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Outcome of 1,000 patients with gastrointestinal stromal tumor (GIST) treated by surgery in the pre- and post-imatinib eras

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Abstract

Objective—To characterize the results of surgery for GIST in the pre- and post-imatinib eras at a single-institution and identify current prognostic clinicopathologic factors.

Summary Background Data—Imatinib has radically changed the management of GIST, yet the magnitude of impact on outcome across the spectrum of GIST presentation and relevance of historical prognostic factors are not well defined.

Methods—We retrospectively analyzed 1,000 patients who underwent surgery for GIST at our institution from 1982–2016. Patients were stratified by presentation status as primary tumor only (PRIM), primary with synchronous metastasis (PRIM+MET), or metachronous recurrence/metastases (MET), as well as imatinib era (before and after it became available). Cox proportional hazard models and Kaplan Meier methods were used to model and estimate overall and recurrence-free survival (OS, RFS).

Results—OS was longer in the imatinib era compared to the pre-imatinib era in each presentation group, including in Miettinen high risk primary tumors. Among PRIM patients from the pre-imatinib era, tumor site, size, and mitotic rate were independently associated with OS and RFS on multivariate analysis. PRIM patients in the imatinib era who received imatinib (neoadjuvant and/or adjuvant) had higher risk tumors, but after adjusting for treatment, only size >10cm remained independently prognostic of RFS (HR 3.85, 95% CI 2.00–7.40, $p < 0.0001$) and OS (HR 3.37, 95% CI 1.60–7.13, $p = 0.001$).

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Conclusions—Patients treated in the imatinib era had prolonged overall survival across all presentations. In the imatinib era, among site, size, and mitotic rate, high risk features were associated with treatment with the drug, but only size >10cm correlated with outcome. Imatinib should still be prescribed for patients with high risk features.

MINI-ABSTRACT

In the pre-imatinib era, primary tumor site, size, and mitotic rate predicted outcome as expected. In the modern era, survival was dramatically longer. While primary tumor high risk features were associated with imatinib treatment, only tumor size >10cm remained associated with outcome. Imatinib should be prescribed for high risk features.

INTRODUCTION

Since the discovery of a gain-of-function mutation in the *KIT* oncogene by Hirota in 1998¹, our understanding of GIST has evolved rapidly. We now know that GIST is the most common sarcoma.² MicroGISTs (<1cm) occur in up to one-third of older patients³. GIST arises from the interstitial cells of Cajal (ICC) and depends on the transcription factor ETV1⁴. *KIT* mutations are present in 75% of GISTs, while 10% instead have a *PDGFRA* mutation⁵. The remaining “wild-type” GISTs have a variety of other mutations and epimutations that may affect the SDH pathway⁶.

Imatinib is a small molecule tyrosine kinase inhibitor of KIT and PDGFR, originally used for chronic myelogenous leukemia⁵. Discovery of *KIT* mutations in GIST quickly led to the successful introduction of the drug in clinical trials⁷, in what became the modern paradigm for targeted therapy⁸. Despite a historical response rate of less than 10% to conventional systemic chemotherapy⁹, partial response or stable disease occurred in 80% of patients with advanced GIST treated with imatinib¹⁰. Median survival was 57 months¹¹, compared to 19 months historically¹².

Adjuvant imatinib was then tested in randomized clinical trials. After resection of primary GISTs ≥ 3 cm, one year of adjuvant therapy prolonged recurrence-free survival (RFS) without affecting OS^{13, 14}, with a similar result seen after two years of therapy in intermediate and high risk GISTs¹⁵, as defined by NIH consensus criteria¹⁰. Three years of adjuvant therapy proved superior to one year in modified NIH high risk patients, with prolonged RFS and a slight benefit in OS^{16, 17}. While further study is ongoing to determine the optimal duration of therapy, these trials have resulted in adjuvant imatinib becoming the standard of care for intermediate and high risk GIST. Neoadjuvant imatinib has been evaluated in locally advanced primary GIST, typically for difficult anatomic locations such as the gastroesophageal junction, duodenum, or rectum, or for large tumors requiring multivisceral resection^{18–20}. While these studies are mostly retrospective or single arm studies, neoadjuvant imatinib is safe and may facilitate R0 resection. Preoperative imatinib has been used before resection of metastatic GIST, with progression-free survival correlating to treatment response^{21, 22}.

In 2000, we reported the recurrence patterns and prognostic factors for 200 GISTs (80 of which were PRIM) treated at Memorial Sloan Kettering Cancer Center¹². While the

randomized controlled trials have established the efficacy of imatinib in GIST in the advanced^{10, 23} and adjuvant^{13–17} settings, here we present the magnitude of imatinib's effect across the spectrum of GIST presentation (PRIM, PRIM+MET, and MET) in the largest single-institution series of surgical management of GIST. Furthermore, we interrogate the factors associated with the PRIM+MET presentation, which are poorly characterized in the literature, and may require closer surveillance or alternate therapy to imatinib. Finally, the current relevance of traditional clinicopathologic prognostic factors in PRIM^{10, 12, 24–27} (i.e., site, size, and mitotic rate) is unclear.

