Chapter 4
Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GIST) were defined as a distinct biological entity in 1998, with the finding of its strong association with mutations in the oncogenes KIT or PDGFRA. Previously, GISTs were considered to be smooth muscle neoplasms often classified as leiomyosarcoma or gastrointestinal autonomic nerve tumors (GANT), or combinations of both. Definition and cellular origin appears to be the interstitial cell of Cajal or a precursor [1]. They commonly present as mass lesions, intra-abdominally, often of large size and with rupture and/or metastatic disease. GISTs make up one third of all visceral sarcomas (Fig. 4.1). Our original report [2] described 200 gastrointestinal stromal tumors, which was approximately 6 % of the 3500 patients with sarcoma admitted to our institution. Age and sex distribution are shown in Fig. 4.2, and lesions are distributed in the stomach, more than the small intestine, and more than other sites (Fig. 4.3). An example of a GIST of the stomach is demonstrated in Fig. 4.4.

4.1 Imaging

Imaging is usually by computed tomography or MRI, designed to examine the primary lesion, site of origin, as well as the presence or absence of metastasis (Figs. 4.5 and 4.6). ^{18}F-FDG PET-CT has been used to identify occult metastatic disease before primary surgery is conducted and can in principle be used to follow the response to metastatic disease. However, in the latter case, routine anatomic imaging with contrast yields nearly identical data with much lower cost and with lower exposure to radioactive agents.

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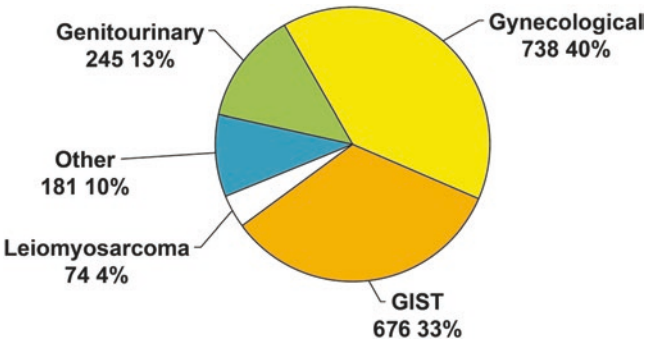

Fig. 4.1 Distribution by site for adult patients with visceral sarcomas. MSKCC 7/1/1982–6/30/2010, $n = 1864$. *GIST* gastrointestinal stromal tumor

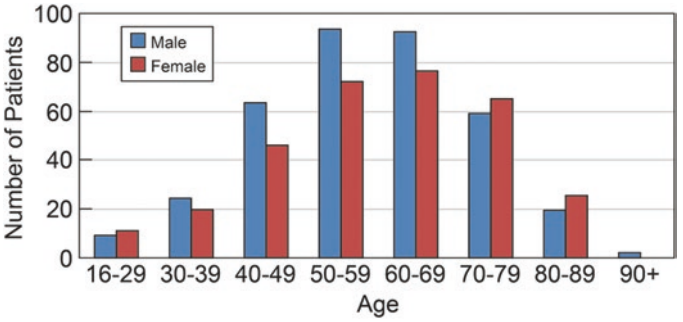

Fig. 4.2 Distribution by age and gender for adult patients with gastrointestinal stromal tumors (GIST). MSKCC 7/1/1982–6/30/2010, $n = 676$

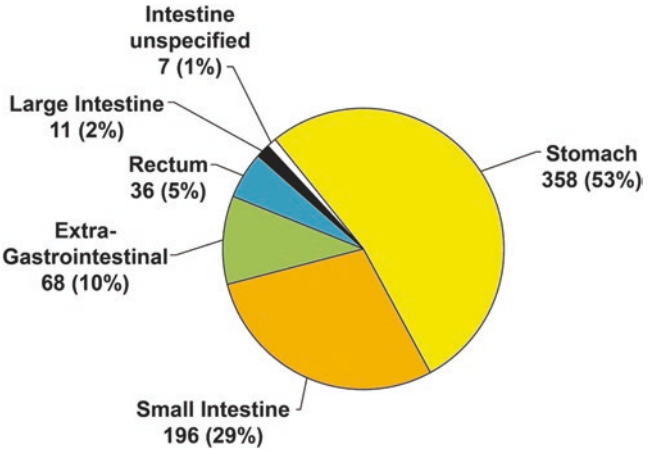

Fig. 4.3 Distribution by visceral site of adult patients with GIST. MSKCC 7/1/1982–6/30/2010, $n = 676$

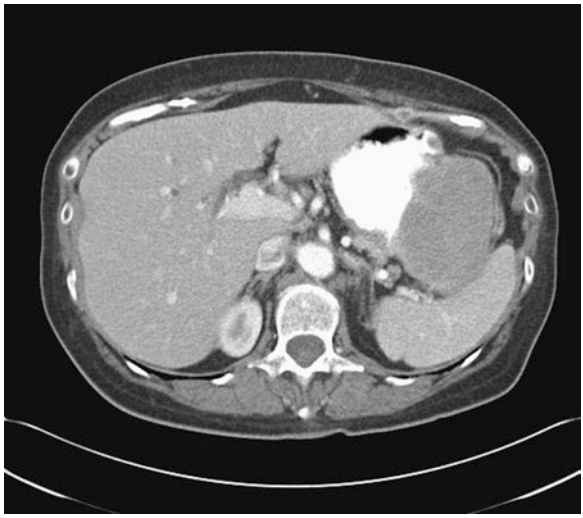

Fig. 4.4 Contrast-enhanced axial CT of a primary large gastric GIST arising from the greater curvature, showing a large gastric wall mass, likely hypodense to spleen owing to central tumor necrosis

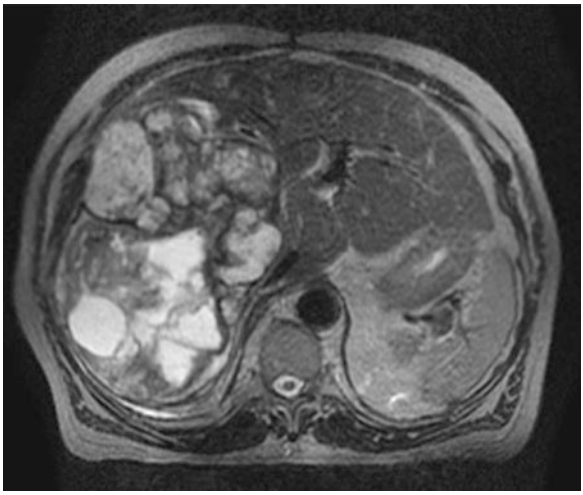

Fig. 4.5 Axial T2 weighted MRI with contrast showing metastatic GIST to liver

4.2 Familial GIST

Familial GIST is a rare hereditary predisposition to develop GIST due to a germ line mutation. Various kindreds have been described; patients typically have multiple tumors involving both stomach and jejunum and occasionally develop bowel diverticuli. In familial GIST, the mean age at diagnosis was 53 [3]. The majority of

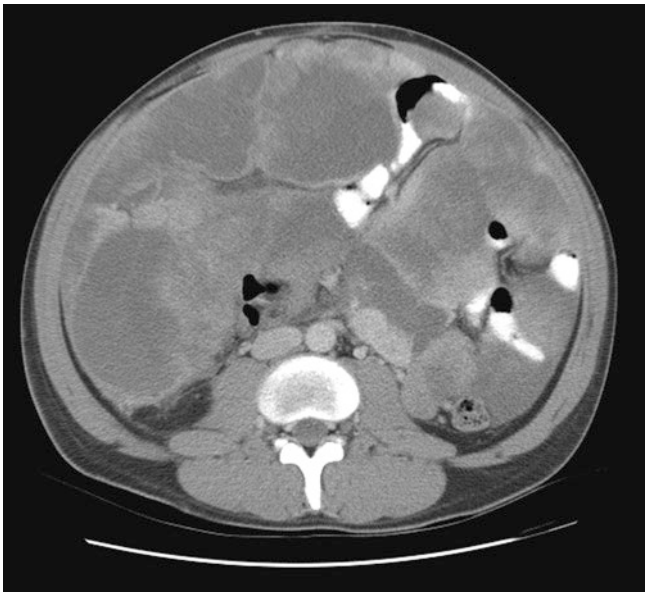

Fig. 4.6 Axial contrast-enhanced CT of extensive peritoneal metastases from GIST

tumors have a low mitotic rate. Mutations may affect *KIT* or rarely *PDGFRA* in these kindreds. Altered pigmentation patterns are common, with increased pigment on the hands, feet, axilla, or groin (Fig. 4.7), and symptoms similar to irritable bowel syndrome from GI dysmotility are common, from hypertrophy of their myenteric plexus. The observation that *KIT* mutations may be inherited was used to develop murine models harboring a germ line gain of function mutation [4].

