 (24.3)
Marital status	
Married	9124 (59.3)
Single	2766 (18)
Divorced and/or widowed	2925 (19)
Unknown	565 (3.7)
Treatment	
Surgery only	9211 (59.9)
Neoadjuvant radiation	1040 (6.8)
Adjuvant radiation	5129 (33.4)

GU = genitourinary; GYN = gynecologic.

*Asian and/or Pacific Islander (7.6%), American Indian and/or Alaskan Native (0.6%), or unknown (0.6%).

†Includes alveolar soft part (0.2%), fibrosarcoma (4.4%), malignant solitary fibrous tumor (0.3%), and myxoid chondrosarcoma (0.8%).

Table 2

Patient demographics and tumor characteristics by age group.

Factor	Age <65 y (*n* = 10.210)	Age >65 y (*n* = 5170)	*P* value
	n (%)	*n* (%)	
Total			
Patients	10,210 (66.4)	5170 (33.6)	
Sex			
Male	5374 (52.6)	2644 (51.1)	0.08
Female	4836 (47.4)	2526 (48.9)	
Year of diagnosis			
1990–1996	1487 (14.6)	829 (16)	0.04
1997–2001	2116 (20.7)	1003 (19.4)	
2002–2006	3183 (31.2)	1585 (30.7)	
2007–2011	3424 (33.5)	1753 (33.9)	
Race			
White	6467 (63.3)	3843 (74.3)	<0.01
Black	1290 (12.6)	389 (7.5)	
Spanish-Hispanic-Latin American	1567 (15.4)	474 (9.2)	
Other*	886 (8.7)	464 (9.0)	
Histology			
Liposarcoma, well differentiated	1012 (9.9)	551 (10.7)	<0.01
Dedifferentiated liposarcoma	380 (3.7)	312 (6)	
Epithelioid	120 (1.2)	35 (0.7)	
Leiomyosarcoma	3207 (31.4)	1425 (27.6)	
Liposarcoma	836 (8.2)	472 (9.1)	
Malignant fibrous histiocytoma	1401 (13.7)	1180 (22.8)	
Malignant peripheral nerve sheath tumor	19 (0.2)	6 (0.1)	
Myxoid liposarcoma	807 (7.9)	213 (4.1)	
Rhabdomyosarcoma	166 (1.6)	75 (1.5)	
Sarcoma	1053 (10.3)	608 (11.8)	
Synovial sarcoma	560 (5.5)	75 (1.5)	
Other†	649 (6.4)	218 (4.2)	
Site			
Extremities	4185 (41)	2139 (41.4)	<0.01
GU/GYN	1769 (17.3)	611 (11.8)	
Head/neck	377 (3.7)	285 (5.5)	
Thoracic	186 (1.8)	76 (1.5)	
Trunk	1560 (15.3)	807 (15.6)	
Visceral	2133 (20.9)	1252 (24.2)	
Grade			
Low	2402 (23.5)	1092 (21.1)	<0.01
Intermediate	2297 (22.5)	975 (18.9)	

Factor	Age <65 y (*n* = 10.210)	Age >65 y (*n* = 5170)	*P* value
	n (%)	*n* (%)	
High	5511 (54)	3103 (60)	
Size			
<5 cm	2696 (26.4)	1221 (23.6)	<0.01
5–10 cm	3059 (30)	1664 (32.2)	
>10–15 cm	2035 (19.9)	975 (18.9)	
>15 cm	2420 (23.7)	1310 (25.3)	
Marital status			
Married	6193 (60.7)	2931 (56.7)	<0.01
Single	2248 (22)	518 (10)	
Divorced/widowed	1384 (13.6)	1541 (29.8)	
Unknown	385 (3.8)	180 (3.5)	
Treatment			
Surgery only	6038 (59.1)	3173 (61.4)	0.015
Neoadjuvant radiation	719 (7)	321 (6.2)	
Adjuvant radiation	3453 (33.8)	1676 (32.4)	

GU = genitourinary; GYN = gynecologic.

*Asian, Pacific Islander, American Indian, Alaskan Native, or unknown.

†Includes alveolar soft part (0.2), fibrosarcoma (4.4), malignant solitary fibrous tumor (0.3), and myxoid chondrosarcoma (0.8).

Table 3

All patients (multivariable Cox PH models).