METHODS

Patients and methods

From a prospective database, we identified patients who underwent surgery for GIST at our institution from July 1982 until April 2016. Diagnosis was confirmed using standard histology as well as immunohistochemistry for CD117 (KIT) and sometimes DOG-1. Patients were grouped by their presentation at our institution as primary tumor only (PRIM), primary with synchronous metastasis (PRIM+MET), or metachronous recurrence/metastasis (MET). Age, sex, characteristics of the primary tumor (size, site, and mitotic rate), histologic variant (spindle, epithelioid, or mixed), margins from first resection (R0/1/2), and significant dates (date of diagnosis, first surgery at MSKCC, recurrence, death, last follow-up), were queried. Fifty high-powered fields (HPF) were counted by the pathologist to determine mitotic rate²⁸. Site of metastasis, mutation (starting in the mid-2000s), and second malignancies were recorded. Postoperative surveillance included history, physical exam, and imaging every 3–6 months. The database was locked in June 2016. Approval for all research was obtained from the Institutional Review Board and was Health Insurance Portability and Accountability Act compliant.

Analysis and Statistics

Patients were stratified by treatment era, with the imatinib era defined as the earliest date when a patient in each group received the drug (8/2001, 3/2001, and 8/2000, respectively). Univariate associations used the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. OS and RFS were estimated from the time of the initial surgery at our institution using Kaplan Meier methods. For RFS, recurrence or death from any cause were counted as an event. Groups were compared using the log-rank test. Cox Proportional hazard models were used to model OS and RFS univariately and to build a multivariate model for each era. All statistical tests were two sided, and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed in SAS 9.4 (SAS Institute, Inc, Cary, NC) and R version 3.4.0.

RESULTS

Clinicopathologic features

Among 11,323 patients with soft tissue sarcomas treated at our institution from 1982–2016, there were 1,000 (8.8%) who underwent surgery for GIST with a median follow-up of 4.6 years (Table 1). Overall, 66% were PRIM patients, 13% PRIM+MET, and 21% MET. The

median time from disease presentation at an outside institution to surgery for MET at our institution was 4.1 years (interquartile range [IQR] 1.9–6.5). PRIM patients were older.

Stomach was by far the most common site of origin in PRIM, whereas small bowel and stomach tumors were seen in similar proportions in the PRIM+MET and MET groups. Notably, there were no rectal tumors in the PRIM+MET group. PRIM patients had smaller tumors, with only 21% >10cm vs. 55 and 41% in the other groups. Primary tumor mitotic rate was available for 74% of all patients and was >5/50 HPF in 34% of PRIM tumors compared to 79 and 81% in the other groups.

Mutational analysis (done by Sanger sequencing prior to 2010¹⁴ and MSK-IMPACT after²⁹) was available in 58% of patients. *KIT* mutations were most common at 75% of all patients, followed by 9% *PDGFRA* (Table 1). *KIT* mutations, when analyzed separately, were most often exon 11 deletions (49% of *KIT* mutations) or other exon 11 mutations (including point mutations and insertions; 27%). Exon 9 mutations were less common (10% of *KIT* mutations), and exon 13 and exon 17 were rare (2.1 and 0.9%). Mutations in multiple *KIT* exons comprised 11% of *KIT* mutations, but were rare in PRIM (2.2% vs. 16% in the other groups), likely reflecting secondary mutations in patients on long-term imatinib. *PDGFRA* mutations were found mostly in the PRIM group and were D842V or D842I (known to be imatinib-resistant) in 46% of patients with *PDGFRA* mutations.

Second malignancy

GIST has previously been reported to have a high prevalence of second malignancy (preceding or synchronous)³⁰, and since this would be expected to affect survival, we included it in our multivariate analysis. Overall, 22% of patients had a second malignancy (Table 1). PRIM patients had the highest rate (29 vs. 9 and 8%). In PRIM patients, among 190 second malignancies, 58 (31%) were synchronous, most commonly gastric, esophageal, colorectal, or pancreatobiliary carcinomas (Supplemental Table 1).

Recurrence and Survival

In patients with recurrence, the peritoneum was involved in 64%, liver in 50%, and both in 19% (Table 1). Rare sites included lymph nodes (2.3%), bone (1.1%), and lung (0.7%). The pattern of recurrence was similar by presentation group, except there was more peritoneal disease in the PRIM+MET group.

PRIM patients had longer median OS than PRIM+MET patients (13.6 vs. 5.3 years, Figure 1a). MET patients had a median OS of 4.0 years (Figure 1b)⁶. Patients in the MET group underwent surgery at our institution a median of 4.1 years after their initial outside surgery. Incomplete resection (R2) was rare in PRIM patients (2.4%) but common in the other groups (44 and 28%, Table 1). Remarkably, there was no difference between negative (R0) and microscopically positive (R1) margins in the 3 groups (Figures 1c–e).