Interestingly, multiple GIST also have been observed in patients with type I neurofibromatosis [5]; however, they often lack the presence of *KIT* or *PDGFRA* mutations. GIST is also characteristic of Carney-Stratakis dyad, along with paragangliomas, and these tumors characteristically harbor loss of function mutations in the succinate dehydrogenase complex (SDH), e.g., mutation of the gene encoding subunit B of this citric acid cycle enzyme (*SDHB*), though *SDHA* or *SDHC* can be affected instead.

Treatment of familial GIST is directed at removal of the largest or symptomatic lesion when feasible. Resection should be as conservative as possible, since all sites along the GI tract are at risk for development of GIST. Continuous long-term follow-up with symptomatic treatment appears appropriate. Imatinib is an effective treatment for unresectable or metastatic disease; however, long-term therapy in a preventative, other than in an adjuvant setting, is unlikely to be tested.

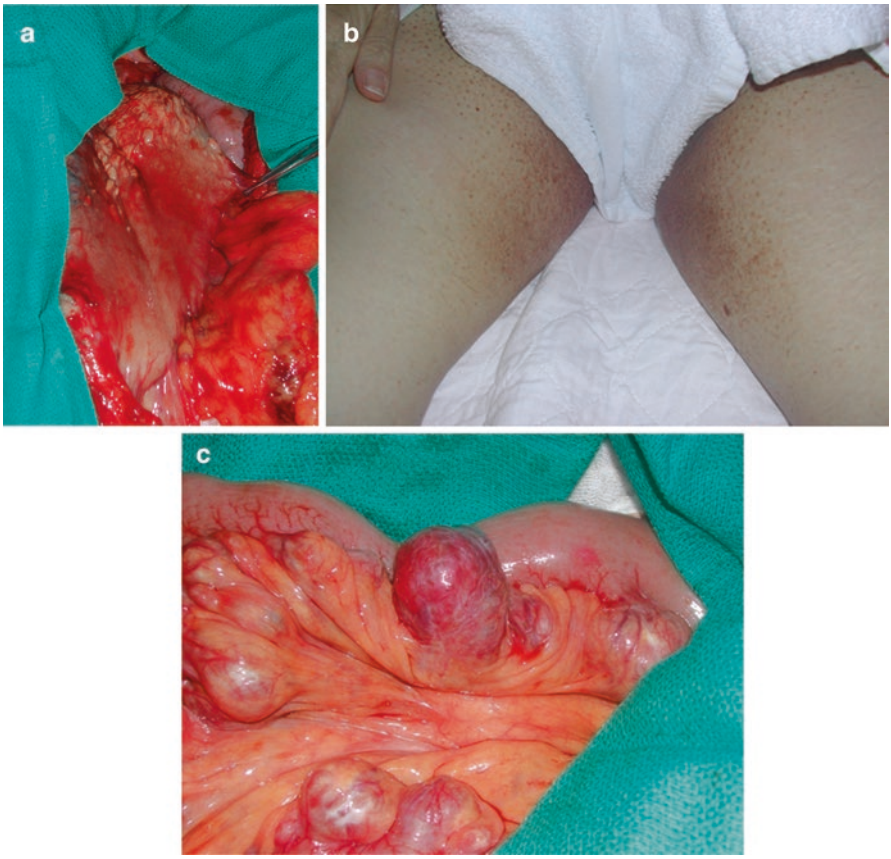

Fig. 4.7 Familial GIST with multifocal gastric and small bowel lesions (**a**), with characteristic inner thigh pigmentation (**c**) and small bowel diverticula (**b**)

4.3 Natural History

Prior to the availability of tyrosine kinase inhibitors (TKI) [6], GIST patients had a 2-year survival of 40 % and a <25 % 5-year survival. Outcome for primary completely resected tumors was more favorable, especially for stomach and small intestine rather than for colon and rectum (Fig. 4.8) [7]. Primary tumor site, size, mitotic rate <5 mitosis per 50 high-powered fields, disease-free interval, and surgical resection were all independent predictors of improved survival. Mutational status did not predict outcome independently. It is recognized that *KIT* genetic alterations, such as deletion in exons 557-558, is a poor prognostic marker for recurrence.

With the advent of TKI, improvement in survival was clear for patients with metastatic disease. In an effort to define the role of adjuvant tyrosine kinase inhibitor, we developed a nomogram to predict relapse-free survival after operation in the absence of adjuvant therapy. This was based on the examination of 127 patients and validated

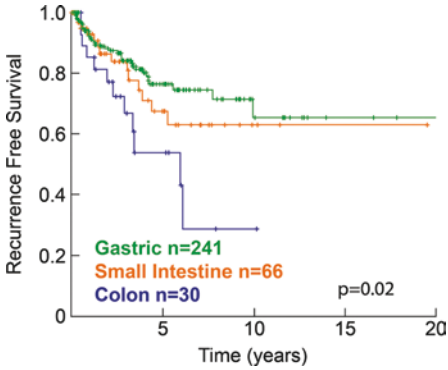

Fig. 4.8 Recurrence-free survival for adult patients with complete resection of localized (GIST) by tumor location. MSKCC 7/1/1982–6/30/2010, $n=337$

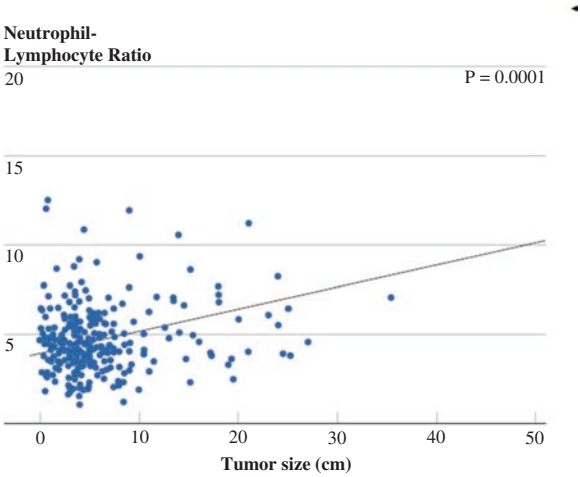

Fig. 4.9 Tumor size is significantly (P<0.01, Pearson correlation coefficient +36) associated with blood NLR ($n=271$). Patients with large tumors have high NLR. Lymphocytes. With permission from: Perez DR, et al. Ann Surg Oncol. 20(2):593–599, 2013

utilizing an additional independent cohort. This nomogram had a concordance probability of 0.78 in the Memorial Sloan Kettering Cancer Center dataset and 0.80 in the validation cohort. We were not able to show that inclusion of mutation status in the nomogram improved discriminatory ability of the nomogram. Utilizing this pre-tyrosine kinase dataset, we were able to show that mitotic rate, size, and location all independently predicted recurrence after resection of primary GIST. Newer versions of GIST nomograms have improved discrimination of outcome based on mitotic rate, which is a binary variable in the original nomogram [8]. In terms of risk stratification, gene expression profiling, examining for genes involved in cell checkpoints and chromosomal instability, seems to show a substantial ability to discern between people who will fare well vs. those who do not [9]. Lastly, an interesting observation is that the blood neutrophil to lymphocytic ratio can be prognostic for outcomes [10]. (Fig. 4.9)

Stratification of risk by anatomic site, size, mitotic rate, and tumor rupture has been captured for patients with primary GIST using heat maps, which allow determination of risk of primary GISTs across multiple continuous variables, and is presently more

effective than currently existing staging systems for discussing risk with patients [11]. Taking advantage of the SSG XVIII study data, discussed above and below, it is possible to assign a risk score for recurrence after use of adjuvant imatinib as well [12].

