The American Journal of Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.elsevier.com/locate/amjsurg

Neoadjuvant tyrosine kinase inhibitor therapy for patients with gastrointestinal stromal tumor: A propensity-matched analysis

Liam H. Wong [a], Thomas L. Sutton [b], Brett C. Sheppard [b], Christopher L. Corless [c], Michael C. Heinrich [d,e], Skye C. Mayo [f,*]

[a] Oregon Health & Science University (OHSU), School of Medicine, Portland, OR, 97239, USA
[b] OHSU Department of Surgery, Division of General Surgery, Portland, OR, 97239, USA
[c] OHSU Department of Pathology, Knight Cancer Institute, Portland, OR, 97239, USA
[d] Portland VA Health Care System, Portland, OR, 97239, USA
[e] OHSU Department of Medicine, Division of Hematology and Oncology, Knight Cancer Institute, Portland, OR, 97239, USA
[f] OHSU Department of Surgery, Division of Surgical Oncology, Knight Cancer Institute, Portland, OR, 97239, USA

ARTICLE INFO

Keywords:
Neoadjuvant tyrosine kinase inhibitor
Neoadjuvant therapy
GIST
oncologic outcomes

ABSTRACT

Background: Tyrosine kinase inhibitor (TKI) neoadjuvant therapy (NAT) is often given in gastrointestinal stromal tumors (GISTs) with the goal to facilitate less morbid resections and improve oncologic outcomes; however, the use of NAT for GIST is poorly studied.

Methods: We reviewed patients with resected nonmetastatic GIST from 2003 to 2019. Overall (OS) and recurrence-free survival (RFS) were assessed with Kaplan-Meier modeling. We performed 1:1 propensity-matching for relevant clinicopathologic variables for receipt of NAT.

Results: We identified 254 patients. Propensity 1:1 matching resulted in 33 patients per group. The median follow-up was 77 months with no difference in 10-year OS (68% vs. 73%), 5-year RFS (13% vs. 10%), or median RFS (24 vs. 27 months) for patients treated with NAT versus upfront resection (all $P > 0.9$). Hospital length-of-stay (both median 7 days) and Clavien-Dindo $\geq$ III complications (12% vs. 3%) were not different between groups (both $P \geq 0.35$).

Discussion: TKI NAT can be used to facilitate resection in select patients with surgically higher-risk GIST, however it does not result in an independent oncologic benefit.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms originating from the interstitial cells of Cajal,[1] with a reported global incidence of 10–15 cases per million.[2] Targeted therapies have greatly improved the outcomes for patients with GISTs because up to 85% of the tumors are associated with activating mutations in *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) tyrosine kinases.[3,4] Tyrosine kinase inhibitors (TKIs) of *KIT*, such as imatinib, have shown improved efficacy and oncologic outcomes in the adjuvant setting for resected GISTs with high-risk features.[5,6] Prolonged adjuvant TKI therapy following resection of high-risk GIST is well-tolerated with 10-year overall survival (OS) up to 79% and increases in 5-year recurrence-free survival (RFS) up to 69% in multiple randomized trials including the European Organization for Research and Treatment of Cancer (EORTC) 62024 and the American College of Surgeons Oncology Group (ACOSOG) Z9001.[7–10]

Given the robust radiologic responses to imatinib therapy in patients with advanced GIST, its use in the neoadjuvant setting has also been investigated. Neoadjuvant therapy (NAT) is commonly used to down-stage disease and enhance local disease control which theoretically would improve the likelihood of definitive curative-intent resection. Studies of intermediate to high-risk GISTs treated with TKI NAT have reported 5-year OS and RFS up to 87% and 65%, respectively.[10,11] The Radiation Therapy Oncology Group (RTOG) 0132 and American College of Radiology Imaging Network (ACRIN) 6665 prospective non-randomized phase II trial found that treatment with NAT TKI for patients with advanced primary GIST was associated with minimal peri-operative complications and toxicity,[12] as well as a 5-year progression-free survival and OS of 57% and 77%, respectively.[13]

* Corresponding author. Associate Professor of Surgery Division of Surgical Oncology, 3181 SW Sam Jackson Park Rd, L-619, Portland, OR, 97239, USA.
E-mail address: mayos@ohsu.edu (S.C. Mayo).