Since imatinib has dramatically altered management of GIST⁵, we sought to dissect the impact of the drug. In order to avoid treatment bias in our retrospective analysis, we stratified each group by when the first patients in that group received imatinib (i.e., when imatinib became available or was employed for that indication). In each of the 3 groups,

survival in the imatinib era was longer. Five-year OS was 87, 63, and 51% in the imatinib era compared to 57, 19, and 35% in the pre-imatinib era, respectively (Figure 2a–c). Since the PRIM group was the largest and most homogenous because the patients had been followed at our institution from their initial diagnosis, we selected these patients for further analysis. Age, sex, and histologic variant were similar between the pre-imatinib and imatinib eras (Table 2). Although statistical comparison of mutation was not possible, the distributions were similar. There were more stomach tumors, and less small bowel, rectal, and other tumors in the imatinib era. Tumors were smaller in the imatinib era as only 16% were >10cm compared to 32%. R1 margins were more common in the pre-imatinib era. Overall, however, better prognostic features in the imatinib era did not explain the survival differences, since similar survival differences were also noted when only Miettinen high risk^{25, 31} patients were analyzed (Figure 2d).

Prognostic factors by era

Among 507 completely resected PRIM patients in the imatinib era, 162 patients received imatinib, 42 as neoadjuvant only, 86 as adjuvant only, and 34 as both (Supplemental Table 2). Patients who received imatinib were younger and were more likely to have a non-gastric site, large tumor size, high mitotic rate, and R1 margin. Tumor site, size, and mitotic rate are well-known traditional prognostic factors of recurrence after resection of primary GIST^{10, 12, 24–27}. In order to determine whether these factors remained important in the era of imatinib, we analyzed RFS separately in the pre-imatinib and imatinib (Table 3) eras using Cox proportional hazards models. In the pre-imatinib era, as expected, site (small bowel or rectal), large size, and high mitotic rate were independently associated with worse RFS on the multivariate analysis. However, in the imatinib era, despite adjusting for imatinib treatment and using a large cohort of patients, of these variables, only size >10cm remained statistically significant on multivariate analysis (HR 3.85, 95% CI 2.00–7.40, $p<0.0001$). Additionally, mixed histologic variant (HR 2.1, 95% CI 1.19–3.79, $p=0.01$) and second malignancy (HR 2.37, 95% CI 1.49–3.76, $p=0.0003$) emerged as negative predictors. Since patients who develop recurrence are often salvaged with further treatment including imatinib, we performed a similar analysis of OS with similar results, this time including the 16 patients who had R2 margins (Supplemental Table 3).

5-year RFS was longer in each size category (<5, 5–10, and >10cm) at 84, 78, and 61% in the imatinib era compared to 62, 49, and 36% in the pre-imatinib era (Figure 3a–c; $p=0.008$, 0.004, 0.016 respectively). Since the <5cm group was the largest ($n=327$), and there is debate about the size threshold to resect a small GIST, we examined it more closely. While there were 75 RFS events in this group (Figure 3a), there were only 11 recurrences of GIST and 5 deaths due to GIST. The other events were deaths due to other causes, usually due to second malignancies which were found in 40% of the patients with GISTs <5cm (Supplemental Table 4). In the <3cm subgroup ($n=150$), there were no recurrences or deaths due to GIST. In the 3–5cm subgroup ($n=177$), 10 of 11 recurrences were seen with non-gastric tumors and/or high mitotic rates. Only one of these patients had received imatinib.

Imatinib treatment

There were 76 PRIM patients treated with neoadjuvant treatment for a median of 6.5 months (IQR 3.3–8.5), with RECIST partial response, stable disease, and progressive disease in 32, 56 and 12%, respectively (not shown). There were 120 patients who received adjuvant imatinib for a median duration of 1.8 years (IQR 0.8–3.5). Most patients were Miettinen moderate and high risk (Figure 4a), although 12% of patients were low or very low risk. These were usually patients who had received the drug in clinical trials before more stringent criteria were adopted. Another 12% had unknown risk stratification due to lack of pre-treatment mitotic rate before neoadjuvant therapy – likely these were moderate or high risk patients. There were 20 recurrences among patients who received adjuvant therapy, of whom 7 died of disease, and another 8 died due to unknown (3) or other (4) causes (Figure 4b). Notably, 14 of these 20 patients developed recurrence with an IQR of 0.9–1.4 years after stopping imatinib. The other six recurred on the drug, with 4 of these recurring early in their course of therapy (0.5–1.6 years on imatinib) – these were later found to have resistant or less responsive mutations (*KIT* exon 9, *KIT* L576P, *PDGFRA*, and wild type). The other two recurred on long-term imatinib at 5.0 and 5.9 years, one with a known sensitive mutation in the primary (*KIT* exon 11 deletion/insertion) and the other unknown due to necrosis after neoadjuvant imatinib. Overall, patients who stayed on imatinib for more than 3 years (n=41; similar Miettinen criteria proportions as Figure 4a, data not shown) had a longer 5-year RFS (92 vs. 60%) than the 79 patients treated less than 3 years (Figure 4c).