4.4 Diagnosis, Molecular Pathology

Based on autopsy series, GIST are the most common sarcoma if 'sarcomalets', such as microscopic GIST and incidentally noted GIST, are included. Without such caveats, GIST are the most common mesenchymal neoplasms of the gastrointestinal tract. Nearly all GIST express the receptor tyrosine kinase KIT, and most have a mutation in the *KIT* gene. Microscopic imaging of an epithelioid GIST with KIT staining is shown in Fig. 4.10. Chi et al. demonstrated oncogene *ETV1* is overexpressed in GIST and also characteristic of its neoplastic phenotype [13]. Less commonly, GIST bears mutations in *PDGFRA*. Five to seven percent of GIST do not have detectable *KIT* or *PDGFRA* and were generally termed "wild type" (WT) GIST, although rare mutations seen in *BRAF* are the exception to the rule. Many wild-type GISTs express insulin-like growth factor 1 receptor (IGF1R) [14], though IGFR1 is itself not mutated in GIST. A number of *KIT* and *PDGFRA* non-mutated GIST show loss of expression of the subunit B of succinate dehydrogenase (SDHB) [15]. SDHB expression is also lost in patients with Carney-Stratakis dyad, in whom paragangliomas are the defining tumor, due to mutations in one of the subunits of the SDH complex. [16] GIST, paraganglioma, and pulmonary chondromas are observed in Carney triad, which also lack SDHB expression in the absence of a known genetic abnormality [17]. Germline *SDHA* mutations have been identified in a significant subset of young adults with *KIT* and *PDGFRA* non-mutated GIST. [18] SDH-deficient GIST

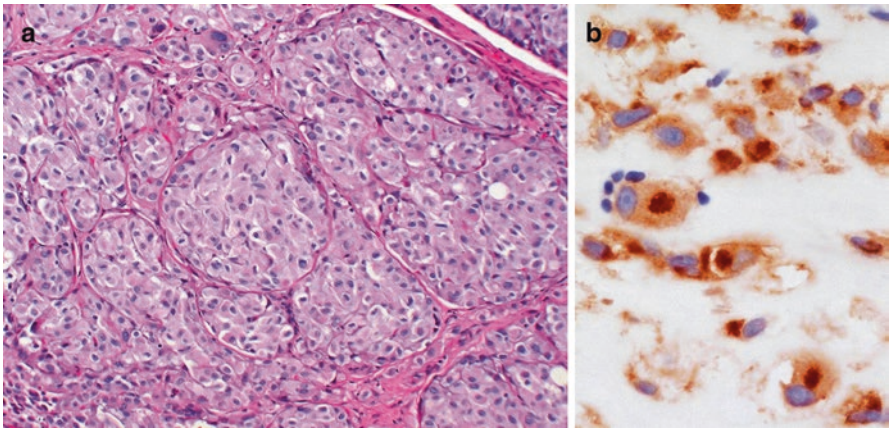

Fig. 4.10 Small bowel epithelioid GIST (**a**) with KIT positivity (**b**)

is associated with characteristic hypermethylation profile compared to *KIT*-mutated GIST, implicating the metabolic derangement of increased succinate levels with alterations in epigenetic targets [19]; the same study showed the Carney-Stratakis dyad GISTs formed a separate group by methylation analysis as well. It is important to be aware that there are other sarcomas that may show variable immunoreactivity for KIT, such as Ewing sarcoma, small cell carcinomas, and desmoid tumors, but such tumors do not carry activating *KIT* mutations and do not respond to imatinib. When other markers are needed to discern GIST from other tumors, *DOG1*, immunohistochemistry can be applied for a more definitive diagnosis [20, 21].

4.5 Treatment

The primary modality for higher risk tumors is surgical resection followed by 3-year adjuvant imatinib as standard of care (see below). Complete resection without encroachment of the pseudocapsule is a dominant factor in survival. The presence of metastatic disease and/or high-risk tumors is a clear indication for tyrosine kinase inhibitor treatment. Radiation has a limited role in the management of these tumors largely due to anatomic constraints and its relative radio-resistance.

4.6 Adjuvant Imatinib for Primary GIST

Adjuvant therapy was tested in a phase II trial before moving to phase III trials that now define the standard of care for primary GIST therapy. Long-term results of the initial Z9000 phase II trial of adjuvant imatinib in high risk (>10 cm, intraperitoneal tumor rupture or up to four intraperitoneal implants) have now been reported [22]. After a median follow-up of 7.7 years, the 1-, 3-, and 5-year overall survival rates were 99, 97 , and 83 %, respectively (Fig. 4.11a). This can be compared to historical 5-year survival of 35 % recurrence-free survival; RFS in the treatment population at 1, 3, and 5 years was 96, 60, and 40 %, respectively. The RFS was lower with increasing tumor size, small bowel site high mitotic rate, *KIT* exon 9 mutation, and older age (Fig. 4.11b).

The issue of adjuvant TKI in the treatment of GIST post-resection was further examined in prospective randomized trials. The first was designed under the aegis of the American College of Surgeons Oncology Group (ACOSOG). Patients with primary gastrointestinal stromal tumors ≥3 cm were randomized following complete gross resection and confirmation of KIT positivity to receive a placebo or imatinib for 1 year. This was a double blind trial with crossover allowed if recurrence was identified. Three hundred twenty-five patients were randomized to imatinib, 319 to placebo, and there were 21 events in the imatinib group and 62 in the placebo group. This trial was positive (Fig. 4.12) with a highly significant recurrence-free survival identified and a hazard ratio of 0.33. Overall survival (Fig. 4.13) has not reached statistical significance [23]. The most dramatic

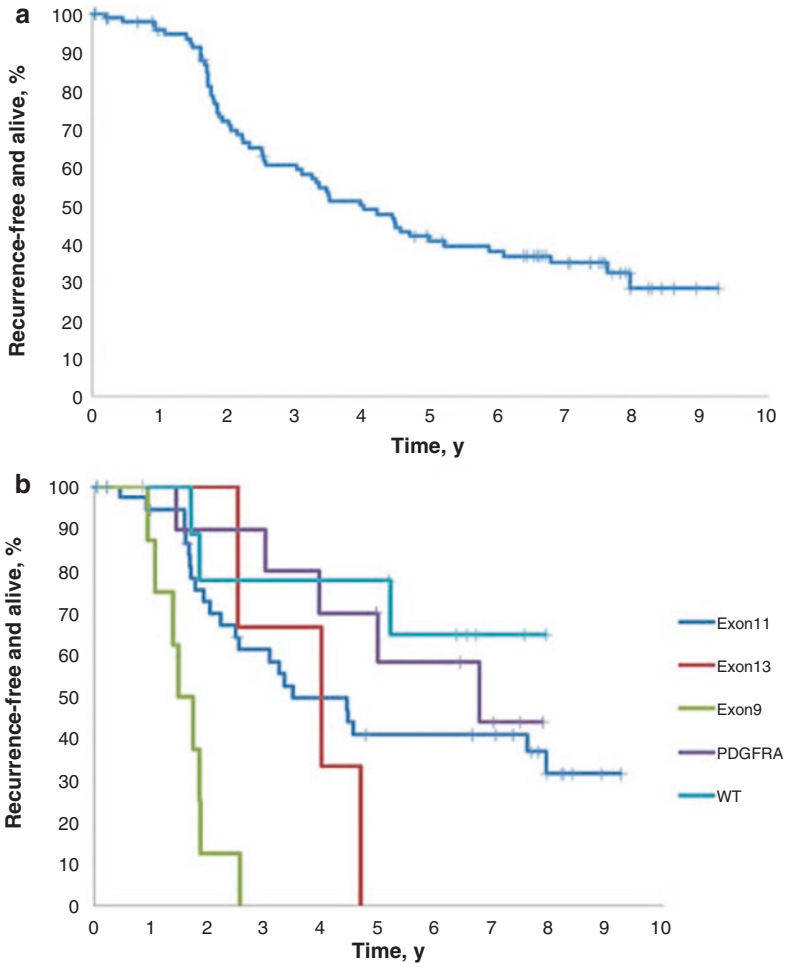

Fig. 4.11 Recurrence-free survival. (**a**) Entire population. (**b**) Mutation status. With permission from: DeMatteo R, et al. Ann. Surg. 258(3):422–429, 2013

effect was seen in patients with tumor size >10 cm (Fig. 4.14). However, 1 year of imatinib does not appear sufficient to eliminate microscopic metastatic disease in most patients.