https://doi.org/10.1016/j.amjsurg.2022.03.045
Received 14 November 2021; Received in revised form 5 February 2022; Accepted 25 March 2022
Available online 31 March 2022
0002-9610/

However, the efficacy of NAT compared to upfront resection has not been studied in a randomized trial assessing whether an independent oncologic benefit exists. In the absence of randomized trials, propensity-matched methodology attempts to reduce the effects of confounding bias where the benefit of randomization is not possible.[14] Propensity-matched methodology including duration of adjuvant TKI treatment has not been used to study TKI NAT for patients with GIST. To gain a better understanding of the benefits of TKI NAT in patients with GIST, we evaluated oncologic outcomes in patients treated with NAT compared to upfront resection using propensity-matched methodology; additionally, we sought to identify the influence TKI NAT has on GIST resectability.

2. Methods

2.1. Data source and study population/Patient data

This is an institutional review board-approved analysis of prospectively collected data from the Oregon Health & Science University (OHSU) Knight Cancer Institute Registry. Additional chart review was performed to supplement and update these data points up to the time of data analysis.

The study population included adult patients (aged 18 years–85 years) with non-metastatic GIST treated surgically at OHSU Knight Cancer Institute between 2003 and 2018. Patients treated with TKI NAT were identified. Data included patient demographics (e.g., age at diagnosis, gender), clinicopathologic characteristics of primary tumors (e.g., baseline tumor size, mutation status for *KIT* and *PDGFRA*, tumor location), National Institute of Health (NIH) risk categories,[15] Memorial Sloan Kettering Cancer Center (MSKCC) prognostic GIST nomogram scores for 5-year RFS,[16,17] surgical and therapeutic treatment details (e.g., neoadjuvant and adjuvant TKI therapy use and length), post-operative complications classified by Clavien-Dindo,[18] and oncologic outcomes including dates and sites of progression and dates of mortality. Staging for primary tumors was modified to reflect the 8th edition of American Joint Commission of Cancer (AJCC) guidelines.

2.2. Outcomes of interest

Patients were separated into two groups based on receipt of TKI NAT prior to curative-intent resection versus upfront resection. Overall survival (OS), measured from date of first radiographic evidence of GIST, and recurrence-free survival (RFS), measured from date of curative-intent resection until radiographic recurrence, were the primary outcomes of interest. Curative-intent resections included resection or ablation of all macroscopic disease (R1/R0 resection).

Evaluation of primary tumor response to NAT prior to curative-intent resection was the secondary outcome of interest. This was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria,[19,20] absolute change in largest radiographic tumor diameter between pre-treatment and pre-operation, and extent of curative-intent resection required to obtain R0 margins.

2.3. Statistical analyses

All statistical analyses and data visualizations were performed using R version 4.0.5 (R Foundation, Vienna, Austria) including package MatchIt.

Propensity scores were determined by a multivariable logistic regression model of covariates using six variables: age at diagnosis, tumor size, tumor location, nomogram-predicted 5-year RFS, KIT mutation status, and duration of adjuvant TKI treatment.[5] Patients with missing data in any of the required covariates were removed from analysis (n = 1). For the purpose of matching, all patients receiving neoadjuvant TKI were assumed to have grade 2 tumors, given that tumor grade was not measurable in most cases due to effect of neoadjuvant therapy.[10,11] Following calculation of propensity scores, patients were 1:1 matched using exact nearest neighbor matching between treatment groups. Inferential statistics included Fisher's exact test and unpaired *t*-test. Kaplan-Meier analysis was used to analyzed oncologic outcomes including 10-year OS and 5-year RFS; all patients not experiencing the event of interest were censored at last date of follow-up. Log-rank tests were performed to compare differences in survival distributions. *P* values less than 0.05 were considered statistically significant. Trends in neoadjuvant TKI use and testing of tyrosine kinase mutation status were analyzed by 4-year intervals of study period.