DISCUSSION

We present here the largest single-institution comprehensive clinical series on the management of GIST. While large pre-imatinib pathologic series on GIST have been published by the Armed Forces Institute of Pathology^{25, 31–33} and others, those were based on specimens submitted for review. Our series is unique not only in number, but in its long time period, spanning the introduction of imatinib. There were clearly different outcomes among the three groups, with a median OS of 13.6 years in PRIM versus 5.3 in PRIM+MET, while MET had 4.0 years following a median additional 4.1 years from initial presentation elsewhere.

Not surprisingly, PRIM+MET and MET had higher risk clinicopathologic variables and mutation profiles than PRIM. For most of these factors, these two groups were indistinguishable, with more small bowel tumors and more high mitotic rate tumors than PRIM, at almost identical proportions. Genomically, PRIM+MET and MET had higher proportions of *KIT* exon 9 mutations, which carry a worse prognosis^{11, 34}. These groups also had more mutations in multiple *KIT* exons, which usually result from secondary mutations due to imatinib use^{35–37}. Despite these similarities between PRIM+MET and MET, several factors were associated with the more aggressive presentation in PRIM+MET. Peritoneal metastasis was more common in PRIM+MET. This group had the largest tumors, with 55% >10cm. R2 resection was associated with poor prognosis in all groups, but was most common in PRIM+MET, with almost half of these patients undergoing incomplete resection. In some cases, R2 resection in this group may reflect a staged resection, or intentionally leaving imatinib-responsive disease *in situ* while resecting progressing disease or a

symptomatic primary tumor. Likewise, mixed histologic variant has previously been shown to be a poor prognostic factor³⁸, and we saw the highest proportion of this subtype in PRIM+MET. Remarkably, there were no rectal tumors in PRIM+MET. Overall, we believe that better understanding of PRIM+MET, the presentation associated with the worst outcome, may lead to closer postoperative radiologic surveillance, and also help identify patients at risk of imatinib failure who may be candidates for more potent KIT inhibitors than imatinib, such as cabozantinib³⁹ or avapritinib⁴⁰.

While R2 margins were associated with poor prognosis in all groups, there was no difference between R0 and R1 margins. In PRIM, this is consistent with ACOSOG Z9001 data in which patients with R0 versus R1 margins had similar outcomes regardless of receiving imatinib⁴¹. We now extend this finding to the PRIM+MET and MET groups. Overall, our institutional approach to GIST of any presentation status is to attempt resection if a complete (R0/R1) resection is possible. In some cases, particularly for rectal GIST, it is reasonable to plan for a close or R1 margin and treat with adjuvant imatinib, if doing so allows for an organ-sparing approach. For example, in the imatinib era, 97% of patients with rectal GIST underwent organ-sparing surgery (local excision or low anterior resection), compared to only 41% in the pre-imatinib era⁴². Despite less radical surgery after resection of rectal GIST in the imatinib era, and approximately 1/3 positive margins in each era, there were no local recurrences in the imatinib era. Analogous considerations occur in the duodenum or gastroesophageal junction, and apply to debulking multiple peritoneal nodules, which we consider as an R1 resection.

Although formal statistical analysis of mutational subgroups was not possible due to so many categories, several observations are noteworthy. The minority (15%) of tumors were categorized as wild type, yet many of these were early cases in which only *KIT* and *PDGFRA* were tested and likely carried other undetected mutations or epimutations. Our institutional approach to genomic analysis has evolved; most GISTs are now interrogated with MSK-IMPACT²⁹, an institutional next-generation sequencing panel of all introns and exons of over 400 cancer-related genes including *SDH*, *NF1*, and others that have been found altered in GIST⁶. True wild-type GISTs are rare.⁶ Initially, we used imatinib empirically, but now generally perform mutational analysis first.

There have been several reports of the high incidence of second malignancies seen with GIST^{43–45}, including one from our institution³⁰. Here we present the largest single-institution analysis of second malignancy in GIST, demonstrating that among PRIM, one-third had a second malignancy, with one third of these synchronous and two-thirds preceding. This is a far higher incidence of cancer than that estimated by the American Cancer Society for the 60–69 year old age group (the median age of PRIM was 65), in which 14% of males and 10% of females would be expected to have cancer⁴⁶. The high incidence is likely related to our status as a tertiary referral center. Synchronous lesions were often incidental during resection or pathologic analysis for other cancers. Preceding lesions were often a patient's index cancer, and GIST was identified subsequently during surveillance. Second malignancies were most commonly coincident with small low risk GISTs, with second malignancies seen in 55% of <3cm tumors, compared to 28% of 3–5cm tumors. Among small tumors, recurrence of GIST was uncommon; in fact, we saw no

recurrences or deaths due to GIST among 150 primary tumors <3cm, although most of those tumors were gastric. The few recurrences in the 3–5cm group occurred in primary tumors with a high mitotic rate or non-gastric origin. Only one of those 11 patients had received imatinib, underscoring the importance of consideration of adjuvant imatinib in small tumors if other high risk features are present.