Recurrence-free survival by type of mutation was also examined [24] showing that patients with *KIT* exon 11 mutant GIST had improved recurrence-free survival over those patients with *KIT* exon 9 and *KIT* exon 11 with a deletion affecting amino acids 557 or 558 (Fig. 4.15). These initial data suggest that 1 year of adjuvant imatinib only delays recurrence but does not prevent it. The FDA and EMA approved use of imatinib in the adjuvant setting. The data from the Z9001 trial were corroborated by an independent trial from the EORTC, examining 0 years vs. 2 years

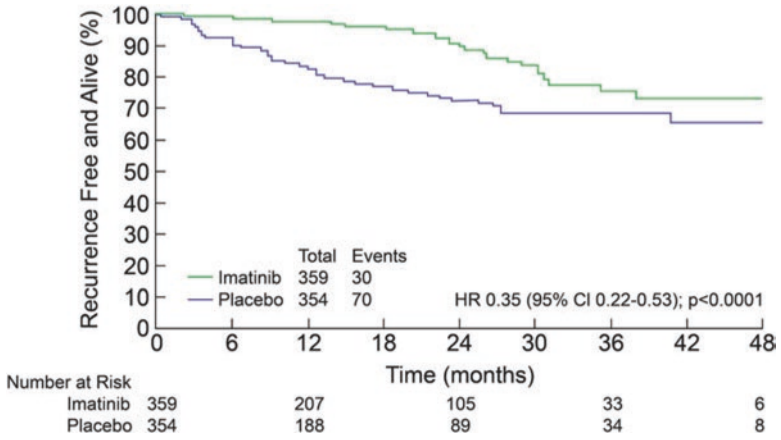

Fig. 4.12 Recurrence-free survival, randomized controlled trial of adjuvant imatinib vs. placebo. From: DeMatteo RP, et al. Lancet. 2009;373:1097–1104

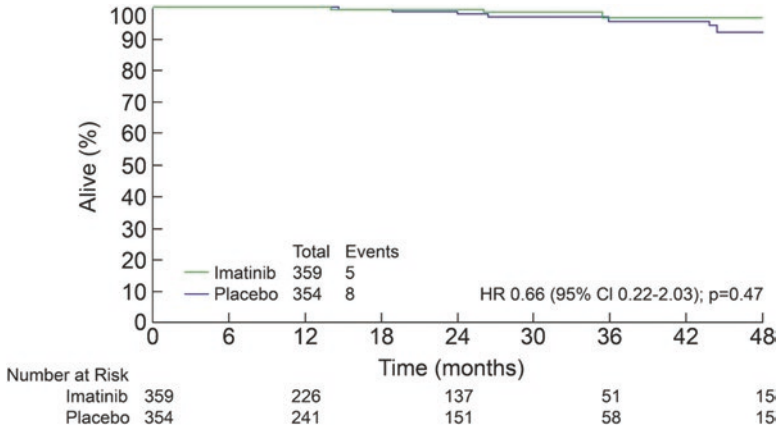

Fig. 4.13 Overall survival, randomized controlled trial of adjuvant imatinib vs. placebo, size ≤5 cm. From: DeMatteo RP, et al. Lancet. 2009;373:1097–1104

imatinib in the adjuvant setting. In this study, PFS and a new metric, "imatinib relapse free survival", were improved with 2 years of therapy vs. none [25].

The defining study for present day adjuvant therapy is the SSG XVIII trial, which compared 3 vs. 1 year of imatinib with overall survival as a primary endpoint. Adjuvant imatinib for 3 years improved recurrence-free survival (RFS) and overall survival (OS) compared with 1 year of adjuvant treatment for GIST patients who had a high risk of recurrence after surgery. Patients assigned 3

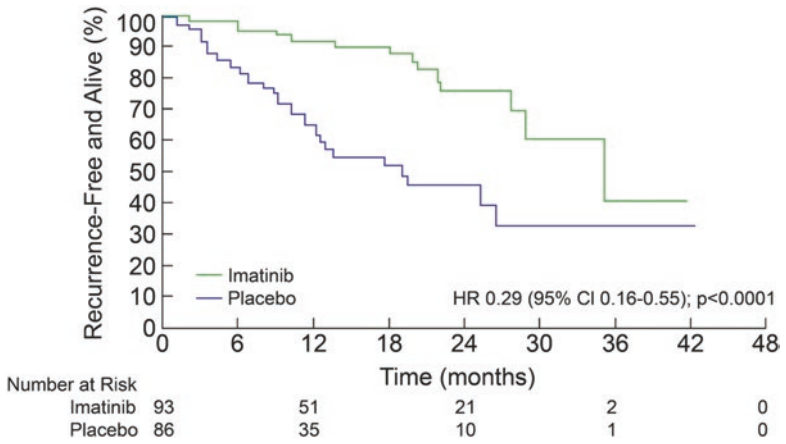

Fig. 4.14 Recurrence-free survival, randomized controlled trial of adjuvant imatinib vs. placebo, size >10 cm. From: DeMatteo RP, et al. Lancet. 2009;373:1097–1104

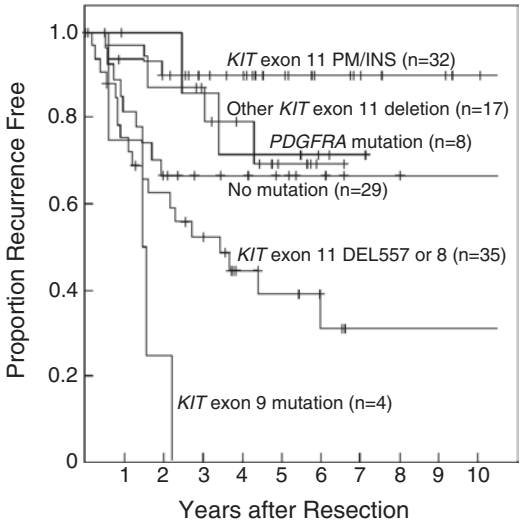

Fig. 4.15 Recurrence-free survival in 127 patients with completely resected localized gastrointestinal stromal tumor (GIST) based on the type of mutation. From: DeMatteo, R.P., et al. Cancer, 2008;112(3):608–15.

years of imatinib had statistically superior relapse-free survival (RFS) compared with those assigned 1 year (5-year RFS 66 % vs. 48 %) and longer OS (5-year OS 92 % vs. 82 %), despite 13 and 26 % of people assigned 1 year vs. 3 years imatinib stopping therapy for reasons other than GIST recurrence. With 7.5 years median follow-up, a 2015 update of these data indicated 5-year RFS was 71 % vs. 52 % for 3 year vs. 1 years of imatinib, and 5 year OS was 92 % vs. 85 %, both statistically significant [26].

The overall survival results were unexpected. Improved survival had not been observed in the 1 year study of adjuvant imatinib nor in the BFR 14 study from France, in which patients with metastatic GIST stopped or continued imatinib after 1, 3, or 5 years of stable disease or better. In the latter case, there was improved PFS for those patients who continued imatinib versus those who interrupted imatinib therapy. However, OS was identical in both groups in BFR14, indicating that even in the setting of metastatic disease one is not penalized by a break-in therapy in terms of survival. However, given that the survival curves are ultimately coming together over time, it is not clear that in the long run if imatinib can be truly curative for a fraction of patients, or if delay of recurrence is all that can be expected from 3 years' treatment with imatinib.

With the understanding that longer exposure may be necessary to achieve the best possible RFS and OS for higher-risk tumors, a subsequent phase II trial looking at 5 years of imatinib has completed accrual and awaits maturation of the data. The SSG have also initiated a 5-year vs. 10-year imatinib study in the adjuvant setting for people with the highest-risk GIST.