3. Results

3.1. Patient and tumor characteristics

Over the study period, 254 patients with non-metastatic GIST were treated surgically at OHSU; 33 patients were treated with TKI NAT prior to resection for a median of 6 months (range, 1–21 months) (Table 1). The median age at diagnosis of GIST was 59; 130 patients (51%) were male. The stomach (n = 157; 62%) and small bowel (n = 85; 33%) (duodenum, n = 27; 31% vs distal small bowel, n = 59; 69%) were the most common primary disease sites. Most tumors were T4 (n = 79; 31%) or T2 (n = 73; 29%) on surgical pathology. The most common driver mutation was *KIT* (n = 110; 43%), followed by *PDGFRA* (n = 21; 8%); 103 patients (41%) did not have a driver mutation analysis available at the time of diagnosis. R0 resection was achieved in 236 patients (93%).[21] Seventy-eight patients (31%) had recurrence following curative-intent resection. The most common site of recurrence was in the peritoneum (n = 30; 38%), followed by the liver (n = 29; 37%). Adjuvant TKI therapy was administered to 114 patients (45%) for a median of 36 months (range, 3–120 months). Each quartile of the study period increased in percentage of driver mutation status tested (2003–2006, 2007–2010, 2011–2014, and 2015–2018 with 42%, 54%, 67%, and 71%, respectively). The last quartile of the study period (2015 through 2018) had the greatest amount of treatment with neoadjuvant TKI therapy (n = 14; 42%).

Propensity 1:1 matching identified 33 patients per treatment group of similar age, tumor size, tumor location, nomogram-predicted 5-year RFS, *KIT* mutation status, and duration of adjuvant TKI treatment (all $P \geq 0.35$) (Table 1). Additionally, groups were similar with respect to sex, primary disease site, tumor T stage, driver mutation, tumor histology, and achievement of R0 resection (all $P \geq 0.40$) (Table 1).

3.2. Post-operative outcomes and complications

Clavien-Dindo grade III or higher complications were not statistically different between both groups ($P = 0.35$).[18] Five patients treated with NAT (15%) had a complication within 30 days of curative-intent resection of which four patients (12%) had a Clavien-Dindo grade III complication or higher; the most common complication being an abscess that required drainage (n = 3; 75%). One patient (3%) who underwent upfront resection suffered a Clavien-Dindo grade IV complication due to respiratory failure. Median length of stay was similar for both groups ($P = 0.61$): seven days (range, 1–18 days) for patients treated with NAT and seven days (range, 1–44 days) for patients treated with upfront resection. There were no deaths reported within 90 days of curative-intent resection for both groups.

3.3. Oncologic outcomes

At the time of analysis, eight patients treated with NAT (24%) and eight patients treated with upfront resection (24%) died from their cancer, with similar 10-year OS (NAT, 68%; 95% CI, 49%–92% vs upfront resection, 73%; 95% CI, 58%–91%; $P = 0.97$) (Fig. 1A). Sixteen patients who underwent NAT (49%) had recurrence following curative-intent resection compared to 21 patients treated with upfront resection

Table 1
Patient demographics and clinical characteristics of the overall cohort and propensity-matched cohort.

