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Surgical Management of Adolescents and Young Adults With Gastrointestinal Stromal Tumors:

A US Population-Based Analysis

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Abstract

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IMPORTANCE—There is a dearth of population-based evidence regarding outcomes of the adolescent and young adult (AYA) population with gastrointestinal stromal tumors (GISTs).

OBJECTIVES—To describe a large cohort of AYA patients with GISTs and investigate the effect of surgery on GIST-specific survival (GSS) and overall survival (OS).

DESIGN, SETTING, AND PARTICIPANTS—This retrospective cohort study of 392 AYA patients and 5373 older adult (OA) patients in the Surveillance, Epidemiology, and End Results (SEER) database with GISTs histologically diagnosed from January 1, 2001, through December 31, 2013, with follow-up through December 31, 2015, compared the baseline characteristics of AYA (13–39 years old) and OA (≥ 40 years old) patients and among AYA patients stratified by operative management. Kaplan-Meier estimates were used for OS analyses. Cumulative incidence functions were used for GSS analysis. The effect of surgery on survival was evaluated with a multivariable Fine-Gray regression model.

EXPOSURE—Tumor resection.

MAIN OUTCOMES AND MEASURES—GIST-specific survival and OS.

RESULTS—This study included 392 AYA and 5373 OA patients diagnosed with GISTs (207 [52.8%] male AYA patients, 2767 [51.5%] male OA patients, 277 [70.7%] white AYA patients, and 3661 [68.1%] white OA patients). Compared with the OA patients, more AYA patients had small-intestine GISTs (139 [35.5%] vs 1465 [27.3%], $P = .008$) and were managed operatively (332 [84.7%] vs 4212 [78.4%], $P = .003$). Multivariable analysis of AYA patients found that nonoperative management was associated with a more than 2-fold increased risk of death from GISTs (subdistribution hazard ratio, 2.27; 95% CI, 1.21–2.25; $P = .01$). On subset analysis of 349 AYA patients with tumors of the stomach and small intestine, small-intestine location was associated with improved survival (OS: 91.1% vs 77.2%, $P = .01$; GSS: 91.8% vs 78.0%, $P = .008$). On subset analysis of 91 AYA patients with metastatic disease, operative management was associated with improved survival (OS: 69.5% vs 53.7%, $P = .04$; GSS: 71.5% vs 56.7%, $P = .03$).

CONCLUSIONS AND RELEVANCE—This study found that AYA patients are more likely to undergo surgical management than OA patients. Operative management is associated with improved OS and GSS in AYA patients, including those with metastatic disease.

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that are commonly found throughout the gastrointestinal tract.^{1,2} These tumors are characterized by immunohistochemical staining for KIT protooncogene receptor tyrosine kinase (*KIT*) (OMIM 164920) (CD117).³ In 2001, a GIST-specific histologic code was adopted, allowing for more accurate coding and reporting among national databases.^{3–6} Our group completed a contemporary analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database since the adoption of this histologic code and found that the US incidence of GISTs is 6.8 cases per million persons.^{7,8} These tumors are most commonly located in the stomach followed by the small intestine and predominantly affect older patients and male patients, as well as black individuals and Asian/Pacific Islanders.^{7–11}

The molecular signature of GISTs has been more completely understood during the past 2 decades.³ The 4 most common sporadic genetic alterations that lead to GISTs include gain-of-function mutations in *KIT* (*c-KIT*; 70%–80%), activating genomic alterations in platelet-

derived growth factor receptor α (*PDGFRA* [OMIM 173490]; 5%–10%), RAS pathway gene mutations (eg, B-Raf proto-oncogene, serine/threonine kinase [*BRAF*] [OMIM 164757]; KRAS proto-oncogene, GTPase [*KRAS*] [OMIM 190070]; or neurofibromin 1 [*NF1*] [OMIM 613113]; 10%–15%), and mutations or epigenetic alterations in the 4 succinate dehydrogenase (SDH) subunits (A [OMIM 600857], B [OMIM 185470], C [OMIM 602413], or D [OMIM 602690]; 2%).^{12–17} In addition, there are known inherited syndromes that include familial GIST syndromes associated with germline *KIT* and *PDGFRA* mutations, neurofibromatosis type 1 (von Recklinghausen disease) often associated with small-intestine GISTs, and Carney-Stratakis syndrome associated with gastric GISTs and paragangliomas.^{18–23} We now know that 85% of pediatric GIST cases lack *KIT* or *PDGFRA* mutations and have thus been called wild-type GISTs.^{17,24,25} Boikos et al¹⁷ recently studied 95 patients with wild-type GISTs seen at the National Institutes of Health. These patients had a mean age of 23 years, and 88% were *SDHB* deficient, highlighting the unique nature of pediatric, adolescent, and young adult GISTs. The study of cancers among the adolescent and young adult (AYA) population has increased substantially during the past decades.^{26–30} The definition of AYA varies but typically ranges from 13 to 40 years of age. This definition is based on differences between younger and older patients with regard to developmental and psychosocial needs, as well as genetic and pathologic differences in disease processes.^{27,28,31–33}

