Abstract. Overexpression of Ki67 is observed in tumor cells, and it has been suggested to be a marker for cancer prognosis. However, the relationship between Ki67 expression and the risk of recurrence of gastrointestinal stromal tumors (GISTs) remains poorly defined. In the present study, a meta-analysis was used to examine the associations between Ki67 levels and GIST recurrence. Studies reporting GIST and Ki67 were found by searching Cochrane Library, PubMed and Embase until October 14, 2021. The Newcastle-Ottawa Scale (NOS) was used to verify the quality of the evidence. Totally, 1682 patient cases were included. The odds ratio (OR) estimates and 95% confidence interval (CI) for each publication were determined by a fixed-effects (Mantel-Haenszel) model. A total of 20 studies that fulfilled the inclusion criteria were finally included in the analysis. The average score of quality evaluation was 6.4 points according to NOS. It was found that Ki67 levels were significantly higher in the NIH L group compared with the NIH VL group (OR: 0.51; 95% CI: 0.26-0.99; P=0.04; P heterogeneity=0.44). There was also greater Ki67 overexpression in the NIH I group compared with the NIH L group (OR: 0.45, 95% CI: 0.31-0.65; P<0.0001; P heterogeneity=0.32), while Ki67 levels were greater in the NIH H group than in the NIH I group (OR: 0.20; 95% CI: 0.15-0.28; P<0.00001; P heterogeneity=0.56). In conclusion, Ki67 overexpression may be a useful marker of the risk of recurrent GIST transformation.

Introduction

Gastrointestinal stromal tumor (GIST) is an uncommon gastrointestinal cancer, accounting for less than 3% of overall gastrointestinal neoplasms but 80% of those of mesenchymal origin (1) and approximately half of the cases are malignant (2). Although tumors may develop in any part of the gastrointestinal tract, they occur most frequently in the stomach (60%) and small intestine (between 20 and 30%) (3-5). The worldwide annual incidence is 7-15 per million (6,7), with geographical variations. For instance, in Europe and North America, the incidence is 10-15 annual cases per million of population but is higher in Asia at 16-20 per million (6). To evaluate the prognosis of GIST, a consensus risk assessment of recurrence was developed by the National Institutes of Health (NIH) in 2008 (Table I), subsequently revised to the modified NIH risk scale (8). According to the scale, the principal evaluation indices are the tumor size and mitosis count, and are divided into four grades: i) very low, ii) low, iii) intermediate and iv) high risk. A relationship between GIST risk and prognosis has been well documented (9). However, there is considerable variation in both the clinical behavior and prognosis of GIST, particularly in high-risk populations. Thus, a comprehensive and objective assessment of GIST biology and malignant progression, particularly in terms of histological and clinical features, is important.

Ki67 is expressed in cell nuclei during proliferation (10), visible in the cortex of the nucleolus in interphase, and associated with chromosomes during mitotic condensation (11). The level of the protein rises between G1 and mitosis, after which it declines sharply and is found in the nucleus during the G1, S and G2 phases but is not expressed during G0 (12,13). Thus, the level of Ki67 can be used as an index of proliferation. Overexpression of Ki67 is observed in tumor cells, and it has been suggested to be a marker for cancer prognosis (14). To date, several studies have reported the use of Ki67 levels in the prediction of GIST prognostic risk, with higher levels indicating an elevated risk of tumor spread and recurrence after surgery and the need for increased observation and management (15-18). Another study has reported that the Ki67 index together with raised levels of RacGAP1 are effective in combination with risk stratification and clinical parameters in assessing the likely outcome of GIST (19). However, did no correlation between Ki67 overexpression and mitotic activity in tumors was identified by Demir et al (20).

It is thus apparent that there is controversy surrounding the use of Ki67 in predicting risk in GIST, possibly due to the influence of small sample sizes. Although the relationship...
between Ki67 and GIST through meta-analysis was examined by Zhou et al (21) in 2017, only 9 studies were included at that time. In addition, the quality of the included studies was not evaluated in the aforementioned study, thus the quality of the studies was difficult to estimate. Thus far, more studies have discussed the relationship between Ki67 and prognosis of GIST. In the present study, a meta-analysis was re-used to examine the associations between Ki67 levels and GIST recurrence.