In the two pivotal trials of imatinib in advanced GIST^{10, 23}, the analyses were not distinguished by whether the patients had an unresectable primary GIST, a primary GIST with metastases, or metastases alone. Here we show the magnitude of imatinib's effect in PRIM+MET and MET patients undergoing surgery. We compared all patients selected for surgery at a single institution stratified based on the availability of the drug to that cohort at the time of their initial surgery, which may provide the most direct evidence. Directly proving an OS benefit of adjuvant imatinib, as opposed to just increasing RFS, has been difficult because recurrence was treated with crossover to imatinib or other tyrosine kinase inhibitors, and metastasectomy.^{13–17} OS was greater in PRIM patients in the imatinib era; although patients in the pre-imatinib era overall had higher risk primary tumors, the difference remained in the subset of high risk patients. Of note, we believe that the modern cohort includes more small, low risk gastric GISTs due to more frequent incidental detection from increased use endoscopy and cross-sectional imaging, as well as the NCCN recommendation that GISTs 2cm or greater should be resected. We did not assess the contribution of the individual components of imatinib therapy (neoadjuvant, adjuvant, or treatment for recurrent/metastatic disease) except we did find that PRIM patients who received chronic adjuvant imatinib 3 years had longer RFS than those who received <3 years despite similar risk group proportions. Although this subanalysis is underpowered, it is in agreement with data for the PERSIST5 trial, a single arm study of 5 years of adjuvant imatinib⁴⁷. Like PERSIST5, in our study, most recurrences in patients treated with adjuvant imatinib occurred after stopping the drug, and the few patients who recurred on long-term imatinib had less responsive or resistant mutations.

Primary tumor site, size, and mitotic rate are currently used clinically to estimate the risk of recurrence after resection, and to guide the need for adjuvant therapy^{10, 12, 24–27}. The pre-imatinib cohort recapitulated their prognostic importance. In contrast, only size >10cm remained independently predictive of RFS or OS in the imatinib era. This does not make site and mitotic rate irrelevant in the imatinib era, since high risk features were associated with imatinib treatment. Rather, these data imply that adjuvant imatinib was appropriately applied to high risk patients, and after treatment, tumor site and mitotic rate did not further estimate outcome. In the ACOSOG Z9001, all three factors were prognostic of recurrence on multivariate analysis after 1 year of adjuvant imatinib or placebo¹⁴. Our PRIM group received longer imatinib treatment (median 1.8 years, IQR 0.8–3.5), with neoadjuvant therapy given to 76 patients with locally advanced tumors, many of whom had rectal or duodenal (included as small bowel) tumors. Our cohort had a higher proportion of rectal tumors at 6.7% compared to 1.4% in the ACOSOG study. Mixed histologic variant was also independently predictive of outcome in the imatinib era. We believe that imatinib should still be prescribed to patients with high risk features, and once appropriately applied, further prognostication of outcome is limited to tumor size and presence of the mixed histologic subtype.

This study is limited by its retrospective nature. While we do report some baseline differences between cohorts, for example larger tumors in the earlier era, there may be additional undetected differences contributing to the associations. In comparing the outcomes of the pre-imatinib era to the imatinib era, we used an “intention to treat” type analysis. In other words, patients from the pre-imatinib era who survived into the imatinib era and received drug when indicated (33 of 246 patients, 13%) were still analyzed with the pre-imatinib era group. The net effect of these patients would have been to dampen the magnitude of the drug in the imatinib era, however, the effect remained striking. Meanwhile, 113 patients either died or had their last follow-up in the imatinib era. Only 9 of these patients had an indication to receive imatinib in the imatinib era, but were never treated. We believe this “intention to treat” analysis was less biased than grouping based on treatment alone, which would carry substantial treatment bias, with higher risk patients receiving the drug.

Thus, we show longer OS regardless of presentation group in the imatinib era. PRIM patients had lower risk primary tumor size, site, and mitotic rate and fewer *KIT* exon 9 and multiple exon mutations. The most aggressive presentation status (PRIM+MET) was associated with incomplete resection and mixed histologic subtype. Among PRIM patients in the imatinib era, high risk features were associated with imatinib treatment, but after accounting for treatment, only large tumor size remained independently prognostic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

OS after surgery by group and margins.

OS after initial surgery is shown for PRIM and PRIM+MET (**a**) and MET (**b**). OS by margin status is shown for PRIM (**c**), PRIM+MET (**d**), and MET (**e**). The number of patients at risk at each time point is indicated on the x axis. The inset in each panel denotes the median survival, 95% confidence interval of the median, and p-value for a log rank test when multiple groups were compared.

Figure 2:

OS after surgery by group, stratified by imatinib era.

OS after initial surgery is shown for PRIM (a), PRIM+MET (b) MET (c), and Miettinen high risk patients from the PRIM group (d) with imatinib era stratified by the date of the first patient in each group to receive the drug. The number of patients at risk at each time point is indicated on the x axis. The inset in each panel denotes the median survival, 95% confidence interval of the median, and p-value for a log rank test comparison between groups.

Figure 3:

RFS after surgery in the PRIM group size categories, stratified by imatinib era.