Characteristic	Neoadjuvant Therapy (n = 33)	Unmatched Upfront Resection (n = 221)	Unmatched *P*-value	Matched Upfront Resection (n = 33)	Matched *P*-value
Age at diagnosis (years), median (IQR)	56 (51–66)	59 (50–68)	0.67	57 (51–63)	0.76
Sex (male), n (%)	20 (61)	110 (50)	0.35	18 (55)	0.80
Primary disease site, n (%)			0.23		0.35
Gastric	18 (55)	139 (63)		15 (46)	
Small bowel	12 (36)	73 (33)		13 (39)	
Colon	0 (0)	5 (2)		3 (9)	
Rectum	3 (9)	3 (1)		2 (6)	
Esophagus	0 (0)	1 (1)		0 (0)	
AJCC T Stage, n (%)			0.010		>0.99
T1	0 (0)	36 (16)		0 (0)	
T2	0 (0)	73 (33)		0 (0)	
T3	0 (0)	66 (30)		0 (0)	
T4	33 (100)	46 (21)		33 (100)	
Primary tumor size (cm), median (IQR)	9.1 (5.3–13.3)	5.1 (3.0–9.0)	0.003	10.6 (6.5–12.5)	0.40
Primary tumor grade, n (%)			N/A		N/A
G1	N/A	147 (67)		6 (18)	
G2	N/A	74 (33)		27 (82)	
Driver mutation, n (%)			0.003		0.96
KIT	22 (67)	88 (40)		20 (61)	
PDGFRA	2 (6)	19 (9)		2 (6)	
Other	3 (9)	17 (8)		4 (12)	
Not tested	6 (18)	97 (44)		7 (21)	
Driver mutations tested within years, n (%)			0.42		0.89
2003–2006	3 (11)	19 (15)		4 (15)	
2007–2010	4 (15)	34 (27)		4 (15)	
2011–2014	8 (30)	31 (25)		9 (35)	
2015–2018	12 (44)	40 (32)		9 (35)	
Tumor rupture, n (%)	3 (9)	10 (5)	0.55	3 (9)	>0.99
Tumor histology, n (%)			0.89		0.40
Spindle	28 (85)	182 (82)		26 (79)	
Epithelioid	2 (6)	20 (9)		5 (15)	
Mixed	3 (9)	19 (9)		2 (6)	
R1 positive resection margin, n (%)	3 (9)	15 (7)	0.80	2 (6)	>0.99
NIH risk assessment, n (%)					
High	33 (100)	98 (44)	<0.001	33 (100)	>0.99
Intermediate	0 (0)	23 (10)		0 (0)	
Low	0 (0)	65 (29)		0 (0)	
Very low	0 (0)	35 (16)		0 (0)	
Nomogram-predicted 2-year RFS (%), median (IQR)	18 (8–51)	53 (15–88)	<0.001	21 (5–49)	0.84
Nomogram-predicted 5-year RFS (%), median (IQR)	3 (1–26)	29 (2–78)	<0.001	4 (1–24)	0.80
Adjuvant TKI therapy, n (%)	23 (70)	91 (41)	0.004	24 (73)	>0.99
Adjuvant duration (months), median (IQR)	36 (12–72)	36 (12–36)	0.47	36 (12–36)	0.39
Recurrence, n (%)	16 (48)	62 (28)	0.015	21 (64)	0.32
Site of recurrence, n (%)			0.44		0.37
Liver	4 (25)	25 (40)		7 (33)	
Peritoneum	8 (50)	22 (35)		10 (48)	
Liver and peritoneum	1 (6)	7 (11)		3 (14)	
Local	3 (19)	8 (13)		1 (5)	

IQR=Interquartile Range; *AJCC* = American Joint Commission on Cancer; *NIH*=National Institute of Health; *RFS* = Recurrence-Free Survival; *TKI* = Tyrosine Kinase Inhibitor.

(64%). Both groups had similar 5-year RFS ($P = 0.91$); 13% for patients treated with NAT (95% CI, 3%–46%; median, 24 months; range, 3–61 months) vs 10% for patients treated with upfront resection (95% CI, 3%–36%; median, 27 months; range, 5–61 months) (Fig. 1B). The most common site of recurrence was in the peritoneum (NAT, n = 8; 50% vs upfront resection, n = 10; 48%), followed by liver (NAT, n = 4; 25% vs upfront resection, n = 7; 33%).

3.4. Efficacy of neoadjuvant tyrosine kinase inhibitor therapy in downstaging

Of patients who were treated with NAT, nine (27%) achieved partial response to therapy based on RECIST criteria, 22 (67%) had stable response, and two (6%) had progressive disease (Table 2). Median tumor size was 9.5 cm (range, 2.6–25.9 cm) before NAT, and 6.9 cm (range, 2.4–26.2 cm) prior to curative-intent resection; median percent decrease in greatest tumor dimension was 11% (interquartile range, 2%–33%). Of 18 patients with gastric GISTs, five underwent wedge gastrectomy, ten underwent partial gastrectomy, and three underwent total gastrectomy (Table 3). Of the seven patients with duodenal GISTs, four underwent pancreatoduodenectomy (Table 3). Overall, 18 patients (55%) had a potentially smaller procedure than would have been needed if the tumor had progressed based upon review of pre-operative and operative notes.