In addition, in many cancer types, survival is increasing at a slower rate within the AYA population compared with other age groups, highlighting the need for increased research on this vulnerable population.^{29,30,34,35} Currently, there is a dearth of knowledge regarding the outcomes of the AYA population with GISTs. Therefore, the aims of this study were to describe a large cohort of AYA patients with GISTs and to investigate the effect of operative management on overall survival (OS) and GIST-specific survival (GSS) using the National Cancer Institute's SEER database.

Methods

We identified patients in the SEER database diagnosed with GISTs from January 1, 2001, through December 31, 2013, with follow-up through December 31, 2015. SEER is a population-based cancer registry with 18 sites that cover approximately 30% of the United States.³⁶ Patients with GISTs were identified using a specific histologic code (*International Classification of Diseases for Oncology* [ICD-O] code 8936). Patient selection is outlined in Figure 1. The institutional review board, overseen by the University of California, San Diego, Human Research Protections Program, deems studies of this nature exempt from review, so no informed consent was required. Demographic variables, including age at diagnosis, sex, and race, were extracted from SEER. We designated patients diagnosed with GIST at ages 13 to 39 years as AYA patients and those diagnosed at or after 40 years of age as older adult (OA) patients. In the United States, puberty usually occurs between the ages of 10 and 14 years in girls and between the ages of 12 and 16 years in boys. To focus primarily on postpubescent adolescent patients who are also distinct from prepubescent patients, we excluded the very small number of pediatric patients who were younger than 13 years old ($n = 8$). The age range was selected based on current but evolving definitions of AYA in the literature; the World Health Organization defines adolescence as 10 to 19 years

of age, the National Comprehensive Cancer Network defines AYA as 15 to 39 years of age, and most studies focus on patients aged 15 to 40 years. Thus, we chose to include patients aged 13 to 39 years in our AYA cohort to embody both US and international standards.^{26–28,31,33,35} Registry regions were grouped based on geographic location: West (Alaska, California, Hawaii, Utah, Washington, and New Mexico), Midwest (Michigan, Iowa), South (Georgia, Kentucky, and Louisiana), and East (Connecticut, New Jersey). Tumor location was defined by *ICD-O* site; we investigated specific sites and sites grouped as stomach, small intestine, colon, rectum and anus, and other. Stage at presentation was defined as localized, regional, distant, or unknown. Tumor size was defined categorically as less than 2.0 cm, 2.0 through 9.9 cm, and 10.0 cm or greater. Beginning in 2004, the mitotic index was explicitly recorded. For patients with these data available, we defined a mitotic index variable as low (<5 mitoses per high-power field) or high (≥ 5 mitoses per high-power field). We defined a binary indicator variable to represent undergoing any cancer-directed surgery in which a specimen was sent for pathologic review (SEER site-specific surgery codes 20–90).

Demographic and baseline clinical characteristics were compared between AYA and OA patients using χ^2 tests for categorical variables and unpaired t tests for continuous variables. We excluded patients with multiple primary tumors from our analyses in the interest of accurately capturing GIST-specific mortality. Noncancer and cancer-specific deaths are explicitly captured in SEER; after limiting our cohort to include only those patients whose GIST was their first and only primary tumor, we were able to consider a cancer-related death as attributable to GIST. Survival time is defined as months from diagnosis to death or last known follow-up. We used competing risk analysis to investigate the effect of surgery on GIST-specific mortality, taking into account noncancer death as a competing event. We used multivariable Fine-Gray proportional hazards regression models to investigate the effect of surgery on GSS while adjusting for age at diagnosis, sex, race, year of diagnosis, geographic region, tumor site, summary stage, histologic grade, and mitotic index. Covariates for inclusion were defined a priori based on known and hypothesized confounders; however, histologic grade and mitotic index were removed from final models because of the large amount of missing data over concern for missing data bias. We performed subset analysis on AYA patients who presented with metastatic GISTs and used a cumulative incidence function to compare GSS between patients who did and did not undergo surgery, taking into account the competing risk of noncancer death. All data analysis was performed using SAS statistical software (SAS Institute Inc). Two-sided $P < .05$ was considered significant.