	Overall survival (*n* = 15,380)		Disease-specific survival (*n* = 15,380)	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Age at diagnosis	1.02 (1.016–1.020)	*	1.01 (1.01–1.02)	*
Sex				
Female	1.00 (reference)	*	1.00 (reference)	*
Male	1.21 (1.14–1.27)		1.14 (1.07–1.21)	
Year of diagnosis				
1990–1996	1.00 (reference)	*	1.00 (reference)	*
1997–2001	0.92 (0.85–0.99)		0.90 (0.82–0.97)	
2002–2006	0.79 (0.73–0.85)		0.78 (0.72–0.85)	
2007–2011	0.70 (0.64–0.76)		0.68 (0.62–0.75)	
Race				
White	1.00 (reference)	*	1.00 (reference)	*
American Indian/Alaska Native	1.19 (0.88–1.61)		1.24 (0.89–1.73)	
Asian or Pacific Islander	0.95 (0.87–1.05)		0.98 (0.88–1.09)	
Black	1.15 (1.06–1.24)		1.15 (1.05–1.26)	
Spanish-Hispanic-Latino	0.93 (0.86–1.01)		0.93 (0.85–1.01)	
Unknown	0.35 (0.19–0.65)		0.22 (0.08–0.57)	
Histology				
Liposarcoma, well differentiated	1.00 (reference)	*	1.00 (reference)	*
Alveolar soft part sarcoma	2.32 (1.25–4.28)		3.44 (1.77–6.68)	
Dedifferentiated liposarcom	1.38 (1.13–1.67)		1.86 (1.43–2.42)	
Epithelioid	3.08 (2.30–4.12)		4.82 (3.39–6.86)	
Fibrosarcoma	1.35 (1.08–1.69)		1.86 (1.37–2.51)	
Leiomyosarcoma	2.30 (1.95–2.72)		3.41 (2.69–4.32)	
Liposarcoma	1.57 (1.32–1.87)		2.02 (1.58–2.58)	
Malignant fibrous histiocytoma	2.15 (1.81–2.55)		2.89 (2.26–3.68)	
Malignant peripheral nerve sheath tumor	4.15 (2.47–6.98)		6.51 (3.71–11.41)	
Malignant solitary fibrous tumor	1.17 (0.69–1.99)		1.59 (0.86–2.95)	
Myxoid chondrosarcoma	1.90 (1.31–2.75)		2.69 (1.68–4.29)	
Myxoid liposarcoma	1.21 (0.99–1.47)		1.86 (1.43–2.42)	
Rhabdomyosarcoma	2.99 (2.37–3.77)		4.54 (3.39–6.09)	
Sarcoma	–2.64 (2.22–3.14)		3.82 (2.99–4.88)	
Synovial sarcoma	2.71 (2.20–3.34)		4.35 (3.32–5.70)	
Site				
Extremities	1.00 (reference)	*	1.00 (reference)	*
GU/GYN	1.81 (1.66–1.97)		2.13 (1.93–2.34)	
Head/neck	1.72 (1.50–1.97)		1.56 (1.31–1.87)	
Thoracic	2.53 (2.15–2.98)		2.92 (2.45–3.49)	
Trunk	1.31 (1.21–1.42)		1.48 (1.35–1.63)	

	Overall survival (*n* = 15,380)		Disease-specific survival (*n* = 15,380)	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Visceral	1.43 (1.33–1.55)		1.64 (1.51–1.79)	
Grade				
Low	1.00 (reference)	*	1.00 (reference)	*
Intermediate	1.44 (1.29–1.62)		1.71 (1.48–1.98)	
High	3.04 (2.74–3.34)		4.09 (3.59–4.68)	
Tumor size (cm)				
<5	1.00 (reference)	*	1.00 (reference)	*
5–10	1.76 (1.63–1.91)		2.12 (1.92–2.34)	
>10–15	2.43 (2.23–2.65)		3.03 (2.73–3.36)	
>15	3.44 (3.16–3.74)		4.64 (4.19–5.14)	
Marital status				
Married	1.00 (reference)	*	1.00 (reference)	*
Single	1.10 (1.03–1.19)		1.07 (0.99–1.16)	
Divorced /widowed	1.50 (1.41–1.60)		1.33 (1.24–1.43)	
Unknown	1.06 (0.91–1.24)		0.96 (0.80–1.15)	
Treatment				
Surgery only	1.00 (reference)	*	1.00 (reference)	*
Neoadjuvant radiation	0.81 (0.72–0.90)		0.86 (0.76–0.97)	
Adjuvant radiation	0.79 (0.74–0.84)		0.83 (0.78–0.89)	

GU = genitourinary; GYN = gynecologic.

*$P < 0.01$ unless otherwise specified.

Table 4

Overall survival (multivariable Cox PH models), stratified by age.