4. Discussion

Targeted therapy with TKI in patients with advanced GIST has been shown to improve recurrence-free survival when delivered in the adjuvant setting. The RTOG 0132/ACRIN 6665 phase II single arm trial demonstrated that neoadjuvant TKI therapy was safe and well-tolerated

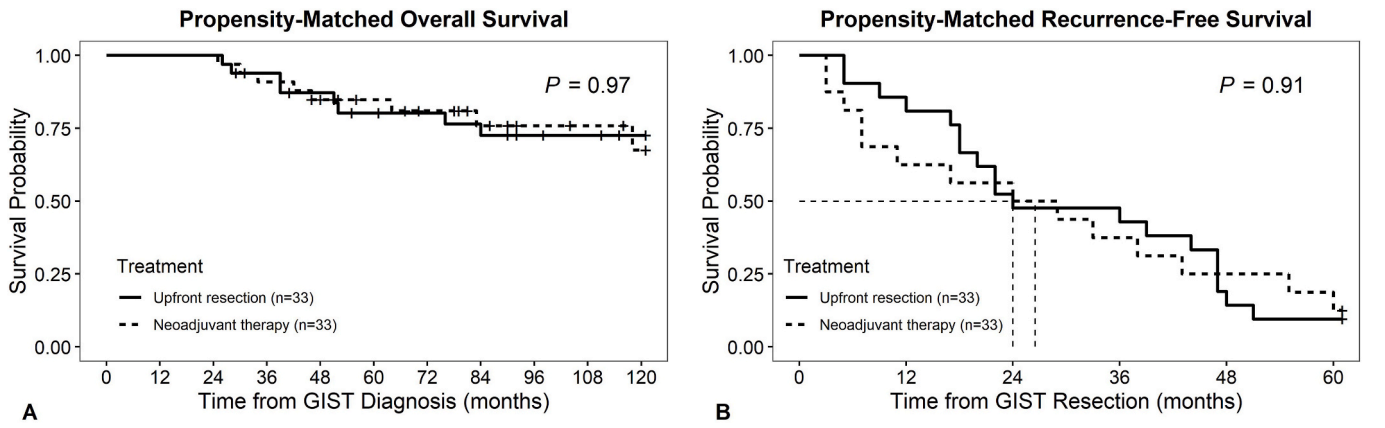

Fig. 1. Kaplan-Meier (**A**) overall survival following radiographic evidence of gastrointestinal stromal tumor (GIST) and (**B**) recurrence-free survival following curative-intent resection of GIST for patients treated with neoadjuvant tyrosine kinase inhibitor (TKI) therapy compared to upfront resection.

Table 2
Characteristics and primary tumor response to neoadjuvant tyrosine kinase inhibitor therapy.

Characteristic	Overall (n = 33)
Pre-NAT tumor size (cm), median (IQR)	9.5 (6.5–12.6)
Pre-operative tumor size (cm), median (IQR)	6.9 (5.0–10.6)
Percent decrease in tumor dimension (%), median (IQR)	11 (2–31)
RECIST response, n (%)	
Partial	9 (27)
Stable	22 (67)
Progressive	2 (6)
Operative approach, n (%)	
Minimally-invasive converted to open	1 (3)
Laparoscopic	5 (15)
Open	27 (82)

NAT=Neoadjuvant Therapy; *IQR*=Interquartile Range; *RECIST* = Response Evaluation Criteria in Solid Tumors.

Table 3
Gastric and duodenal tumor response to neoadjuvant tyrosine kinase inhibitor therapy.

Characteristic	Partial RECIST Response	Stable RECIST Response
Gastric GIST (n = 18)		
Wedge gastrectomy, n (%)	2 (40)	3 (60)
Partial Gastrectomy, n (%)	2 (20)	6 (60)
Total gastrectomy, n (%)	0 (0)	3 (100)
Duodenal GIST (n = 7)		
Pancreatoduodenectomy, n (%)	0 (0)	4 (100)
Partial duodenectomy, n (%)	1 (50)	1 (50)
Partial duodenectomy with reconstruction, n (%)	0 (0)	1 (100)

RECIST = Response Evaluation Criteria in Solid Tumors; *GIST* = Gastrointestinal Stromal Tumor.

with a 77% 5-year OS.[12,13] However, the long-term effects of TKI therapy in the neoadjuvant setting on relapse and overall survival remains unclear and has not been prospectively evaluated in a randomized controlled trial. After 1:1 propensity-matching we found that TKI NAT did not result in significant changes in 10-year OS or 5-year RFS (both $P > 0.9$). However, we did identify that NAT may be efficacious in helping to stabilize or reduce the size of the tumor prior to curative-intent resection with 55% of patients having a potentially smaller procedure than would have been needed if the tumor had progressed based on pre-operative and operative notes.