Results

Cohort Characteristics

This study included 392 AYA and 5373 OA patients diagnosed with GISTs (207 [52.8%] male AYA patients, 2767 [51.5%] male OA patients, 277 [70.7%] white AYA patients, and 3661 [68.1%] white OA patients). The demographic and clinical characteristics of the patients are compared in Table 1.

The stomach was the most common site of disease in both groups (AYA patients: 210 [53.6%]; OA patients: 3048 [56.7%]). However, there was a significantly higher proportion

of AYA patients who had GISTs located in the small intestine (139 [35.5%] vs 1465 [27.3%], $P = .008$). Those GISTs located in the colon or rectum and anus were less common in AYA patients (colon: 6 [1.5%] vs 143 [2.7%]; rectum and anus: 9 [2.3%] vs 165 [3.1%]; $P = .008$ for both). Most patients presented with localized disease (AYA patients: 212 [54.1%]; OA patients: 2937 [54.7%]), whereas 91 AYA patients (23.2%) and 1225 OA patients (22.8%) presented with distant disease. Tumors were most commonly 2.0 to 9.9 cm in size (AYA patients, 217 [55.4%]; OA patients, 2747 [51.1%]), although 110 AYA patients (28.1%) and 1481 OA patients (27.6%) had GISTs 10 cm or larger. Despite these similarities, the AYA patient population was more likely to undergo tumor resection than the OA population (332 [84.7%] vs 4212 [78.4%], $P = .003$).

Surgical Management of AYA Patients

Of the 392 AYA patients with GISTs, 332 (84.7%) were managed operatively (Table 2). The age and sex distributions were similar between AYA patients who did and did not undergo surgery. Fewer AYA patients with small GISTs underwent an operation (GISTs <2 cm: 27 [8.1%] vs 20 [33.3%], $P < .001$); similarly, fewer AYA patients with metastatic disease underwent an operation (55 [16.6%] vs 36 [60.0%], $P < .001$). Of AYA patients with GISTs located in the small intestine, more underwent an operation (127 [38.3%] vs 12 [20.0%], $P < .001$). There were no significant associations between registry region or race and operative management of GISTs.

Survival Analysis

The 5-year GSS was 83.3% for AYA patients and 75.4% for OA patients ($P < .001$) (Figure 2A). The 5-year OS was 82.4% for AYA patients and 67.1% for OA patients ($P < .001$), although this finding may be biased because of other comorbidities in the OA group (eFigure in the Supplement). In unadjusted analysis, 5-year GSS and OS were significantly higher in AYA patients who were managed operatively compared with those who were managed nonoperatively (GSS: 86.9% vs 64.3%, $P < .001$; OS: 86.1% vs 62.4%, $P < .001$) (Figure 2B and eFigure in the Supplement).

On multivariable analysis of the 392 AYA patients, non-operative management was associated with a 127% increased risk of GIST-specific death (subdistribution hazard ratio, 2.27; 95% CI, 1.21–2.25; $P = .01$) after adjusting for age, sex, race, year of diagnosis, and tumor size, site, and stage (Table 3). Male sex also increased the risk of death attributable to GISTs by 78% (subdistribution hazard ratio, 1.78; 95% CI, 1.04–3.04). Patients with regional or distant disease were at increased risk of GIST-specific death compared with patients with localized disease; similarly, patients with gastric tumors were at increased risk of GIST-specific death compared with patients with small-intestine tumors (Table 3).

Given the finding that tumor location was associated with survival, we performed subset analysis of AYA patients with tumors of the small intestine ($n = 139$) or stomach ($n = 210$). There was improved GSS and OS among AYA patients with tumors of the small intestine compared with those with tumors of the stomach (GSS: 91.8% vs 78.0%, $P = .008$; OS: 91.1% vs 77.2%, $P = .01$) (Figure 2C and eFigure in the Supplement).

Finally, given the lack of consensus on the management of many young patients with metastatic GISTs, we investigated the effect of resection in the subset of 91 AYA patients with metastatic disease. For these patients, the 5-year OS was 62.9% and the 5-year GSS was 65.3%. In stratified analysis, 5-year GSS and OS were significantly higher in AYA patients with metastatic disease managed operatively compared with those managed nonoperatively (GSS: 71.5% vs 56.7%, $P = .03$; OS: 69.5% vs 53.7%, $P = .04$) (Figure 2D and eFigure in the Supplement). Because of the limited number of patients who presented with distant disease, we were unable to perform multivariable analysis in this subset.