Materials and methods

Literature search and selection criteria. PubMed, Cochrane Library and EMBASE databases were searched for relevant articles using the terms ‘GIST’ and ‘Ki67’ by JL and ARW. Differences were resolved through discussion with a third researcher SQL. The search took place on October 14, 2021. In situations where patients were described in multiple publications, the most complete or recent articles were selected. As the analysis was based on published studies, neither ethical approval nor patient consent was required.

Inclusion criteria. The criteria for inclusion were as follows: i) Patients must be assessed for Ki67 expression by immunohistochemistry; ii) The prognostic risk of GIST was assessed by the NIH Risk System; iii) The full text or original data could be retrieved during October 2021.

Exclusion criteria. Articles that did not include information on Ki67 in relation to NIH risk assessment were excluded, as were case reports and articles describing studies in animals or cell lines.

Data extraction. The required information from the publications was independently recorded by JL and ARW. Specifically, this information included the first author, publication date, classification method, number of NIH risk categories, demographic parameters (such as age and sex), the sample size and Ki67 measurement. Any disagreements between the two researchers were resolved through discussion with the third researcher (SQL).

Statistical analysis. The Newcastle-Ottawa Scale (NOS) was used to verify the quality of the evidence. Data were analyzed with Review Manager Version 5.3 (Cochrane Collaboration), with P<0.05 representing statistical significance. Inter-study heterogeneity was evaluated using the I2 statistic and Cochrans' Q test. When there was no significant heterogeneity (Q test: P>0.1), the fixed-effects (Mantel-Haenszel) model was used to combine odds ratio (OR) values; otherwise, the random-effect (DerSimonian and Laird) model was used. The significance of combined ORs was evaluated using the z-test. Examination of the effects of changes in inclusion criteria on the final results was conducted by sensitivity analysis. The combined OR and 95% confidence interval (CI) of dichotomous variables were calculated. Funnel plots were used to assess possible publication bias, with bias indicated by plot asymmetry. Egger's test was applied to evaluate asymmetry in funnel plots, and unpaired t-tests were used to measure intercept significance (P<0.05).

Results

Features of the included studies. The titles and abstracts of the publications were reviewed, resulting in the exclusion of a number of studies due to insufficient information for calculating the OR (Fig. 1). A total of 20 studies that fulfilled the inclusion criteria were finally included in the analysis (15,22-40). The NOS was used to verify the quality of the evidence. Table II summarizes the principal characteristics of these studies. In all, 1682 patient cases were included. A flow chart of the screening process is shown in Fig. 1.

Meta-analysis. It was found that Ki67 levels were significantly higher in the NIH L group compared with the NIH VL group (OR: 0.51, 95% CI: 0.26-0.99; P=0.04; P heterogeneity=0.44) (Fig. 2A). There was also greater Ki67 overexpression in the NIH I group compared with the NIH L group (OR: 0.45, 95% CI: 0.31-0.65; P<0.0001; P heterogeneity=0.32) (Fig. 2B), while Ki67 levels were greater in the NIH H group than in the NIH I group (OR: 0.20, 95% CI: 0.15-0.28; P<0.00001, P heterogeneity=0.56) (Fig. 2C). Due to the small heterogeneity, the fixed-effects (Mantel-Haenszel) model was used. Heterogeneity analysis of the 20 studies revealed no heterogeneity (P>0.05), and sensitivity analysis indicated that no individual study influenced the pooled OR (data not shown).