To the authors' knowledge, this is the first study to report 10-year OS from the time of radiographic diagnosis of GIST for patients treated with neoadjuvant TKI therapy. Previous studies have demonstrated improved oncologic outcomes in patients who received TKI NAT[5,13,22]; with reported 5-year OS ranging from 77% to 87%.[10,11] However, these studies did not adjust for the receipt of adjuvant therapy or GIST risk assessment in their cohorts or had difficulty identifying which patients received adjuvant therapy.[11,13] Our results better align with a recent study that matched groups by receipt of adjuvant therapy and demonstrated no significant survival benefit between those who were treated with NAT compared to upfront resection.[5] In addition to the methodology of their study which matched for receipt of adjuvant TKI therapy,[5] we also matched for duration of adjuvant therapy to fully investigate the role of NAT. Our results may more appropriately demonstrate the survival outcomes in patients with higher-risk GIST, irrespective of receipt of adjuvant TKI therapy. Notably, the 5-year RFS calculated in this study (13%) was considerably lower than previously reported (65%), most likely due to analyzing only "high-risk" patients.[11] Given the established benefit of prolonged adjuvant TKI therapy following resection of high-risk GIST in multiple randomized trials including the European Organization for Research and Treatment of Cancer (EORTC) 62024 and the American College of Surgeons Oncology Group (ACOSOG) Z9001,[7–10] further research is needed to clearly identify if NAT independently decreases recurrence and ultimately leads to improved overall survival outcomes.

Overall, TKI NAT appeared to be efficacious for stabilization or reduction in the greatest dimension of GIST prior to resection (11%) given our limited data in our retrospective study. Our findings identified that 55% of patients had a potentially smaller procedure than would have been needed if the tumor progressed based on review of pre-operative and operative notes. Other studies have demonstrated that NAT has enabled sphincter-preserving resection in 33%–77% of patients with rectal GIST,[23,24] and over half of the stomach in 84% of patients with gastric GIST.[22] Two-thirds of patients treated with NAT in our cohort achieved a stable RECIST response, with 27% achieving a partial RECIST response. The RTOG 0132/ACRIN 6665 study demonstrated a similar stable RECIST response (83%) in higher-risk GIST.[12] Our results add to the growing understanding on the effects, safety, and tolerability of TKI NAT in patients with higher risk GIST. However, GISTs do not fully regress with TKI therapy but rather, often become more cystic. Currently it is unclear if GISTs regress from the point of origin where TKI NAT would have a benefit in allowing R0 resection with potentially more minimal operations. Additionally, the ability to determine if response in the setting of NAT TKI treatment for high-risk GIST (e.g., allowing the surgeon to do a partial vs a total gastrectomy) is highly subjective and difficult to assess retrospectively, and will likely pose similar challenges in a prospective analysis. However, we believe it is important to highlight that equivalent RFS and OS outcomes in these two groups of propensity matched patients—one of which was high

enough risk that pre-operative NAT was considered to be potentially beneficial—underscore the difficult to capture clinical impact of NAT in this disease. The role of NAT for patients with higher-risk GIST should be guided by a multi-disciplinary team to select patients most likely to benefit from its use and minimize risks of TKI intolerance.[25]

Our study has several limitations. Notably, 41% of the overall cohort did not have driver mutation data available. The majority of missing mutation analyses were from earlier years of the study (42% of patients tested in 2002 through 2005); testing became more routine in later years and is now considered standard of care.[26] This study is subject to potential transfer bias where patients with insufficiently long or incomplete follow-up could influence our results. However, patients with GIST, particularly those treated with adjuvant TKI therapy, have extensive follow-up (our cohort median, 88 months). Finally, an objective aim of measuring the utility of TKI NAT in allowing a smaller resection for precariously positioned tumors remains elusive given the subjective nature of response assessment. However, our study provides expanded insight into the role of TKI NAT for patients with GIST and utilizes 1:1 propensity-matching methodology to minimize the risk of statistical fragility and any confounding effects from receipt of adjuvant TKI therapy.[14]