Discussion

This study provides the first statistical examination of a large cohort of AYA patients with GISTs since the adoption of precise immunohistochemical disease diagnosis in the United States. In general, the AYA cohort is an understudied population with unique characteristics, treatment responses, and psychosocial needs. Thus, we evaluated the characteristics of this cohort and investigated the effects of surgical intervention on patient survival, including among patients with metastatic disease. In our study, we found that AYA patients with GISTs have different characteristics than OA patients with GISTs, including a higher percentage of tumors in the small intestine and an increased likelihood of undergoing tumor resection. In addition, when evaluating AYA patients with metastatic disease, we found that there are significantly higher survival rates among patients selected for operative management compared with those selected for nonoperative management.

Some specific characteristics of the AYA cohort are similar to those currently reported among all patients with GISTs. Adolescent and young adult patients have an equal distribution between the sexes and most frequently had localized disease in the stomach.⁷ Among AYA patients, 23% presented with metastatic disease, which is comparable to previously reported rates among all patients with GISTs.^{7,37} In contrast to the OA cohort, AYA patients were more likely to be managed operatively irrespective of the stage of disease.

Limitations

When we investigated AYA patients with metastatic disease, we found that patients who were managed operatively had significantly higher GSS and OS compared with those who did not undergo surgery. There is potential for the introduction of selection bias related to patients undergoing operative management. Because of the limited amount of information collected by cancer registrars (ie, presence or absence of distant disease), it is not possible to quantify tumor burden or describe patterns of metastatic disease (eg, lymph node, liver, or peritoneal based), which may have significant bearing on clinical decision making. Thus, although patients with a single metastasis and patients with a larger tumor burden beyond the primary site technically have distant disease, the former patients may be more likely to undergo resection compared with the latter. In the current study, it is not possible to specifically attribute improved outcomes to the operative management or a lower metastatic disease burden. Despite these limitations, these results support the concept that, in properly selected patients, the presence of resectable metastatic disease should not preclude young

patients from undergoing surgical management because it is associated with improved survival end points. Our new findings complement prior studies^{38,39} that have found that operative management is associated with improved survival in adult patients with metastatic GISTs.

Numerous studies^{40–42} evaluating adult patients with GISTs have reported that GISTs located in the small intestine have poorer outcomes than those located in the stomach. We now report a new and contradictory finding in AYA patients. In the current study, small-intestine location is associated with improved OS and GSS when compared with gastric location. The underlying mechanism for these differences may be attributable to differences in tumor biology (eg, genetic mutations). For example, *NF1* mutant GISTs associated with neurofibromatosis type 1 most frequently occur in the small intestine, whereas *SDHB*-deficient GISTs (caused by *SDHA*, *SDHB*, *SDHC*, or *SDHD* mutations or *SDHC* epimutations) associated with Carney-Stratakis syndrome most frequently occur in the stomach.^{17,43} Further studies are necessary to elucidate the underlying biology or reasons leading to this unique finding among AYA patients compared with OA patients and current conventional wisdom in the GIST field.

In addition to the aforementioned limitations, our study is confined to describing the AYA population of the SEER database; underreporting of GISTs has been found at the national cancer registry level because cancer registrars inappropriately code GISTs as benign.⁴⁴ However, this factor is unlikely to introduce systemic bias because this misreporting is likely relatively random and evenly distributed across the reporting sites. In recent years, SEER has captured mitotic index and tumor grade; however, we found that this field was often blank during the period studied. Thus, we were unable to control for high-risk tumor biology in our model. Over time with improved recording, these additional data will be valuable. Finally, the SEER registry only robustly captures the first course of any cancer-directed therapy. Without linking to a prospective data set (such as the Medicare claims data, which adds value only in patients 65 years and older), we do not have data regarding the role of adjuvant therapy in the AYA population.