RFS after initial surgery is shown for PRIM patients with tumors <5cm (**a**), 5–10cm (**b**) and >10 (**c**), stratified by imatinib era. Along the x axis of each panel, the number of patients at risk at each time point is indicated. The inset in each panel denotes the median survival, 95% confidence interval of the median, and p-value for a log rank test comparison between groups.

Figure 4:

Adjuvant imatinib therapy in primary GIST.

Miettinen risk category (a) is listed for 120 patients who received adjuvant imatinib. Patients listed as unknown could not be classified due to lack of available mitotic rate to complete classification – these patients had undergone neoadjuvant imatinib therapy without pre-treatment core biopsy. (b) Time to recurrence or death is plotted relative to discontinuation of imatinib. Open circles represent patients who were alive at last follow-up or censored. Closed triangles represent GIST recurrence, while asterisks depict deaths due to unknown or other causes. The Y axis shows time from discontinuing the drug to the depicted event. The horizontal line represents the median time to recurrence or death from stopping the drug by the Kaplan-Meier method. Patients at 0 remained on the drug, and a negative number in one patient indicates staying on the drug briefly after recurrence was detected. (c) RFS is shown stratified by time on imatinib. The solid line represents all PRIM patients who received

adjuvant imatinib. The upper dashed line represents chronic (>3 years) imatinib, while the lower dashed line shows short term (≤3 years) treatment. The number of patients at risk at each time point is indicated on the x axis. The inset denotes the median survival, 95% confidence interval of the median, and p-value for a log rank test comparison between the <3 and ≥3 year groups.

Table 1:

Characteristics of 1,000 GISTs by presentation status.

For this and all following tables, percentages reflect the proportion of those where variable is known, with unknowns excluded from statistical analysis.

			PRIM n=660	PRIM+MET n=128	MET n=212	p-value
Age at first surgery (yrs)	Median (range)	61.0 (8.1–94.7)	64.5 (8.1–94.7)	56.6 (22.6–85.3)	54.7 (9.4–85.2)	<0.001
Sex	F	468 (46.8)	326 (49.4)	47 (36.7)	95 (44.8)	0.025
	M	532 (53.2)	334 (50.6)	81 (63.3)	117 (55.2)	
Survivor follow-up (yrs)	Median (range)	4.6 (0.0–29)	4.6 (0.0–28)	4.4 (0.20–22)	5.3 (0.03–29)	
Primary tumor site	Stomach	606 (60.6)	467 (70.8)	59 (46.1)	80 (37.7)	<0.001
	Small Bowel	264 (26.4)	116 (17.6)	55 (43)	93 (43.9)	
	Rectum	51 (5.1)	44 (6.7)	0 (0)	7 (3.3)	
	Other ^a	79 (7.9)	33 (5)	14 (10.9)	32 (15.1)	
Primary tumor Size (cm)	<5	377 (38.7)	327 (49.5)	17 (13.5)	33 (17.5)	<0.001
	5–10	314 (32.2)	195 (29.5)	40 (31.7)	79 (41.8)	
	>10	284 (29.1)	138 (20.9)	69 (54.8)	77 (40.7)	
	Unknown	25 (N/A)	0 (N/A)	2 (N/A)	23 (N/A)	
Primary tumor mitotic rate per 50 HPF	5	406 (54.8)	370 (66)	13 (21)	23 (19.5)	<0.001
	>5	335 (45.2)	191 (34)	49 (79)	95 (80.5)	
	Unknown	259 (N/A)	99 (N/A)	66 (N/A)	94 (N/A)	
Histologic variant	Spindle	485 (73.8)	355 (76.8)	59 (67)	71 (66.4)	0.047
	Epithelioid	88 (13.4)	55 (11.9)	12 (13.6)	21 (19.6)	
	Mixed	84 (12.8)	52 (11.3)	17 (19.3)	15 (14)	
	Unknown	343 (N/A)	198 (N/A)	40 (N/A)	105 (N/A)	
Margins^b	R0	744 (75)	597 (90.5)	49 (38.6)	98 (47.8)	<0.001
	R1	118 (11.9)	47 (7.1)	22 (17.3)	49 (23.9)	
	R2	130 (13.1)	16 (2.4)	56 (44.1)	58 (28.3)	
	Unknown	8 (N/A)	0 (N/A)	1 (N/A)	7 (N/A)	
Site of metastasis^c						
<i>any</i>	No	557 (55.7)	557 (84.4)	0 (0)	0 (0)	c
	Yes	417 (42.8)	82 (12.8)	128 (100)	207 (100)	
<i>any liver</i>	No	207 (49.6)	40 (48.8)	61 (47.7)	106 (51.2)	
	Yes	210 (50.4)	42 (51.2)	67 (52.3)	101 (48.8)	
<i>liver only</i>	No	293 (70.3)	58 (70.7)	85 (66.4)	150 (72.5)	
	Yes	124 (29.7)	24 (29.3)	43 (33.6)	57 (27.5)	
<i>any peritoneum</i>	No	151 (36.2)	36 (43.9)	53 (41.4)	62 (30)	
	Yes	266 (63.8)	46 (56.1)	75 (58.6)	145 (70)	
<i>peritoneum only</i>	No	230 (55.2)	51 (62.2)	73 (57)	106 (51.2)	
	Yes	187 (44.8)	31 (37.8)	55 (43)	101 (48.8)	