Publication bias. No asymmetry was visible in the funnel plots, indicating an absence of publication bias (Fig. 3A-C).
Discussion

GIST develops from the gastrointestinal mesenchyme and is a relatively common sarcoma of soft tissue (41). The outcome usually depends on the size, site, and mitotic index of the tumor with tumors <5 cm in diameter originating in the stomach, with mitotic indices below 5/50 high-power field linked to more favorable prognoses (42,43). The NIH used these parameters to develop prediction tools for GIST progression and outcome, assessing the risk of poor outcome as very low, low, intermediate, or high as outcome prediction tools using these (8). In addition to this, numerous studies have been undertaken to investigate the possibility of basing prediction on molecular, as well as clinical, factors. A meta-analysis of Asian, European, and North American patients found that mutations in KIT exon 11 were associated with superior treatment responses and survival compared with exon 9 polymorphisms (44,45). A previous study showed that deletions in exon 11 (codons 557

| Risk class | Tumor size, cm | Mitotic count | Primary tumor location |
|------------|---------------|---------------|------------------------|
| Very low   | <2            | <5/50 HPF     | Any location           |
| Low        | 2-5           | ≤5/50 HPF     | Any location           |
| Intermediate | 2-5           | >5/50 HPF     | Stomach                |
|            | ≤5            | >5/50 to ≤10/50 HPF | Any location          |
|            | >5 to ≤10     | ≤5/50 HPF     | Stomach                |
| High       | Any size      | Any mitotic rate | Tumor rupture       |
|            | >10           | Any mitotic rate | Any location         |
| Any size   | >10/50 HPF    | Any location   |
| >5         | >5/50 HPF     | Not in the stomach |
| 2-5        | >5/50 HPF     | Not in the stomach |
| >5 to ≤10  | ≤5/50 HPF     | Not in the stomach |

GIST, gastrointestinal stromal tumor; HPF, high-power field.

Table I. National Institutes of Health system of risk grading for GIST.

| Risk class | Tumor size, cm | Mitotic count | Primary tumor location |
|------------|---------------|---------------|------------------------|
| High       | Any size      | Any mitotic rate | Tumor rupture       |
|            | >10           | Any mitotic rate | Any location         |
| Any size   | >10/50 HPF    | Any location   |
| >5         | >5/50 HPF     | Not in the stomach |
| 2-5        | >5/50 HPF     | Not in the stomach |
| >5 to ≤10  | ≤5/50 HPF     | Not in the stomach |

H, high risk; I, intermediate risk; L, low risk; NIH, National Institutes of Health; VL, very low risk; NOS, Newcastle-Ottawa Scale; all studies report clinicopathological outcomes.

Table II. Main characteristics of all studies included in the meta-analysis.

| First author (year) | Country | NIH (VL/L/I/H) | Age, years | Sex (male/female) | Total cases | NOS score | (Refs.) |
|---------------------|---------|----------------|------------|-------------------|-------------|-----------|---------|
| Nakamura (2005)     | Japan   | 0/22/25/33     | -          | 39/41             | 80          | 6         | (22)    |
| Pilea (2014)        | Romania | 0/1/2/12       | 62.4       | 10/5              | 15          | 6         | (23)    |
| Peker (2014)        | Turkey  | 0/28/21/31     | 58.55±10.59 | -                 | 72          | 7         | (24)    |
| Tsumuraya (2010)    | Japan   | 1/4/4/6        | 59.2±14.05 | 7/8               | 15          | 6         | (25)    |
| Jiang (2016)        | China   | 6/12/10/12     | 58.5 (40-83)| 22/18             | 40          | 5         | (26)    |
| Güler (2015)        | Turkey  | 3/6/7/20       | 57.2 (23-74)| 15/22             | 37          | 6         | (27)    |
| Li (2018)           | China   | 10/61/29/48    | 61 (9-86)  | 69/82             | 151         | 5         | (15)    |
| Wang (2014)         | China   | 5/26/17/36     | 61.5 (23-78)| 46/38             | 84          | 8         | (28)    |
| Zhao (2014)         | China   | 32/152/62/124  | 59         | 199/171           | 370         | 6         | (29)    |
| Nanding (2014)      | China   | 3/12/4/22      | 52.52±13.21| 20/21             | 41          | 6         | (30)    |
| Lu (2013)           | China   | 5/15/16/75     | 57 (18-82) | 59/52             | 111         | 6         | (31)    |
| Segales-Rojas (2018)| Mexico  | 0/6/11/26      | 55 (23-86) | 21/22             | 43          | 8         | (32)    |
| Jiang (2012)        | China   | 3/24/24/45     | 55 (26-82) | 57/39             | 96          | 5         | (33)    |
| Liu (2013)          | China   | 5/15/16/77     | 60         | 61/52             | 113         | 6         | (34)    |
| Alghamdi (2019)     | Saudi Arabia | 0/5/17/14     | 54 (17-28) | 13/23             | 36          | 6         | (35)    |
| Ngo (2019)          | Vietnam | 6/42/40/67     | 55 (15-88) | 72/83             | 155         | 6         | (36)    |
| Poddà (2020)        | Italy   | 16/10/3/10     | 58.6±17.3  | 25/14             | 39          | 8         | (37)    |
| Tepeoğlu (2018)     | Turkey  | 24/17/7/17     | -          | 31/34             | 65          | 7         | (38)    |
| Wei (2020)          | China   | 16/25/27/33    | -          | 49/52             | 101         | 6         | (39)    |
| Taniguchi (2021)    | Japan   | 0/10/6/2       | 63.6±12    | 8/10              | 18          | 7         | (40)    |