Conclusions

To our knowledge, this study is the first population-based analysis of GIST outcomes in the AYA population. These patients are more likely to undergo surgical management than OA patients. Moreover, operative management was associated with improved OS and GSS in all AYA patients, including among those with metastatic disease. Further studies are needed to understand the long-term outcomes of AYA patients with GISTs and to determine the role of surgery among patients with metastatic disease in a more personalized manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Roggin KK, Posner MC. Modern treatment of gastric gastrointestinal stromal tumors. *World J Gastroenterol*. 2012; 18(46):6720–6728. [PubMed: 23239909]
2. Rammohan A, Sathyanesan J, Rajendran K, et al. A gist of gastrointestinal stromal tumors: a review. *World J Gastrointest Oncol*. 2013; 5(6):102–112. [PubMed: 23847717]
3. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science*. 1998; 279(5350):577–580. [PubMed: 9438854]
4. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol*. 1998; 152(5):1259–1269. [PubMed: 9588894]
5. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. *Am J Surg Pathol*. 1983; 7(6):507–519. [PubMed: 6625048]
6. Sircar K, Hewlett BR, Huizinga JD, Chorneyko K, Berezin I, Riddell RH. Interstitial cells of Cajal as precursors of gastrointestinal stromal tumors. *Am J Surg Pathol*. 1999; 23(4):377–389. [PubMed: 10199467]
7. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. *Cancer Epidemiol Biomarkers Prev*. 2015; 24(1):298–302. [PubMed: 25277795]
8. Coe TM, Fero KE, Fanta PT, et al. Population-based epidemiology and mortality of small malignant gastrointestinal stromal tumors in the USA. *J Gastrointest Surg*. 2016; 20(6):1132–1140. [PubMed: 27025710]
9. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. *Am J Gastroenterol*. 2005; 100(1):162–168. [PubMed: 15654796]
10. Perez EA, Livingstone AS, Franceschi D, et al. Current incidence and outcomes of gastrointestinal mesenchymal tumors including gastrointestinal stromal tumors. *J Am Coll Surg*. 2006; 202(4):623–629. [PubMed: 16571433]
11. Rubin JL, Sanon M, Taylor DC, Coombs J, Bollu V, Sirulnik L. Epidemiology, survival, and costs of localized gastrointestinal stromal tumors. *Int J Gen Med*. 2011; 4:121–130. [PubMed: 21475624]
12. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. *Nat Rev Cancer*. 2011; 11(12):865–878. [PubMed: 22089421]
13. Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. *Lancet*. 2007; 369(9574):1731–1741. [PubMed: 17512858]
14. Fanta PT, Sicklick JK, Betz BL, Peterson MR. In vivo imatinib sensitivity in a patient with GI stromal tumor bearing a PDGFRA deletion DIM842–844. *J Clin Oncol*. 2015; 33(8):e41–e44. [PubMed: 24638008]
15. Liegl-Atzwanger B, Fletcher JA, Fletcher CDM. Gastrointestinal stromal tumors. *Virchows Arch*. 2010; 456(2):111–127. [PubMed: 20165865]
16. Agaram NP, Wong GC, Guo T, et al. Novel V600E *BRAF* mutations in imatinib-naïve and imatinib-resistant gastrointestinal stromal tumors. *Genes Chromosomes Cancer*. 2008; 47(10):853–859. [PubMed: 18615679]