Further mutation data have become available regarding adjuvant therapy from the ACOSOG Z9000 and Z9001 studies. These data will help discriminate which patients should receive therapy [27]. In particular, people had better RFS with 1 year of imatinib vs. placebo if they had deletions in KIT, as opposed to insertions or point mutations. Patients with *PDGFRA* D842V mutation did not appear to benefit from 1 year of imatinib, nor did patients with *KIT* exon 9 mutations or no mutation in *KIT* or *PDGFRA*. There was the suggestion of benefit in patients who had *PDGFRA* mutations that were not D842V. These data help select patients who will not benefit from imatinib, by virtue of the lower risk of their tumors. However, questions around the use of adjuvant therapy for exon 9 *KIT* mutated GIST or GIST without *KIT* or *PDGFRA* mutation remain. Assuming a clinical trial is not available, our general approach is to opt for a trial of adjuvant therapy in these borderline cases, understanding there may be a lower threshold to stop treatment for toxicity in these patients.

4.7 Neoadjuvant Therapy for Primary Disease Not Amenable to Surgery

Patients with clinically unresectable primary GIST provide an opportunity for neoadjuvant therapy prior to resection. In such a situation, an unresectable or marginally resectable tumor can be rendered resectable in difficult anatomical locations

such as the rectum [28]. It is generally advocated that patients continue imatinib after such surgery, given the high frequency of relapse off imatinib in such patients. In the setting of resectable disease, it is not clear at this time whether it will be better to consider imatinib with surgery as an "adjuvant" to imatinib, or imatinib as an adjuvant to surgery [29, 30]. Two studies of neoadjuvant imatinib for resectable disease indicate that such an approach is both feasible and effective [29, 30]. The long-term implications of such therapy will require longer follow-up.

4.8 Treatment of Recurrence

In terms of risk factors for local-regional recurrence, the influence of positive microscopic margin on tumor recurrence has been examined [31]. Approximately 9 % of 819 GIST patients had an R1 resection. Significant factors associated with R1 resection include tumor size ≥10 cm, location, and rupture. The difference in recurrence-free survival with or without imatinib therapy in those undergoing an R1 vs. R0 resection was not statistically significant at a median follow-up of 4 years. (Fig. 4.16)

The primary management of metastatic disease remains tyrosine kinase inhibitors, while the role of surgery in the treatment of recurrent disease is unclear. It does appear that there is a role for surgery or other interventions, such as radiofrequency ablation (RFA) or cryotherapy, particularly in the presence of non-responding lesions or lesions that develop resistance to tyrosine kinase inhibitor therapy. Studies to examine early vs. later surgery for metastatic GIST have failed to accrue and were closed.

4.9 First line Imatinib For Metastatic GIST

The initial demonstration of imatinib-induced KIT inhibition and apoptosis in a GIST cell line [32] led to the first treatment of a patient with GIST with imatinib. [33] The activity of imatinib was most remarkable, given the resistance of GIST to standard cytotoxic chemotherapy. The response of the first patient rapidly led to phase I [34], randomized phase II [35], and confirmatory phase II studies [36], demonstrating activity of imatinib in successively larger cohorts of patients.

Patients with bulky disease showed improved symptoms within days of starting therapy, eventually prompting two randomized studies of 400 mg daily versus 400 mg twice daily imatinib in patients with metastatic GIST. [37, 38] The studies showed consistent ~50 % RECIST (Response Evaluation Criteria in Solid Tumors) response rates in patients with metastatic disease, with survival being no different in the 400 mg and 800 mg arms, and allowed registration of imatinib at 400 mg oral daily as a first line standard of care for metastatic GIST.

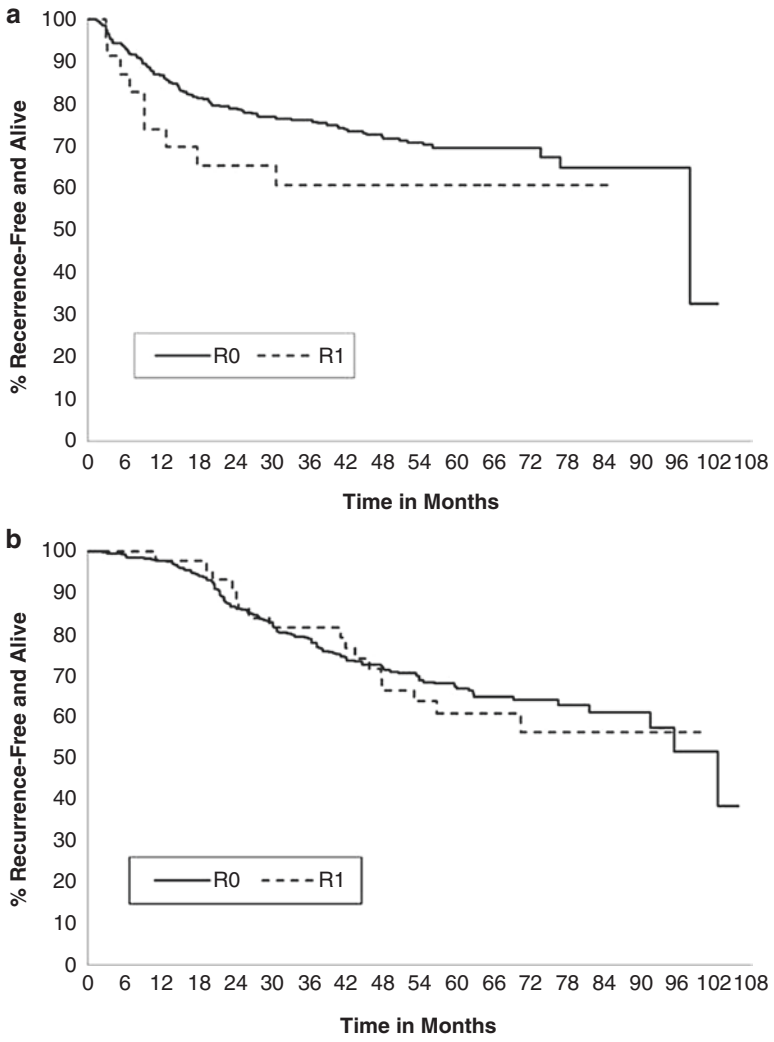

Fig. 4.16 (**a**) Recurrence-free survival (RFS) by margin status for patients in the placebo arm ($n=330$ for R0 and 23 for R1); hazard ratio 1.5; 95 % CI 0.76, 2.99; $p=0.24$. (**b**) Recurrence-free survival by margin status for patients in the imatinib arm ($n=415$ for R0 and 49 for R1); hazard ratio 1.1; 95 % CI 0.66, 1.83; $p=0.73$. With permission from: McCarter MD, et al. J Am Coll Surg. 215:53–60, 2012

Overall survival of patients with metastatic GIST in the first published phase III study of imatinib ($n=946$) is shown (Fig. 4.17). The third, non-randomized comparator arm was a group of patients with gastrointestinal leiomyosarcoma/GIST treated with doxorubicin in older clinical trials, giving a sense of the improvement in survival achieved in patients with metastatic disease. The United States-randomized study B2222 gave similar results, with median overall survival of 58

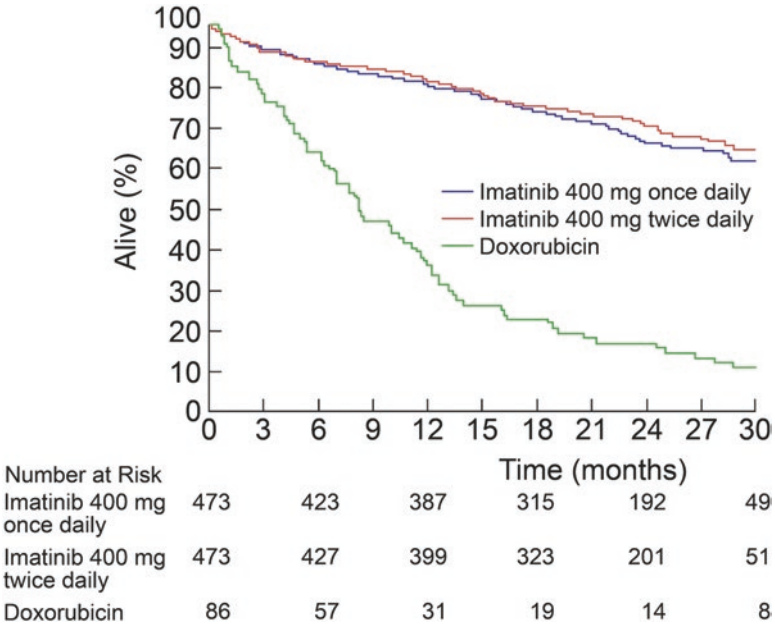

Fig. 4.17 Overall survival for patients receiving imatinib for metastatic GIST, 400 mg vs. 800 mg oral daily, European/Australasian randomized study, $n = 946$. From: Verweij J, et al. Lancet 2004;364:1127–1134

months for all patients treated in this 746 patient study [37]. Patients with RECIST stable disease survived just as long as patients with an overt RECIST partial or complete response, confirming that RECIST is inadequate for determining clinical outcomes for patients receiving imatinib for GIST. [39, 40] The lack of progression thus is the most important radiologic finding suggesting clinical benefit. PET scans can also track response of GIST to imatinib and other TKI, but add little to contrast-enhanced CT scans (Figs. 4.18 and 4.19).