H, high risk; I, intermediate risk; L, low risk; NIH, National Institutes of Health; VL, very low risk; NOS, Newcastle-Ottawa Scale; all studies report clinicopathological outcomes.
Figure 2. Meta-analysis of incidence of Ki67 overexpression among NIH subgroups. (A) NIH VL group vs. NIH L group. (B) NIH L group vs. NIH I group. (C) NIH I group vs. NIH H group. H, high risk; I, intermediate risk; L, low risk; NIH, National Institutes of Health; VL, very low risk.
and/or 558) of KIT were linked to significantly lower rates of
disease-free survival in European patients with GIST (46).
Mutations in exon 18 of PDGFRA have also been associated
with significantly reduced GIST progression and improved
outcomes (47,48). In the present study, a meta-analysis was
conducted at the molecular level to determine whether Ki67
can determine the prognosis of GIST.

Ki67 was discovered by Gerdes et al (48) in 1983. Ki67 is a nucleoprotein marker for cell proliferation and is
associated particularly with mitosis, although it is present
throughout the cell cycle apart from G0. The mitosis index
is related to tumor morphology and refers specifically to
the m-phase of the cell cycle. Therefore, Ki67 is a more
accurate reflection of the degree of tumor malignancy than
the mitotic index (49). Ki67 expression can be induced by
hypoxia (50). In breast, lung, prostate, cervical, and central
nervous system cancers, Ki67 is recognized as a reliable
marker of important prognostic significance (51). It is
currently considered that the expression level of Ki67 is an
independent factor affecting the prognosis of GIST (29). Nilsson et al (52) described both tumor size and Ki67 >5% as
independent risk factors for poor prognosis of GIST. It is
known that Ki67 defines cell proliferation in relation to
the cell cycle, and is, therefore, a useful measure of GIST
recurrence (53,54). However, Wong et al (55) considered
that Ki67 was not as reliable as the mitotic count, despite its
usefulness in measuring the proliferative rate of GIST cells.
Furthermore, Segales-Rojas et al (32) reported that tumor
recurrence was not related to Ki67 but only to tumor size
and gender. Kramer et al (56) reached a similar conclusion,
reporting that patients with GIST younger than 50 years old
and female patients have an improved prognosis.