5. Conclusions

Neoadjuvant tyrosine kinase inhibitor therapy can be used to facilitate resection in select patients with surgically higher-risk GIST and does not result in worse oncologic outcomes. However, there is no evidence for an independent oncologic benefit for TKI neoadjuvant therapy compared to upfront resection. In the absence of evidence of an oncologic benefit, the predominant benefit of TKI NAT may be in allowing more limited resections of tumors in difficult locations, such as the duodenum or lesser gastric curvature. Therapy delivered in the NAT setting may be efficacious in stabilizing or reducing the size of GISTs prior to curative-intent resection, but definitive evidence of successful downstaging is difficult to determine. To fully appreciate the effects of tyrosine kinase inhibitor neoadjuvant therapy, we recommend further investigation to compare NAT to upfront resection in patients who additionally are treated with equal lengths of adjuvant TKI therapy utilizing a randomized controlled trial.

Financial disclosure

Please complete for any additional explanatory information: The authors of this manuscript have no conflicts of interest to disclose. This research project was undertaken without financial assistance of any kind.

Funding

MCH received partial funding from the following sources: GIST Cancer Research Fund, Jonathan David Foundation; VA Merit Review Grant (partial salary support from a Veterans Affairs Merit Review Grant (I01BX005358); and NCI R21 grant (R21CA263400).

Declaration of competing interest

Dr. Michael Heinrich receives consulting fees from Novartis, Deciphera Pharmaceuticals, Blueprint Medicines, and Theseus Pharmaceuticals. Dr. Michael Heinrich holds multiple patents on the diagnosis and/or treatment of GIST. One patent on treatment of GIST has been licensed by OHSU to Novartis. The other authors have no conflicts of interest or financial ties to disclose.