17. Boikos SA, Pappo AS, Killian JK, et al. Molecular subtypes of *KIT/PDGFR* wild-type gastrointestinal stromal tumors: a report from the National Institutes of Health Gastrointestinal Stromal Tumor Clinic. *JAMA Oncol.* 2016; 2(7):922–928. [PubMed: 27011036]
18. Agaimy A, Hartmann A. Hereditary and non-hereditary syndromic gastrointestinal stromal tumours [in French]. *Pathologie.* 2010; 31(6):430–43. [PubMed: 20848108]
19. Neuhaus TM, Mansmann V, Merkelbach-Bruse S, et al. A novel germline *KIT* mutation (p.L576P) in a family presenting with juvenile onset of multiple gastrointestinal stromal tumors, skin hyperpigmentations, and esophageal stenosis. *Am J Surg Pathol.* 2013; 37(6):898–905. [PubMed: 23598963]
20. Stratakis CA, Carney JA. The triad of paragangliomas, gastric stromal tumours and pulmonary chondromas (Carney triad), and the dyad of paragangliomas and gastric stromal sarcomas (Carney-Stratakis syndrome): molecular genetics and clinical implications. *J Intern Med.* 2009; 266(1):43–52. [PubMed: 19522824]
21. Ponti G, Luppi G, Martorana D, et al. Gastrointestinal stromal tumor and other primary metachronous or synchronous neoplasms as a suspicion criterion for syndromic setting. *Oncol Rep.* 2010; 23(2):437–444. [PubMed: 20043105]
22. Kuroda N, Tanida N, Hirota S, et al. Familial gastrointestinal stromal tumor with germ line mutation of the juxtamembrane domain of the *KIT* gene observed in relatively young women. *Ann Diagn Pathol.* 2011; 15(5):358–361. [PubMed: 20952281]
23. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2014; 25(suppl 3):iii21–iii26. [PubMed: 25210085]
24. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup Phase III Trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. *J Clin Oncol.* 2008; 26(33):5360–536. [PubMed: 18955451]
25. Janeway KA, Albritton KH, Van Den Abbeele AD, et al. Sunitinib treatment in pediatric patients with advanced GIST following failure of imatinib. *Pediatr Blood Cancer.* 2009; 52(7):767–771. [PubMed: 19326424]
26. Bleyer WA. Cancer in older adolescents and young adults: epidemiology, diagnosis, treatment, survival, and importance of clinical trials. *Med Pediatr Oncol.* 2002; 38(1):1–10. [PubMed: 11835231]
27. Bleyer A. Young adult oncology: the patients and their survival challenges. *CA Cancer J Clin.* 2007; 57(4):242–255. [PubMed: 17626120]
28. Thomas DM, Seymour JF, O'Brien T, Sawyer SM, Ashley DM. Adolescent and young adult cancer: a revolution in evolution? *Intern Med J.* 2006; 36(5):302–30. [PubMed: 16650195]
29. Soliman H, Agresta SV. Current issues in adolescent and young adult cancer survivorship. *Cancer Control.* 2008; 15(1):55–62. [PubMed: 18094661]
30. Adolescent and Young Adult Oncology Progress Review Group. Closing the gap: research and care imperatives for adolescents and young adults with cancer. Bethesda, MD: National Institutes of Health; http://deainfo.nci.nih.gov/advisory/ncab/archive/139_0906/presentations/AYAO.pdf. Published 2006. Accessed October 8, 2016
31. Bleyer A, Barr R, Hayes-Lattin B, Thomas D, Ellis C, Anderson B. Biology and Clinical Trials Subgroups of the US National Cancer Institute Progress Review Group in Adolescent and Young Adult Oncology. The distinctive biology of cancer in adolescents and young adults. *Nat Rev Cancer.* 2008; 8(4):288–298. [PubMed: 18354417]
32. Bleyer A, Montello M, Budd T, Saxman S. National survival trends of young adults with sarcoma: lack of progress is associated with lack of clinical trial participation. *Cancer.* 2005; 103(9):1891–189. [PubMed: 15795902]
33. Bellizzi KM, Smith A, Schmidt S, et al. Adolescent and Young Adult Health Outcomes and Patient Experience (AYA HOPE) Study Collaborative Group. Positive and negative psychosocial impact of being diagnosed with cancer as an adolescent or young adult. *Cancer.* 2012; 118(20):5155–5162. [PubMed: 22415815]

34. Zebrack BJ. Psychological, social, and behavioral issues for young adults with cancer. *Cancer*. 2011; 117(10 suppl):2289–2294. [PubMed: 21523748]
35. Pollock BH, Birch JM. Registration and classification of adolescent and young adult cancer cases. *Pediatr Blood Cancer*. 2008; 50(5 suppl):1090–1093. [PubMed: 18360832]
36. Stiller CA, Benjamin S, Cartwright RA, et al. Patterns of care and survival for adolescents and young adults with acute leukaemia: a population-based study. *Br J Cancer*. 1999; 79(3–4):658–665. [PubMed: 10027346]
37. Harlan LC, Eisenstein J, Russell MC, Stevens JL, Cardona K. Gastrointestinal stromal tumors: treatment patterns of a population-based sample. *J Surg Oncol*. 2015; 111(6):702–70. [PubMed: 25900896]
38. Zaydfudim V, Okuno SH, Que FG, Nagorney DM, Donohue JH. Role of operative therapy in treatment of metastatic gastrointestinal stromal tumors. *J Surg Res*. 2012; 177(2):248–254. [PubMed: 22831567]
39. Mussi C, Ronellenfitsch U, Jakob J, et al. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? *Ann Oncol*. 2010; 21(2):403–408. [PubMed: 19628568]
40. Sicklick JK, Lopez NE. Optimizing surgical and imatinib therapy for the treatment of gastrointestinal stromal tumors. *J Gastrointest Surg*. 2013; 17(11):1997–2006. [PubMed: 23775094]
41. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol*. 2006; 23(2):70–83. [PubMed: 17193820]
42. Miettinen M, Lasota J. Gastrointestinal stromal tumors. *Gastroenterol Clin North Am*. 2013; 42(2):399–415. [PubMed: 23639648]
43. Gasparotto D, Rossi S, Polano M, et al. Quadruple-negative GIST is a sentinel for unrecognized neurofibromatosis type 1 syndrome. *Clin Cancer Res*. published online July 7, 2016.
44. Choi AH, Hamner JB, Merchant SJ, et al. Underreporting of gastrointestinal stromal tumors: is the true incidence being captured? *J Gastrointest Surg*. 2015; 19(9):1699–1703. [PubMed: 26001370]