To clarify these conflicting reports, the relationship
between Ki67 levels and GIST prognosis was investigated
through meta-analysis. In this meta-analysis, Ki67 levels
were found to be higher in the NIH L group than in the NIH
VL group, while those in the NIH I group were significantly
increased in comparison with the NIH L group. Ki67 was
also overexpressed in the NIH H group compared with the
NIH I group. In the present study, different results were
obtained compared with Zhou et al (21). The results revealed
that the higher the risk, the higher the overexpression rate of
Ki67, suggesting that Ki67 expression may be a useful addi-
tion to the NIH assessment system for GIST risk prediction.
Although the mitotic index has been considered to be only
an indication of the M mitotic phase (57), Ki67 is expressed
throughout the cell cycle apart from the G0 phase and is an
important predictor of poor prognosis in GIST (P<0.0003). It
was found that Ki67 had higher observer reliability than the
mitotic count in the evaluation of mitotic activity (32), and the
Ki67 index may thus be used as a replacement index for the
mitotic count in the future.

Nevertheless, the present meta-analysis has several limi-
tations. First, it is difficult to reach a precise conclusion due
to the limited sample size, differences in antibody clones
and possible heterogeneity. Second, the clinicopathological
information of patients was derived from case reports, and
differences in the practices and diagnostic criteria of different
pathologists may also lead to bias. Therefore, since adjuvant
imatinib is standard for high risk GIST, it is considered that a
large-scale, multi-center prospective study is necessary in the
future, taking the low-risk group not receiving imatinib as the
control group, and the high-risk group receiving treatment as
the experimental group, to compare the long-term survival of
the results of the two groups, and use multivariate regression
analysis to clarify whether the Ki67 index, gene mutation site,
medication compliance and blood drug concentration were
related to survival outcomes. Despite these limitations, the
present findings contributed to the further discovery of new
predictors of adverse outcomes and to the improvement of
existing classification criteria.

Figure 3. Begg funnel plot for publication bias test. (A) NIH VL group vs.
NIH L group. (B) NIH L group vs. NIH I group. (C) NIH I group vs. NIH H
group. H, high risk; I, intermediate risk; L, low risk; NIH, National Institutes
of Health; VL, very low risk.
Acknowledgements
Not applicable.

Funding
No funding was received.

Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions
JL and SQL contributed to the conception, design and modification of the study. ARW, XDC and HP extracted the data and organized the database search. JL and ARW performed the statistical analysis. SQL, XDC and HP drafted the manuscript. JL and SQL confirm the authenticity of all the raw data. All authors contributed to manuscript revision, read, and approved the submitted version. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