Data from France indicated that patients with metastatic disease need to be treated on a lifelong basis. The basis of this recommendation is the first portion of the French BFR14 study, in which patients received 12 months of imatinib. Patients doing well were randomized to continue or stop imatinib. Those stopping imatinib progressed with a median time of 6 months, compared to 28 months for those who continued imatinib. [41] Nearly all patients responded again when re-challenged with imatinib. Overall survival for the two groups was not different. These data show imatinib can be interrupted for periods of time without a negative impact on survival. Nonetheless, as in patients with HIV receiving antiretroviral therapy, the general consensus among medical oncologists is that patients tolerating imatinib well should continue imatinib unless there is intolerance despite dose reduction or disease progression. These data were confirmed in a similar study, in this case using 3 years of imatinib before randomization. A 5-year follow-up study has also been reported, with similar findings [42].

Although the overall survival was not different between patients receiving 400 mg vs. 800 mg imatinib daily for metastatic disease, progression-free survival (PFS) was superior for patients taking 800 mg daily, with a hazard ratio of 0.89 at 3 years in favor of the higher dose, $p = 0.04$ [43]. It has become clear that the group of patients with largest difference in PFS by dose is that with exon 9 *KIT* mutations [43]. In this group, PFS was 6 months at the 400 mg daily dose, versus 17 months for those taking 800 mg oral daily ($p = 0.017$). There is also a trend to improved

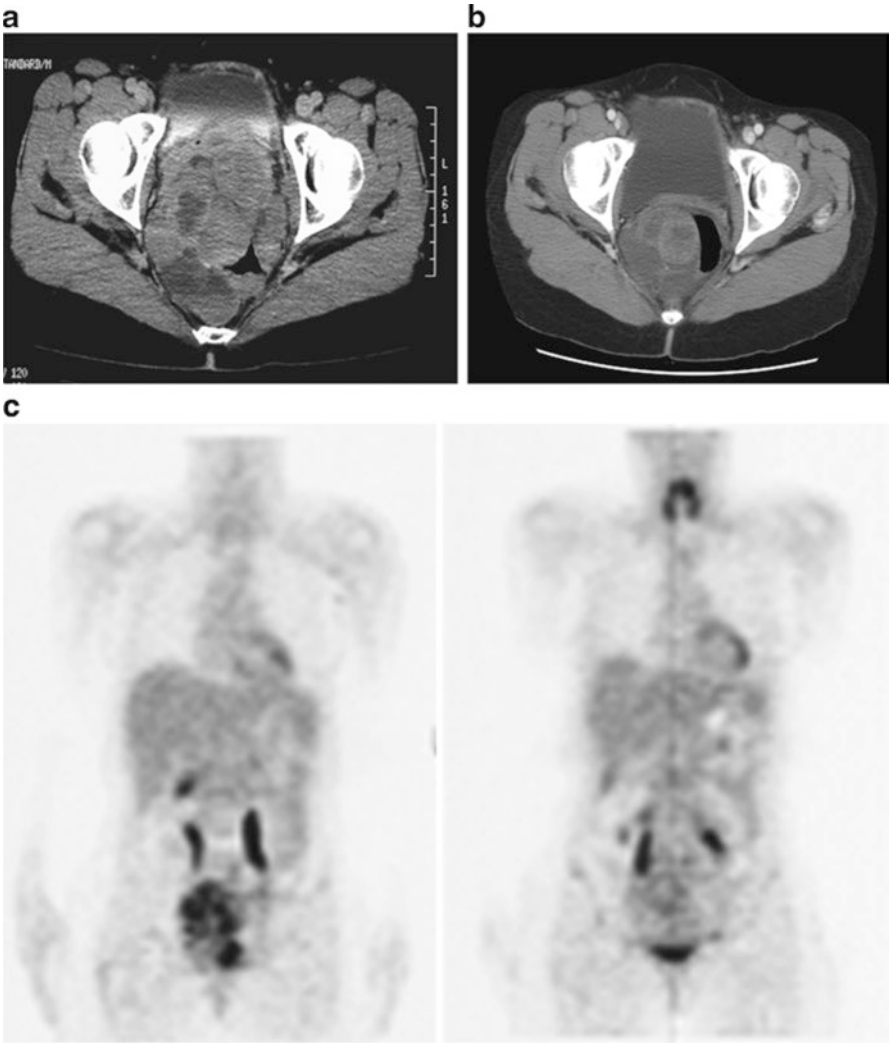

Fig. 4.18 CT and PET scan showing response to imatinib (exon 11 KIT mutation) (**a** and **b**) CT at 0 and 2 months, (**c**) PET at 0 and 2 weeks

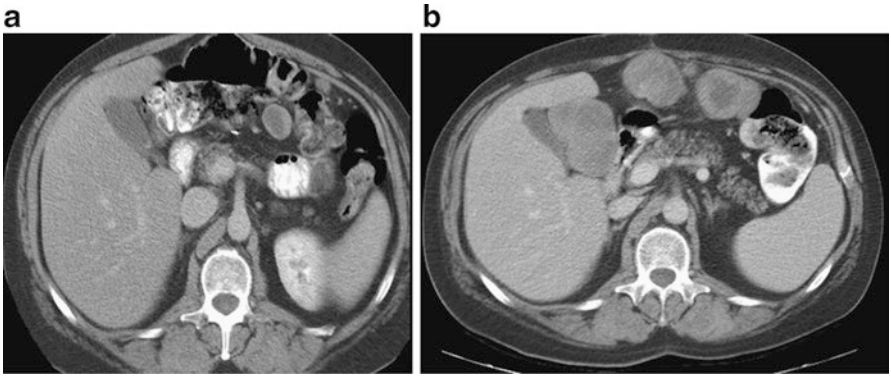

Fig. 4.19 CT and PET showing progression in response to imatinib (exon 9 *KIT* mutation), (**a** and **b**) CT before therapy and 2 months after starting therapy

survival for patients receiving the higher dose. Because of this subset analysis, NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) guidelines for GIST incorporate imatinib dose based on mutation status, specifically 400 mg oral BID for people with exon 9 *KIT* mutations, and 400 mg oral daily for other patients [42]. *KIT* mutation testing is now commercially available and can also be used to guide this decision.

Who should have mutation testing for their GIST? Arguably, this test should be a standard of care for people with high enough risk disease to potentially merit adjuvant therapy. While testing every 1 cm GIST has no clinical import, since the risk of recurrence is so low, it is useful to know which genomic subtype of GIST is being treated in order to tailor adjuvant therapy, and in several instances metastatic disease. For example, in *KIT* exon 9 mutant GIST, there are retrospective data that show that people have superior progression-free survival on higher (800 mg oral daily) rather than lower doses of imatinib, thus it makes sense to ascertain these data if they have not been collected previously [44]. Notably, the vast majority of exon 9 *KIT* mutation GISTs arise in the small bowel, thus consideration can be given to testing this subgroup. Of note, exon 9 KIT mutation GISTs are still the minority, even in the small bowel. Similarly, *PDGFRA* mutations are most commonly found in the stomach.