References

1. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumors: recent advances in understanding of their biology. *Hum Pathol*. 1999;30(10):1213–1220. https://doi.org/10.1016/s0046-8177(99)90040-0.
2. Søreide K, Sandvik OM, Søreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. *Cancer Epidemiol*. 2016;40:39–46. https://doi.org/10.1016/j.canep.2015.10.031.
3. Corless CL, Heinrich MC. Molecular pathobiology of gastrointestinal stromal sarcomas. *Annu Rev Pathol*. 2008;3:557–586. https://doi.org/10.1146/annurev.pathmechdis.3.121806.151538.
4. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol*. 2003;21(23):4342–4349. https://doi.org/10.1200/JCO.2003.04.190.
5. Marqueen KE, Moshier E, Buckstein M, Ang C. Neoadjuvant therapy for gastrointestinal stromal tumors: a propensity score-weighted analysis. *Int J Cancer*. 2021;149(1):177–185. https://doi.org/10.1002/ijc.33536.
6. Cavnar MJ, Seier K, Curtin C, et al. Outcome of 1000 patients with gastrointestinal stromal tumor (GIST) treated by Surgery in the pre- and post-imatinib eras. *Ann Surg*. 2021;273(1):128–138. https://doi.org/10.1097/SLA.0000000000003277.
7. Casali PG, Le Cesne A, Poveda Velasco A, et al. Time to definitive failure to the first tyrosine kinase inhibitor in localized GI stromal tumors treated with imatinib as an adjuvant: a European organisation for research and treatment of cancer soft tissue and bone Sarcoma group intergroup randomized trial in collaboration with the Australasian Gastro-intestinal trials group, UNICANCER, French Sarcoma group, Italian Sarcoma group, and Spanish group for research on sarcomas. *J Clin Oncol*. 2015;33(36):4276–4283. https://doi.org/10.1200/JCO.2015.62.4304.
8. Joensuu H, Eriksson M, Sundby Hall K, et al. Survival outcomes associated with 3 Years vs 1 Year of adjuvant imatinib for patients with high-risk gastrointestinal stromal tumors: an analysis of a randomized clinical trial after 10-year follow-up. *JAMA Oncol*. 2020;6(8):1241–1246. https://doi.org/10.1001/jamaoncol.2020.2091.
9. Corless CL, Ballman KV, Antonescu CR, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol*. 2014;32(15):1563–1570. https://doi.org/10.1200/JCO.2013.51.2046.
10. Keung EZ, Raut CP, Rutkowski P. The landmark series: systemic therapy for resectable gastrointestinal stromal tumors. *Ann Surg Oncol*. 2020;27(10):3659–3671. https://doi.org/10.1245/s10434-020-08869-w.
11. Rutkowski P, Gronchi A, Hohenberger P, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. *Ann Surg Oncol*. 2013;20(9):2937–2943. https://doi.org/10.1245/s10434-013-3013-7.
12. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol*. 2009;99(1):42–47. https://doi.org/10.1002/jso.21160.
13. Wang D, Zhang Q, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumors: long-term follow-up results of Radiation Therapy Oncology Group 0132. *Ann Surg Oncol*. 2012;19(4):1074–1080. https://doi.org/10.1245/s10434-011-2190-5.
14. Stürmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. *J Clin Epidemiol*. 2006;59(5):437–447. https://doi.org/10.1016/j.jclinepi.2005.07.004.
15. Rutkowski P, Bylina E, Wozniak A, et al. Validation of the Joensuu risk criteria for primary resectable gastrointestinal stromal tumour - the impact of tumour rupture on patient outcomes. *Eur J Surg Oncol*. 2011;37(10):890–896. https://doi.org/10.1016/j.ejso.2011.06.005.
16. Gold JS, Gönen M, Gutiérrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol*. 2009;10(11):1045–1052. https://doi.org/10.1016/S1470-2045(09)70242-6.
17. Chok AY, Goh BKP, Koh YX, et al. Validation of the MSKCC gastrointestinal stromal tumor nomogram and comparison with other prognostication systems: single-institution experience with 289 patients. *Ann Surg Oncol*. 2015;22(11):3597–3605. https://doi.org/10.1245/s10434-015-4400-z.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications. *Ann Surg*. 2004;240(2):205–213. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. https://doi.org/10.1016/j.ejca.2008.10.026.
20. Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1-Update and clarification: from the RECIST committee. *Eur J Cancer*. 2016;62:132–137. https://doi.org/10.1016/j.ejca.2016.03.081.
21. Pantuso G, Macaione I, Taverna A, et al. Surgical treatment of primary gastrointestinal stromal tumors (GISTs): management and prognostic role of R1 resections. *Am J Surg*. 2020;220(2):359–364. https://doi.org/10.1016/j.amjsurg.2019.12.006.
22. Kurokawa Y, Yang HK, Cho H, et al. Phase II study of neoadjuvant imatinib in large gastrointestinal stromal tumours of the stomach. *Br J Cancer*. 2017;117(1):25–32. https://doi.org/10.1038/bjc.2017.144.

23. Wilkinson MJ, Fitzgerald JEF, Strauss DC, et al. Surgical treatment of gastrointestinal stromal tumour of the rectum in the era of imatinib. *Br J Surg*. 2015; 102(8):965–971. https://doi.org/10.1002/bjs.9818.
24. Pai VD, Demenezes JL, Patil PS, Saklani AP. Multimodality therapy of rectal gastrointestinal stromal tumors in the era of imatinib-an Indian series. *J Gastrointest Oncol*. 2016;7(2):262–268. https://doi.org/10.3978/j.issn.2078-6891.2015.088.
25. Sutton TL, Walker BS, Billingsley KG, et al. Disease-free interval is associated with oncologic outcomes in patients with recurrent gastrointestinal stromal tumor. *Ann Surg Oncol*. 2021. https://doi.org/10.1245/s10434-021-10062-6. Published online May 9.
26. von Mehren M, Randall RL, Benjamin RS, et al. Soft tissue Sarcoma, version 2.2018, NCCN clinical practice guidelines in Oncology. *J Natl Compr Cancer Netw JNCCN*. 2018;16(5):536–563. https://doi.org/10.6004/jnccn.2018.0025.