References
1. El-Menayar A, Mekodathil A and Al-Thani H: Diagnosis and management of gastrointestinal stromal tumors: An up-to-date literature review. J Cancer Res Ther 13: 899-900, 2017.
2. Schaefer JM, Marinho-Enriquez A and Fletcher JA: What is new in gastrointestinal stromal tumor? Adv Anat Pathol 24: 259-267, 2017.
3. Nishida T, Blay JY, Hirota S, Kitagawa Y and Kang YK: The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer 19: 3-14, 2016.
4. Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, Pisters PW, Raut CP, Riedel RF, Schuetze S, et al: NCCN task force report: Update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 8 (Suppl 2): S1-S44, 2010.
5. Miettinen M and Lasota J: Histopathology of gastrointestinal stromal tumor. J Surg Oncol 104: 865-873, 2011.
6. van der Graaf WTA, Tielen R, Bovenkamp JJ, Lemmens V, Verhoeven RHA and de Wilt JHW: Nationwide trends in the incidence and outcome of patients with gastrointestinal stromal tumor in the imatinib era. Br J Surg 105: 1020-1027, 2018.
7. MaGL, Murphy JD, Martinez ME and Sicklick JK: Epidemiology of gastrointestinal stromal tumors in the era of histology codes: Results of a population-based study. Cancer Epidemiol Biomarkers Prev 24: 298-302, 2015.
8. Joesu H: Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 39: 1411-1419, 2008.
9. Kitamura Y: Gastrointestinal stromal tumors: Past, present, and future. J Gastroenterol 43: 499-508, 2008.
10. Scholzen T and Gerdes J: The Ki-67 protein: From the known and the unknown. J Cell Physiol 182: 311-322, 2000.
11. Isola J, Helin Hand Kallioniemi OP: Immuno-electronic-microscopic localization of a proliferation-associated antigen Ki-67 in MCF-7 cells. Histochem J 22: 498-506, 1990.
12. da Mauer S, Guilraud P, Carus E, Seigneurin D and Brugal G: Ki-67 labeling in postmitotic cells defines different Ki-67 pathways within the 2c compartment. Cytometry 12: 455-463, 1991.
13. Hutchins JR, Toyoda Y, Hegemann B, Poser I, Hériché JK, Sykora MM, Augsburg M, Hudecz O, Buschhorn BA, Buklescher J, et al: Systematic analysis of human protein complexes identifies chromosome segregation proteins. Science 328: 593-599, 2010.
14. Visapää H, Bui M, Huang Y, Seligson D, Tsai H, Pantuck A, Figlin R, Rao JY, Belldegrun A, Horvath S and Palatiet A: Correlation of Ki-67 and gelsolin expression to clinical outcome in renal clear cell carcinoma. Urology 61: 845-850, 2003.
15. Li H, Ren G, Cai R, Chen J, Wu X and Zhao J: A correlation research of Ki67 index, CT features, and risk stratification in gastrointestinal stromal tumor. Cancer Med 7: 4467-4474, 2018.
16. Zhang H and Liu Q: Prognostic indicators for gastrointestinal stromal tumors: A review. Transl Oncol 13: 100812, 2020.
17. Wang JP, Liu L, Li ZA, Wang Q, Wang XY and Lin J: Ki-67 labelling index is related to the risk classification and prognosis of gastrointestinal stromal tumours: A retrospective study. Gastroenterol Hepatol 44: 103-114, 2021 (In English, Spanish).
18. Liu X, Qiu H, Zhang P, Feng X, Chen T, Li Y, Tao K, Li G, Sun X and Zhou Z; China Gastrointestinal Stromal Tumor Study Group (CN-GIST): Ki-67 labeling index may be a promising indicator to identify ‘very high-risk’ gastrointestinal stromal tumor: A multicenter retrospective study of 1022 patients. Hum Pathol 74: 17-24, 2018.
19. Sahin S, Ekinci O, Seckin S and Dursun A: Proliferation markers RacGAP1 and Ki-67 in gastrointestinal stromal tumors by immunohistochemistry with respect to clinicopathological features and different risk stratification systems. Int J Clin Exp Pathol 10: 11723-11736, 2017.
20. Demir L, Ekinci N, Erten C, Kucukzeybek Y, Alacagio glu A, Somali I, Can A, Dirican A, Bayoglu V, Akoylu M, et al: Does immunohistochemistry provide additional prognostic data in gastrointestinal stromal tumors? Asian Pac J Cancer Prev 14: 4751-4758, 2013.