			PRIM n=660	PRIM+MET n=128	MET n=212	p-value
liver and peritoneum	No	339 (81.3)	67 (81.7)	108 (84.4)	164 (79.2)	
	Yes	78 (18.7)	15 (18.3)	20 (15.6)	43 (20.8)	
any other ^d	No	398 (95.4)	73 (89)	122 (95.3)	203 (98.1)	
	Yes	19 (4.6)	9 (11)	6 (4.7)	4 (1.9)	
Second malignancy						
any	No	782 (78.2)	470 (71.2)	116 (90.6)	196 (92.5)	<0.001
	Yes	218 (21.8)	190 (28.8)	12 (9.4)	16 (7.5)	
prior	No	835 (83.5)	521 (78.9)	119 (93)	195 (92)	<0.001
	Yes	165 (16.5)	139 (21.1)	9 (7)	17 (8)	
synchronous	No	938 (93.8)	602 (91.2)	125 (97.7)	211 (99.5)	<0.001
	Yes	62 (6.2)	58 (8.8)	3 (2.3)	1 (0.5)	
Mutation ^f	KITexon 9	44 (7.6)	13 (4.1)	11 (10.9)	20 (12.4)	f
	KITexon 11 deletion	216 (37.1)	128 (40)	43 (42.6)	45 (28)	
	KITexon 11 other	117 (20.1)	76 (23.8)	11 (10.9)	30 (18.6)	
	KITexon 13	9 (1.5)	4 (1.3)	3 (3)	2 (1.2)	
	KITexon 17	4 (0.7)	1 (0.3)	0 (0)	3 (1.9)	
	KIT multiple exons	48 (8.2)	7 (2.2)	16 (15.8)	25 (15.5)	
	PDGFRA D842V/I	23 (4)	20 (6.3)	0 (0)	3 (1.9)	
	PDGFRA other	27 (4.6)	20 (6.3)	3 (3)	4 (2.5)	
	NFI	5 (0.9)	4 (1.3)	0 (0)	1 (0.6)	
	SDH	3 (0.5)	0 (0)	2 (2)	1 (0.6)	
	Wild type ^e	86 (14.8)	47 (14.7)	12 (11.9)	27 (16.8)	
	Unknown	418 (N/A)	340 (N/A)	27 (N/A)	51 (N/A)	

^aOther primary sites included 12 (1.2%) colon, 9 (0.9%) esophagus, 2 (0.2%) pancreas, 1 (0.1%) appendix, and 1 (0.1%) perineum. The remainder of this group was comprised of tumors designed as omentum, mesentery, retroperitoneum or abdomen where a source organ could not be determined.

^bR2 margins include tumor rupture

^cPercentages in top category 'any' metastasis rows reflect percentage of total patients in that group. Percentages in the other rows (i.e. 'any liver') reflect percentages of those who developed metastases from that group. For PRIM, metastatic site denotes the site of metastasis in the 103 patients who recurred. For PRIM, MET, and PRIM+MET there were 21, 0, and 5 patients per group, respectively, for whom the site of metastasis was unknown, and these were not included in the percentages listed. There were too many categories for meaningful statistical comparison.

^dOther metastatic sites occurred either in isolation or concomitantly with liver and/or peritoneal metastasis and included 10 lymph node (2.3% of 443 total patients with metastases), 5 bone (1.1%), 3 lung (0.7%), and 1 each chest, chest wall, bronchus, perineum, paraspinal, and adrenal (0.7% each).

^eearly mutational analysis included only *KIT* and *PDGFRA*, so some "wild type" likely carry other mutations/epimutations

^fThere were too many categories (many with low numbers) for statistical comparison. Values listed here represent proportions of all mutations. Note that percentages in results section (where noted) reflect proportion of all *KIT* mutations.

Table 2:

Characteristics of completely resected^a primary GISTs (PRIM) by imatinib era.