We remain somewhat skeptical of the use of higher-dose imatinib for patients with *KIT* exon 9 mutations since the benefit is modest in the existing randomized clinical trials data in the two large randomized studies of metastatic disease [37, 45]. Specifically, the response rate after increasing the imatinib dose is 2–3 % and disease stabilization rate 27–28 % in the two randomized studies, with a median PFS of 2.5–5 months, and a 1-year PFS of ~20 %. Other people have significant adverse events at 400 mg oral daily that only worsen at 800 mg daily. Nonetheless, if a patient can tolerate the higher dose, a higher dose for exon 9 *KIT* mutant GIST remains a worthy goal, given that there remain so few options beyond imatinib for metastatic disease.

4.10 Dose Intensity Over Time

The first patient with GIST being treated with imatinib was in March, 2000 [33]. It is worthwhile reviewing the dosing of this remarkable drug. Specifically, why is a flat dose of imatinib typically given to GIST patients, i.e., 400 mg oral daily? To a first approximation, in the five phase I–II–III studies, there appears to be no improvement in RECIST response rate or survival in patient who receive 400, 600, or 800 mg oral daily [34–38, 46]. What we do not know with this patient population is whether there will be long-term survival benefits in patients who receive lower or higher doses of imatinib. A more detailed analysis of data from the EORTC 62005 intergroup study of 400 mg vs. 800 mg imatinib daily for patients with metastatic GIST [36] showed that a higher dose of imatinib was associated with improved response rate and survival in metastatic GIST patients who had exon 9 mutations in the *KIT* gene in their GIST. [47] Patients with exon 9 mutations fared poorly overall compared to other patients on this study.

A variety of factors that lead to imatinib resistance may be a function of dose, while others are not. Compliance, treatment interruptions, and variability of the pharmacokinetics of imatinib distribution in the body all affect the dose intensity of imatinib. However, secondary *KIT* mutations, *KIT* amplification, loss of *KIT* expression, or other factors such as OCT-1 or ABCB1 channel proteins responsible for influx and efflux of imatinib into the tumor cell are not likely so affected by dose intensity.

Reanalysis of the first large scale randomized phase II data of patients treated with 400 mg vs. 600 mg oral imatinib daily for GIST (B2222) showed that those patients in the lowest quartile of plasma drug concentration had the shortest time to progression, in comparison to all other patients [48]. These data are consistent with data from chronic myelogenous leukemia (CML), in which those patients with major molecular responses to therapy had a higher median trough level in comparison to patient who did not have a major molecular response; [49] however, other data do not support this contention [50].

The assessment of plasma levels of imatinib in patients with hematological malignancies is becoming a standard of care, and imatinib trough level testing should be considered in GIST in at least some clinical scenarios, though data are limited. For example, a 120 kg patient without side effects who has radiological progression on imatinib 400 mg daily could have trough level testing to indicate if dose escalation is appropriate to try and achieve a better result. These data also highlight a problem with oral therapy. It is difficult to monitor treatment on an ongoing basis when administering oral therapy, while it is much easier to document treatment compliance with intravenous agents. In examining patients with CML on imatinib, only lack of compliance was associated with failure to achieve a major molecular response [51].

Actual dose (as opposed to assigned dose) received can thus be an important indicator of benefit of imatinib therapy. In the EORTC 62005 400 mg vs. 800 mg phase III study, patients with lower actual administered dose fared less well than

those maintaining the full assigned dose. Furthermore, those patients crossed over in the 62005 study and the S0033 (US 400 mg vs. 800 mg) study showed that about one third of patients had benefit when their dose was increased, i.e., stable disease or partial response as best outcome [45]. While some of this effect could be due to the well-recognized increased clearance of imatinib over time, a compliance effect was likely also important with more patients continuing the higher dose of therapy understanding their tumor was getting worse.

Does surgery impact upon time to progression? Patients with resectable disease after imatinib therapy have a longer time to progression than those who did not have surgery. While these data are not randomized, these data suggest that resection for remaining residual disease is a way to eliminate disease that will become resistant later [52–55]. Unfortunately, studies in Europe and the US have failed to ask this question owing to lack of accrual.

4.11 Imatinib Pharmacokinetics

Regarding imatinib pharmacokinetics, imatinib has an excellent oral bioavailability exceeding 95 %, unaffected by food intake [56]. It is thought that ATP-binding cassette (ABC) pumps such as P-glycoprotein and Breast Cancer Resistance protein (BCP) mediate absorption of imatinib from the lining of the bowel into the circulation. ABC pumps, which are expressed in the gastrointestinal tract, are thought to pump imatinib back to the gastrointestinal lumen, thereby decreasing the absorption of imatinib. [57] As only the unbound fraction of imatinib is active, binding of imatinib to blood components also plays a major role in the activity of imatinib. The most important blood protein to which imatinib binds is alpha1-acid glycoprotein (AAG) [58].

Imatinib is converted into several metabolites. CPG74588, an N-demethylated piperazine derivate, is the most important. CPG74588 exhibits similar anti-tumor activity as imatinib in vitro and has an area under the curve (AUC) approximately 10 % of that of imatinib. [56] The main metabolizing enzymes include the cytochrome P450 isoenzymes CYP3A4 and CYP3A5, though others contribute [56]. Elimination of imatinib and its metabolites occurs mainly via the bile. ABC transporters are also involved in this process, pumping imatinib and the metabolites into the bile. The remaining 15–20 % is excreted by the kidneys [56]. Surprisingly, imatinib pharmacokinetics is not affected by severe hepatic dysfunction [59], and no dose modifications are required even in the case of moderate renal impairment (creatinine clearance of 20–39 mL/min) [60].

It appears that there are decreased imatinib plasma levels over time. In patients who used imatinib over approximately 12 months, the AUC after prolonged imatinib use was approximately 40 % of that shortly after treatment initiation [61]. Two mechanisms have been suggested to underlie this phenomenon of decreasing imatinib levels over time. The first is increased expression of ABC transporters in the gut wall causing decreased absorption; [57] the other is increased uptake by erythrocytes [62]. Compliance and other factors may be involved.

One expects that there is a certain threshold blood level required for imatinib activity against GIST. Given the IC50 of different *KIT* isoforms, this threshold appears to differ by *KIT* or *PDGFRA* mutation status, with the highest levels required for *KIT* exon 9 mutated tumors and the lowest levels for patients with *KIT* exon 11 mutated tumors, consistent with the observed clinical data. Imatinib trough level testing may eventually become important in this setting, as a result.

4.12 Second Line Sunitinib for Imatinib-Resistant Metastatic GIST

Sunitinib was given regulatory approval based on a single phase III study, where imatinib-resistant (400 mg daily) or intolerant patients were randomized (2:1) to sunitinib (50 mg, 4 on, 2 off) or placebo with an option to crossover at progression. In this trial, 310 patients were randomized and received sunitinib ($n=205$) or placebo ($n=105$). Partial responses and stable disease was seen in 7 and 58 % of patients in the sunitinib arm, and no responses were seen with placebo. Median PFS in the treatment arm was 6.3 and 1.5 months on placebo (Fig. 4.20) [63]. Interestingly, changes in serum KIT levels and other correlates of KIT and VEGF receptor blockade were observed in the sunitinib arm when compared to placebo [64, 65]. Specifically, a rising serum KIT level after 12 weeks of treatment was correlated with inferior outcome compared to those without such a rise. Responding patients tended to have either exon 9 mutations in GIST or wild-type GIST.

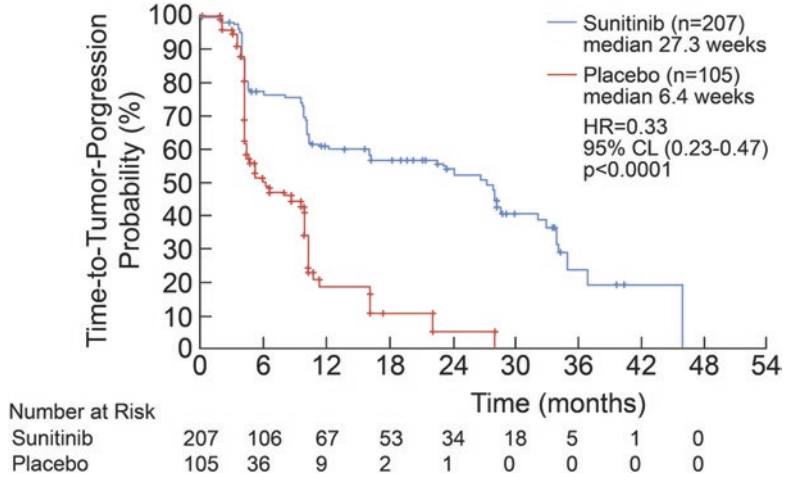

Fig. 4.20 Time to progression on sunitinib vs. placebo in GIST patients failing or intolerant of imatinib. From: Demetri GD, et al. Lancet 2006;368:1329–1338

Those patients with imatinib resistance and exon 11 *KIT* mutations often had secondary mutations that rendered the masses resistant to imatinib. [66]

In retrospect, an appropriate control group may have been to continue imatinib. It is now clear to medical oncologists that there can be an acceleration of symptoms for patients with metastatic disease when tyrosine kinase inhibitors are stopped. These data contribute to the concept that imatinib or sunitinib should be continued even in the setting of radiological or clinical progression, since treatment may still limit tumor growth and be associated with longer survival.