Key Points

Question

What is the association of operative management with overall and gastrointestinal stromal tumor-specific survival in adolescent and young adult patients with gastrointestinal stromal tumors?

Findings

In this retrospective cohort study of 392 adolescent and young adult patients and 5373 older adult patients with histologically diagnosed gastrointestinal stromal tumors in the Surveillance, Epidemiology, and End Results database, the adolescent and young adult patients were more likely to undergo surgical management than the older adult patients.

Meaning

Additional studies are needed to understand the long-term outcomes of adolescent and young adult patients with gastrointestinal stromal tumors and to further define the role of operative management among patients with metastatic disease in a more personalized manner.

Figure 1. Patient Selection Criteria

Some patients met more than 1 exclusion criterion. AYA indicates adolescent and young adult; GIST, gastrointestinal stromal tumor; *ICD-O*, *International Classification of Diseases of Oncology*; and OA, older adult.

Figure 2. Gastrointestinal Stromal Tumor (GIST)-Specific Survival Among the Older Adult (OA) Cohort and Adolescent and Young Adult (AYA) Cohort

A, GIST-specific survival stratified by age group. Also shown are GIST-specific survival of AYA patients stratified by resection (B), tumor site (C), and resection in the setting of metastatic disease (D).

Table 1

Characteristics of AYA and OA Patients With GISTs

Characteristic	No. (%) of Patients		P Value (χ^2 Test)
	AYA Patients (Aged, 13–39 y) (n = 392 [6.8%])	OA Patients (Aged, 40y) (n = 5373 [93.2%])	
Age at diagnosis, y			
13–19	27 (6.9)	NA	<.001
20–29	92 (23.5)	NA	
30–39	273 (69.6)	NA	
40–49	NA	798 (14.9)	
50–59	NA	1344 (25.0)	
60–69	NA	1415 (26.3)	
70–79	NA	1143 (21.3)	
>80	NA	673 (12.5)	
Sex			
Male	207 (52.8)	2767 (51.5)	.62
Female	185 (47.2)	2606 (48.5)	
Race			
White	277 (70.7)	3661 (68.1)	.18
Black	62 (15.8)	964 (17.9)	
Asian/Pacific Islander	46 (11.7)	13 (0.2)	
American Indian/Alaska Native	3 (0.8)	702 (13.1)	
Unknown	4 (1.0)	33 (0.6)	
Tumor site			
Stomach	210 (53.6)	3048 (56.7)	.004
Small intestine	139 (35.5)	1465 (27.3)	
Rectum and anus	9 (2.3)	165 (3.1)	
Colon	6 (1.5)	143 (2.7)	
Esophagus	1 (0.3)	30 (0.6)	
Other	27 (6.9)	522 (9.7)	
Tumor stage			
Localized	212 (54.1)	2937 (54.7)	.99
Regional	57 (14.5)	767 (14.3)	
Distant	91 (23.2)	1225 (22.8)	
Unknown	32 (8.2)	444 (8.3)	
Tumor size, cm			
<2	47 (12.0)	945 (17.6)	.03
2–9.9	217 (55.4)	2747 (51.1)	
10	110 (28.1)	1481 (27.6)	
Unknown	18 (4.6)	200 (3.7)	

Characteristic	No. (%) of Patients		P Value (χ^2 Test)
	AYA Patients (Aged, 13–39 y) (n = 392 [6.8%])	OA Patients (Aged, 40y) (n = 5373 [93.2%])	
Mitotic index			
Low	69 (17.6)	1104 (20.6)	.35
High	22 (5.6)	317 (5.9)	
Unknown	301 (76.8)	3952 (73.6)	
Histologic grade			
Poorly differentiated or undifferentiated	43 (11.0)	526 (9.8)	.65
Well or moderately differentiated	70 (17.9)	915 (17.0)	
Unknown	279 (71.2)	3932 (73.2)	
Treatment			
Resection	332 (84.7)	4212 (78.4)	.003
No resection	60 (15.3)	1161 (21.6)	
Region			
West	217 (55.4)	2706 (50.4)	.20
South	86 (21.9)	1217 (22.7)	
East	60 (15.3)	1018 (19.0)	
Midwest	29 (7.4)	432 (8.0)	

Abbreviations: AYA, adolescent and young adult; GIST, gastrointestinal stromal tumor; NA, not applicable; OA, older adult.