21. Zhou Y, Hu W, Chen P, Abe M, Shi L, Tan SY, Li Y and Zong L: Ki67 is a biological marker of malignant risk of gastrointestinal stromal tumors: A systematic review and meta-analysis. Medicine (Baltimore) 96: e7911, 2017.
22. Nakamura N, Yamamoto H, Yao T, Oda Y, Nishiyama K, Imamura M, Yamada T, Nawata H and Tsuneyoshi M: Prognostic significance of expressions of cell-cycle regulatory proteins in gastrointestinal stromal tumor and the relevance of the risk grade. Hum Pathol 36: 828-837, 2005.
23. Plesca IE, Chiţuţa L, Borda SI, Georgescu I, Georgescu EF, Ciobanu D, Mărgăritescu ND, Comănescu V and Nemeş R: Prognostic impact of gastrointestinal stromal tumors and its clinical significance. Anticancer Res 30: 2705-2715, 2010.
24. Akimoto K and Sunagawa M: Comprehensive analysis of genes involved in the malignancy of gastrointestinal stromal tumors. Anticancer Res 30: 2715-2719, 2010.
25. Liu J, Cao M, Hu J and Chen J: Expression of PIN1 in gastrointestinal stromal tumors and its clinical significance. Anticancer Res 36: 3239-3245, 2016.
26. Güler B, Özysılmaz F, Tokuc B, Can N and Taştekin E: Histopathological features of gastrointestinal stromal tumors and the contribution of DOG1 expression to the diagnosis. Balkan Med J 32: 388-396, 2015.
27. Wang H, Chen P, Liu XX, Zhao W, Shi L, Gu XW, Zhu CR, Zong LF and Zhou J: Prognostic impact of gastrointestinal bleeding and expression of PTEN and Ki-67 on primary gastrointestinal stromal tumors. World J Surg Oncol 12: 89, 2014.
29. Zhao WY, Xu J, Wang M, Zhang ZZ, Tu L, Wang CJ, Lin TL, Shen YY, Liu Q and Cao H: Prognostic value of Ki67 index in gastrointestinal stromal tumors. Int J Clin Exp Pathol 7: 2798‑2304, 2014.
30. Nanding A, Tang L, Cai L, Chen H, Geng J, Liu X, Ning X, Li X and Zhang Q: Low ING4 protein expression detected by paraffin‑section immunohistochemistry is associated with poor prognosis in untreated patients with gastrointestinal stromal tumors. Gastric Cancer 17: 87‑96, 2014.
31. Lu C, Liu L, Wu X and Xu W: CD133 and Ki‑67 expression is associated with gastrointestinal stromal tumor prognosis. Oncol Lett 6: 1289‑1294, 2013.
32. Segales‑Rojas P, Lino‑Silva LS, Aguilar‑Cruz E and Salcedo‑Hernández RA: Association of ki67 index with recurrence in gastrointestinal stromal tumors. J Gastrointest Cancer 49: 543‑547, 2018.
33. Jiang J, Cao XY, Suo J, Wang YP, He L and Cao XY: Evaluation of malignancy using Ki‑67, p53, EGFR and COX‑2 expressions in gastrointestinal stromal tumors. World J Gastroenterol 18: 2569‑2575, 2012.
34. Liu LC, Xu WT, Wu X, Zhao P, Lv YL and Chen L: Overexpression of carbonic anhydrase II and Ki‑67 proteins in prognosis of gastrointestinal stromal tumors. World J Gastroenterol 19: 2473‑2480, 2013.
35. Alghamdi HM, Amr SS, Shawarby MA, Sheikh SS, Alsayyah AA, Alamri AM, Ismail MH, Almarhabti A, Alrefaee MA and Ahmed MI: Gastrointestinal stromal tumors. A clinicopathological study. Saudi Med J 40: 126‑130, 2019.
36. Ngo QD, Pham QT, Phan DAT, Hoang AV, Hua TNH and Nguyen ST: Molecular and clinicopathological features of gastrointestinal stromal tumors in vietnamese patients. J Pathol Transl Med 53: 361‑368, 2019.
37. Podda M, Ferraro G, Di Saverio ME, Pisciotta V, Poilucci G, Marino MV and Pisano A: Association between gastrointestinal stromal tumors and other malignancies: It is only a matter of time ? A case series and an overview of systematic reviews. J Gastroenterol 51: 914‑924, 2020.
38. Tepeoğlu M, Özgün G, Tunca MZ, Teczaner T and Özdemir BH: Gastrointestinal stromal tumors: A clinicopathological and immunohistochemical study of 65 cases. Turk Patoloji Derg 34: 207‑214, 2018.