		Pre-imatinib era (n=137)	Imatinib era (n=507)	p-value
Age at first Surgery (yrs)	Median (range)	66.6 (15.8–94.7)	64.0 (8.1–90.1)	0.657
Sex	F	57 (41.6)	260 (51.3)	0.054
	M	80 (58.4)	247 (48.7)	
Primary tumor site	Stomach	83 (60.6)	380 (75)	0.003
	Small Bowel	29 (21.2)	83 (16.4)	
	Rectum	14 (10.2)	28 (5.5)	
	Other	11 (8)	16 (3.2)	
Primary tumor Size (cm)	<5	46 (33.6)	281 (55.4)	<0.001
	5–10	47 (34.3)	144 (28.4)	
	>10	44 (32.1)	82 (16.2)	
Primary tumor mitotic rate per 50 HPF	5	61 (54)	306 (70)	0.002
	>5	52 (46)	131 (30)	
	Unknown	24 (N/A)	70 (N/A)	
Histologic variant	Unknown	117 (N/A)	72 (N/A)	0.268
	Epithelioid	3 (15)	52 (12)	
	Mixed	0 (0)	52 (12)	
	Spindle	17 (85)	331 (76.1)	
Margins ^a	R0	121 (88.3)	476 (93.9)	0.040
	R1	16 (11.7)	31 (6.1)	
Second malignancy ^b	No	108 (78.8)	348 (68.6)	0.020
	Yes	29 (21.2)	159 (31.4)	
Mutation	<i>KIT</i> exon 9	3 (2.9)	10 (4.8)	^c
	<i>KIT</i> exon 11 deletion	44 (42.7)	78 (37.1)	
	<i>KIT</i> exon 11 other	21 (20.4)	55 (26.2)	
	<i>KIT</i> exon 13	0 (0)	4 (1.9)	
	<i>KIT</i> exon 17 only	1 (1)	0 (0)	
	<i>KIT</i> mult exons	1 (1)	6 (2.9)	
	<i>PDGFRA</i> D842V/I	3 (2.9)	17 (8.1)	
	<i>PDGFRA</i> other	4 (3.9)	16 (7.6)	
	<i>NFI</i>	0 (0)	4 (1.9)	
	<i>SDH</i>	0 (0)	0 (0)	
	Wild type (WT)	26 (25.2)	20 (9.5)	
	Unknown	34 (N/A)	297 (N/A)	

^aR2 margins were excluded from this analysis of disease-free survival.

^bAny preceding or synchronous second malignancy

^cThere were too many categories (many with low numbers) for statistical comparison.

Table 3:

Univariate and multivariate analysis of RFS in the pre-imatinib era (**top**) and imatinib era (**bottom**).

PRE-IMATINIB ERA ^a			Univariate Analysis		Multivariate Analysis	
	Class value	Reference	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at first surgery (yrs)	N/A	N/A	1.01 (0.998–1.029)	0.088	1.02 (1.002–1.037)	0.030
Sex	M	F	1.52 (0.99–2.33)	0.053	-	-
Primary tumor site	Small Bowel	Stomach	1.35 (0.81–2.25)	0.250	2.13 (1.67–3.90)	0.014
	Rectum		2.63 (1.41–4.91)	0.002	2.25 (1.08–4.68)	0.030
	Other		1.47 (0.73–2.95)	0.280	1.36 (0.65–2.83)	0.409
Primary tumor size (cm)	5–10	<5	1.21 (0.73–2.00)	0.466	1.72 (0.96–3.09)	0.071
	>10		1.82 (1.10–3.01)	0.020	2.63 (1.44–4.8)	0.002
Primary tumor mitotic rate per 50 HPF	>5	5	2.56 (1.65–3.99)	<0.001	2.80 (1.71–4.61)	<0.001
Margins ^b	R1	R0	1.10 (0.58–2.07)	0.769	-	-
Second Malignancy ^c	Yes	No	0.79 (0.47–1.32)	0.370	-	-

IMATINIB ERA			Univariate Analysis		Multivariate Analysis ^d	
	Class value	Reference	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at first surgery (yrs)	N/A	N/A	1.02 (1.00–1.04)	0.014	-	-
Sex	M	F	1.24 (0.85–1.81)	0.274	-	-
Primary tumor site	Small Bowel	Stomach	1.29 (0.78–2.11)	0.318	-	-
	Rectum		0.93 (0.38–2.30)	0.873	-	-
	Other		2.06 (0.95–4.47)	0.068	-	-
Primary tumor size (cm)	5–10	<5	1.43 (0.90–2.25)	0.138	1.66 (0.96–2.87)	0.070
	>10		2.72 (1.71–4.32)	<0.001	3.85 (2.00–7.40)	<0.001
Primary tumor mitotic rate per 50 HPF	>5	5	1.91 (1.21–3.00)	0.005	-	-
Histologic variant	Epithelioid	Spindle	1.25 (0.63–2.47)	0.526	1.09 (0.55–2.16)	0.811
	Mixed		2.64 (1.50–4.66)	<.001	2.1 (1.19–3.79)	0.011
Margins ^b	R1	R0	1.29 (0.63–2.65)	0.492	-	-
Imatinib treatment	Any	None	1.78 (1.21–2.63)	0.004	1.11 (0.65–1.91)	0.693
Second Malignancy ^c	Yes	No	1.90 (1.30–2.77)	<0.001	2.37 (1.49–3.76)	0.0003

^a Histologic variant was not routinely recorded in the pre-imatinib era.

^b R2 margins were excluded from this analysis of recurrence-free survival.

^c Any preceding or synchronous second malignancy

^d All statistically significant values from the univariate analysis were included in the initial multivariate model. The least significant values (p>0.05) were removed stepwise to provide the final strongest model which is shown. Although age and mitotic rate were significant univariately in the imatinib era, they were never significant on multivariate analysis. Imatinib treatment was left in the final model to adjust for any undetected treatment bias.