Table 2

Characteristics of Adolescent and Young Adult Patients Stratified by Surgical Management

Characteristic	No. (%) of Patients		<i>P</i> Value (χ^2 and Fisher Exact Tests)
	Resection (n = 332 [84.7%])	No Resection (n = 60 [15.3%])	
Age at diagnosis, y			
13–19	26 (7.8)	1 (1.7)	.17
20–29	75 (22.6)	17 (28.3)	
30–39	231 (69.6)	42 (70.0)	
Sex			
Male	169 (50.9)	38 (63.3)	.08
Female	163 (49.1)	22 (36.7)	
Race			
White	241 (72.6)	36 (60.0)	.08
Black	51 (15.4)	11 (18.3)	
Asian/Pacific Islander	36 (10.8)	10 (16.7)	
American Indian/Alaska Native	2 (0.6)	1 (1.7)	
Unknown	2 (0.6)	2 (3.3)	
Tumor site			
Stomach	177 (53.3)	33 (55.0)	<.001
Small intestine	127 (38.3)	12 (20.0)	
Rectum and anus	6 (1.8)	3 (5.0)	
Colon	5 (1.5)	1 (1.7)	
Esophagus	0 (0.0)	1 (1.7)	
Other	17 (5.1)	10 (16.7)	
Tumor stage			
Localized	205 (61.8)	7 (11.7)	<.001
Regional	52 (15.7)	5 (8.3)	
Distant	55 (16.6)	36 (60.0)	
Unknown	20 (6.0)	12 (20.0)	
Tumor size, cm			
<2	27 (8.1)	20 (33.3)	<.001
2–9.9	200 (60.2)	17 (28.3)	
10	95 (28.6)	15 (25.0)	
Unknown	10 (3.0)	8 (13.3)	
Mitotic index			
Low	68 (20.5)	1 (1.7)	<.001
High	22 (6.6)	0 (0.0)	
Unknown	242 (72.9)	59 (98.3)	
Histologic grade			

Characteristic	No. (%) of Patients		<i>P</i> Value (χ^2 and Fisher Exact Tests)
	Resection (n = 332 [84.7%])	No Resection (n = 60 [15.3%])	
Poorly differentiated or undifferentiated	33 (9.9)	10 (16.7)	<.001
Well or moderately differentiated	69 (20.8)	1 (1.7)	
Unknown	230 (69.3)	49 (81.7)	
Region			
West	184 (55.4)	33 (55.0)	.91
South	71 (21.4)	15 (25.0)	
East	52 (15.7)	8 (13.3)	
Midwest	25 (7.5)	4 (6.7)	

Table 3

Multivariable Analysis of the Risk of Gastrointestinal Stromal Tumor-Specific Mortality in Adolescent and Young Adult Patients^a

Characteristic	SDHR (95% CI)	P Value
Resection		
Yes	1 [Reference]	NA
No	2.27 (1.21–2.25)	.01
Age	1.03 (0.98–1.07)	.25
Sex		
Female	1 [Reference]	NA
Male	1.78 (1.04–3.04)	.04
Race		
White	1 [Reference]	NA
Black	1.50 (0.84–2.69)	.17
Other	0.49 (0.20–1.19)	.11
Year of diagnosis	0.92 (0.82–1.03)	.16
Tumor size, cm		
<2	1 [Reference]	NA
2–9.9	0.70 (0.31–1.58)	.39
10	1.68 (0.79–3.57)	.18
Unknown	1.77 (0.56–5.54)	.33
Stage		
Localized	1 [Reference]	NA
Regional	2.54 (1.25–5.16)	.01
Distant	3.62 (1.85–7.11)	<.001
Unknown	2.44 (0.94–6.29)	.07
Site		
Small intestine	1 [Reference]	NA
Stomach	2.02 (1.16–3.53)	.01
Colon or rectum and anus	0.78 (0.15–4.17)	.73
Other or unknown	0.85 (0.34–2.11)	.77

Abbreviations: NA, not applicable; SDHR, subdistribution hazard ratio.

^aAge at diagnosis and year of diagnosis were included as continuous variables; all other covariates were categorical.