	Age <65 y (*n* = 10,210)		Age >65 y (*n* = 5170)	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Sex				
Female	1.00 (reference)	*	1.00 (reference)	*
Male	1.21 (1.12–1.30)		1.21 (1.12–1.32)	
Year of diagnosis				
1990–1996	1.00 (reference)	*	1.00 (reference)	*
1997–2001	0.89 (0.81–0.98)		0.97 (0.86–1.08)	
2002–2006	0.73 (0.66–0.80)		0.91 (0.82–1.02)	
2007–2011	0.67 (0.59–0.75)		0.76 (0.67–0.86)	
Race				
White	1.00 (reference)	*	1.00 (reference)	0.18
American Indian/Alaska Native	1.36 (0.96–1.92)		0.90 (0.48–1.69)	
Asian or Pacific Islander	0.94 (0.83–1.06)		0.97 (0.84–1.12)	
Black	1.12 (1.01–1.23)		1.10 (0.95–1.26)	
Spanish-Hispanic-Latino	0.90 (0.82–1.00)		0.91 (0.79–1.04)	
Unknown	0.22 (0.07–0.70)		0.49 (0.23–1.03)	
Site				
Extremities	1.00 (reference)	*	1.00 (reference)	*
GU/GYN	2.07 (1.84–2.32)		1.54 (1.35–1.76)	
Head/neck	1.80 (1.48–2.19)		1.66 (1.38–2.00)	
Thoracic	2.79 (2.28–3.40)		1.98 (1.49–2.64)	
Trunk	1.39 (1.25–1.55)		1.26 (1.12–1.42)	
Visceral	1.57 (1.42–1.73)		1.27 (1.14–1.42)	
Grade				
Low	1.00 (reference)	*	1.00 (reference)	*
Intermediate	1.46 (1.26–1.70)		1.41 (1.18–1.67)	
High	3.41 (2.97–3.92)		2.64 (2.25–3.09)	
Tumor size (cm)				
<5	1.00 (reference)	*	1.00 (reference)	*
5–10	1.38 (1.24–1.53)		2.52 (2.21–2.86)	
>10–15	2.06 (1.84–2.29)		3.20 (2.78–3.68)	
>15	3.53 (3.17–3.93)		3.65 (3.18–4.20)	
Marital status				
Married	1.00 (reference)	*	1.00 (reference)	*
Single	1.04 (0.96–1.14)		1.04 (0.91–1.19)	
Divorced/widowed	1.50 (1.37–1.64)		1.54 (1.41–1.69)	
Unknown	1.01 (0.83–1.24)		1.11 (0.87–1.41)	
Treatment				
Surgery only	1.00 (reference)	*	1.00 (reference)	*

	Age <65 y (*n* = 10,210)		Age >65 y (*n* = 5170)	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Neoadjuvant radiation	0.96 (0.83–1.10)		0.63 (0.53–0.75)	
Adjuvant radiation	0.83 (0.77–0.90)		0.71 (0.65–0.78)	

GU = genitourinary; GYN = gynecologic.

* $P < 0.01$ unless otherwise specified.

Table 5

Disease-specific survival (multivariable Cox PH models), stratified by age.

	Age <65 y (*n* = 10,210)		Age >65 y (*n* = 5170)	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Sex				
Female	1.00 (reference)	*	1.00 (reference)	0.01
Male	1.14 (1.05–1.23)		1.14 (1.03–1.26)	
Year of diagnosis				
1990–1996	1.00 (reference)	*	1.00 (reference)	*
1997–2001	0.87 (0.78–0.96)		0.95 (0.83–1.09)	
2002–2006	0.74 (0.67–0.82)		0.88 (0.77–1.00)	
2007–2011	0.67 (0.59–0.75)		0.73 (0.62–0.85)	
Race				
White	1.00 (reference)	*	1.00 (reference)	0.14
American Indian/Alaska Native	1.46 (1.01–2.12)		0.76 (0.34–1.73)	
Asian or Pacific Islander	0.94 (0.82–1.08)		1.02 (0.86–1.21)	
Black	1.11 (0.99–1.23)		1.15 (0.98–1.36)	
Spanish-Hispanic-Latino	0.89 (0.80–0.99)		0.93 (0.79–1.10)	
Unknown	0.20 (0.05–0.78)		0.24 (0.06–0.97)	
Site				
Extremities	1.00 (reference)	*	1.00 (reference)	*
GU/GYN	2.20 (1.94–2.50)		2.05 (1.75–2.39)	
Head/neck	1.58 (1.24–2.02)		1.60 (1.24–2.09)	
Thoracic	2.93 (2.36–3.63)		2.76 (2.01–3.79)	
Trunk	1.47 (1.30–1.67)		1.54 (1.331.78)	
Visceral	1.66 (1.48–1.85)		1.62 (1.41–1.85)	
Grade				
Low	1.00 (reference)	*	1.00 (reference)	*
Intermediate	1.73 (1.44–2.08)		1.67 (1.32–2.11)	
High	4.43 (3.75–5.25)		3.67 (2.95–4.56)	
Tumor size (cm)				
<5	1.00 (reference)	*	1.00 (reference)	*
5–10	1.82 (1.61–2.05)		2.84 (2.40–3.37)	
>10–15	2.71 (2.39–3.07)		3.86 (3.22–4.64)	
>15	4.56 (4.02–5.17)		5.33 (4.47–6.37)	
Marital status				
Married	1.00 (reference)	*	1.00 (reference)	*
Single	1.04 (0.94–1.14)		0.97 (0.83–1.14)	
Divorced/widowed	1.36 (1.23–1.50)		1.33 (1.20–1.48)	
Unknown	0.91 (0.72–1.15)		1.02 (0.76–1.38)	
Treatment				
Surgery only	1.00 (reference)	*	1.00 (reference)	*

	Age <65 y (*n* = 10,210)		Age >65 y (*n* = 5170)	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Neoadjuvant radiation	0.99 (0.85–1.14)		0.68 (0.55–0.84)	
Adjuvant radiation	0.85 (0.78–0.92)		0.79 (0.71–0.88)	

GU = genitourinary; GYN =gynecologic.

* $P < 0.01$ unless otherwise specified.