In a study of schedule, 60 patients were treated on a phase II trial of with imatinib-resistant or -intolerant GIST with daily continuous dosing of sunitinib at 37.5 mg; PFS and OS were 8.5 and 28 months, respectively [67]. This study indicated that with treatment, serum VEGF levels increased, while soluble KIT and VEGFR2 and VEGFR3 decreased. While there was a trend toward improvement in PFS and OS in patients whose serum KIT levels dropped from baseline, this was not significant until cycle 6 of treatment or later.

4.13 Regorafenib in Third Line for Metastatic GIST

As a practical matter, after failure of sunitinib, regorafenib has wide regulatory approved, by virtue of a placebo controlled randomized trial, the "GRID" trial. In this study patients were randomized to regorafenib 160 mg oral daily 3 weeks on 1 off or placebo, with crossover to regorafenib allowed if there was worsening of disease on placebo. In this study people with any primary genomic subtype had benefit (*KIT* or *PDGFRA* or no mutation in either) [75]. Median PFS was 4.8 months in the treatment group and 0.9 months in the control group. Patients crossed over from placebo experienced similar benefit.

After failure of all tyrosine kinase inhibitors, systemic treatment is better than no treatment. In a small randomized trial, imatinib was compared to placebo for patients who failed other lines of systemic therapy. Median PFS was 0.9 months on placebo vs. 1.8 months on imatinib. Thus, imatinib may slow progression, even though resistant clones may continue to grow. These data support the clinical finding of people doing worse when on breaks from their tyrosine kinase inhibitor [76].

4.14 Other Tyrosine Kinase Inhibitors for Metastatic GIST Failing Imatinib and Sunitinib

Of the other existing tyrosine kinase inhibitors, sorafenib [68], nilotinib [69], vatalanib [70], and others appear to have activity greater than observation alone. Masitinib has activity in first line metastatic GIST patients [72] and thus may be useful in later lines as well, as may be pazopanib. [73]. Dasatinib appears to have activity specifically in *PDGFRA* D842V mutation-positive GIST [74]. Activity of

these agents in later lines of therapy [69] suggests examination of these drugs as an earlier line of treatment during a patient's clinical course.

4.15 Newer Agents for GIST

It appears that at least three quarters of *KIT* mutant GIST patients progressing on imatinib develop secondary mutations in *KIT* that render the molecule insensitive to imatinib and often to other tyrosine kinase inhibitors. The heterogeneity of secondary mutations in one tumor limits the utility of tyrosine kinase inhibitors in this setting. How can these multiple resistant clones be managed medically? After imatinib, sunitinib, and regorafenib, other TKI appear [77] to have some activity, as noted above, but by and large responses are limited, as is the duration of response.

It is clear that resistant GISTs are genetically heterogeneous, even within one tumor or anatomical site [52, 66, 78–81]. Resistant clones can be identified by polymerase chain reaction, indicating selection of clones as a reason for imatinib resistance [82]. Other than differences in mitotic rate, it is not at all clear why some patients develop resistance more rapidly than others. Regardless, patients need a therapy with a different mechanism for activity against a wide spectrum of evolving mutations.

One approach to imatinib- and/or sunitinib-refractory GIST is to "vertically" target multiple steps in *KIT* signaling. The recent availability of new inhibitors of downstream target TOR (target of rapamycin) and more recently the PI3K (phosphatidylinositol 3-kinase) family of proteins makes combinations with receptor tyrosine kinase inhibitors natural combinations to examine [83].

Drugs targeting the molecular chaperone hsp90 (heat shock protein of 90kD molecular mass) may provide an avenue to pursue for tyrosine kinase inhibitor-resistant GIST. The hsp90 family of proteins (two proteins in humans, termed hsp84 and hsp86) are "chaperone" proteins, in that they are responsible for proper folding and function of oncogenic and normal proteins alike. It is hypothesized that proteins expressed from mutated genes are more structurally unstable, and thus more dependent upon the re-folding function of hsp90 family members than their wild-type counterparts [84]. Interestingly, both imatinib-sensitive and -resistant GIST cell lines are sensitive to the effects of hsp90 inhibitors such as retaspimycin (IPI504), a more soluble version of the classic geldanamycin analogue 17-AAG. It is also notable that a *PDGFRA* mutant GIST cell line is sensitive to IPI504.

These translational data informed a clinical trial of retaspimycin in patients with GIST. Decreased activity by PET (positron emission tomography) scan was observed in 16 of 22 evaluable patients, although only 1 of 36 had a RECIST response to therapy (as did 1 of 11 patients with other sarcomas treated with retaspimycin) [85]. Thus, like in CML and BCR-ABL, these findings provide some support for the contention that GIST remains dependent upon *KIT* expression and signaling even after the development of multiple mutations. However, a phase III

Table 4.1 Recommendations for systemic therapy for patients with GIST[a]

Clinical scenario		Comments
Adjuvant setting		PFS and overall survival are improved with 3 years of imatinib in the adjuvant setting for higher risk tumors. The use of imatinib in patients with GIST bearing exon 9 *KIT* mutations is controversial. Based on available data, patients with WT *KIT* and *PDGFRA* or D842V *PDGFRA* mutant GIST should not receive adjuvant imatinib, although patients with *PDGFRA* mutation other than D842V may benefit
Metastatic disease	First line	Imatinib 400 mg daily; consider increase to 800 mg oral daily if exon 9 *KIT* mutant. Patients with recurrent *PDGFRA* mutant or WT *KIT*/*PDGFR* GIST should be considered for alternative clinical studies given the low response rate with imatinib
	Second line	Sunitinib; we favor dosing at 37.5 mg oral daily without interruption instead of the 50 mg oral daily 4 weeks on, 2 weeks off schedule
	Third line	Regorafenib; since most patients require a dose reduction, starting at a lower than regulator-approved doses may be appropriate
	Fourth line and beyond	Continuing or recycling an approved inhibitor. Some clinicians will try pazopanib or other RTK inhibitors

[a]Clinical trials are always appropriate if available

study of retaspimycin against best supportive care was stopped early owing to early deaths on the treatment arm. These data will be important in planning future studies of other agents in third and greater line of treatment.

The biology of GIST continues to fascinate biologists and clinicians alike, looking for a means to treat patients with this difficult clinical problem. Rational combinations of existing agents and new drugs targeted against non-kinase portions of *KIT* or components of the downstream signaling cascade may become increasingly important, and it will be important to rigorously prove benefit so that GIST remains an effective proof-of-concept disease for innovative drug development. For example, IGF1R (insulin-like growth factor 1 receptor) antagonists administration caused stable disease in at least some GIST patients without *KIT* or *PDGFRA* mutations [86, 87]. Perhaps, *KIT* inhibitors will have to be administered with IGF1R, EGFR (epidermal growth factor), or other inhibitors to block activation of parallel kinase pathways usurped by GIST to maintain AKT signaling. This example is one in which horizontal blockade of signaling pathways may prove as important as the vertical blockade of one pathway at different steps. Thanks to new basic and translational science, the near future will be exciting for GIST research, in particular as the signaling pathway and dependence of GIST upon *KIT* signaling are unraveled (Table 4.1). As noted above as a general concept for sarcomas in general, immunotherapy, metabolic therapy, and epigenetic agents remain largely untested in GIST.

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