39. Wei SC, Xu L, Li WH, Li Y, Guo SF, Sun XR and Li WW: Risk stratification in GIST: Shape quantification with CT is a predictive factor. Eur Radiol 30: 1856‑1865, 2020.
40. Taniguchi K, Suzuki A, Serizawa A, Kotake S, Itó S, Suzuki K, Yamada T, Noguchi T, Amano K, Ota M, et al: Rapid flow cytometry of gastrointestinal stromal tumours closely matches the modified fletcher classification. Anticancer Res 41: 131‑136, 2021.
41. Jochens H, Hohenberger P and Corless CL: Gastrointestinal stromal tumour. Lancet 382: 973‑983, 2013.
42. McCarter MD, Antonescu CR, Ballman KV, Maki RG, Pisters PW, Demetri GD, Blanke CD, von Mehren M, Brennan MF, McCall L, et al: Microscopically positive margins for primary gastrointestinal stromal tumors: Analysis of risk factors and tumor recurrence. J Am Coll Surg 215: 53‑60, 2021.
43. Gold JS, Ginen M, Gutiérrez A, Broto JM, García‑del‑Muro X, Smyrk TC, Maki RG, Singer S, Brennan MF, Antonescu CR, 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 10: 1045‑1052, 2009.
44. Zhi X, Zhou X, Wang W and Xu Z: Practical role of mutation analysis for imatinib treatment in patients with advanced gastrointestinal stromal tumors: A meta‑analysis. PLoS One 8: e79275, 2013.
45. Yan L, Zou L, Zhao W, Wang Y, Liu B, Yao H and Yu H: Clinicopathological significance of c‑KIT mutation in gastrointestinal stromal tumors: A systematic review and meta‑analysis. Sci Rep 5: 13718, 2015.
46. Wozniak A, Rukowski P, Schöffski P, Ray‑Coquard I, Hostein I, Schildhaus HU, Le Cesne A, Bylina E, Limon J, Blay JY, et al: Tumor genotype is an independent prognostic factor in primary gastrointestinal stromal tumors of gastric origin: A European multicenter analysis based on ConticaGIST. Clin Cancer Res 20: 6105‑6116, 2014.
47. Rubió‑Casadevall J, Borràs JL, Carmona‑García MC, Ameijide A, Gonzalez‑Vidal A, Ortiz MR, Bosch R, Riu F, Parada D, Martí E, et al: Correlation between mutational status and survival and second cancer risk assessment in patients with gastrointestinal stromal tumors: A population‑based study. World J Surg Oncol 13: 47, 2015.
48. Gerdes J, Schwab U, Lemke H and Stein H: Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. Int J Cancer 31: 13‑20, 1983.
49. Belev B, Breči I, Prejac J, Golubić ZA, Vrbanec D, Božikov J, Alerić I, Boban M and Razumović JJ: Role of Ki‑67 as a prognostic factor in gastrointestinal stromal tumors. World J Gastroenterol 19: 523‑527, 2013.
50. Jia YF, Xiao DJ, Ma XL, Song YY, Hu R, Kong Y, Zheng Y, Han SY, Hong RL and Wang YS: Differentiated embryonic chondrocyte‑expressed gene I is associated with hypoxia‑inducible factor 1α and Ki67 in human gastric cancer. Diagn Pathol 8: 37, 2013.
51. Seidal T and Edvardsson H: Expression of c‑kit (CD117) and Ki67 provides information about the possible cell of origin and clinical course of gastrointestinal stromal tumours. Histopathology 34: 416‑424, 1999.
52. Nilsson B, Büming P, Meis‑Kindblom JM, Ödén A, Dortok A, Gustavsson B, Säblinska K and Kindblom LG: Gastrointestinal stromal tumors: The incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era‑a population‑based study in western Sweden. Cancer 103: 821‑829, 2005.
53. Nagasako Y, Misawa K, Kohashi S, Hasegawa K, Okawa Y, Sano H, Takada A and Sato H: Evaluation of malignancy using Ki‑67 labeling index for gastric stromal tumor. Gastric Cancer 6: 168‑172, 2003.
54. Gumurduלר D, Erdogan S, Kayaselekul F, Seydaoglu G, Parsak CK, Demircan O and Tuncer I: Expression of COX‑2, PCNA, Ki‑67 and p53 in gastrointestinal stromal tumors and its relationship with histopathological parameters. World J Gastroenterol 13: 426‑431, 2007.
55. Wong NA, Young R, Malcomson RD, Nayar AG, Jamieson LA, Save VE, Carey FA, Brewster DH, Han C and Al‑Nafussi A: Prognostic indicators for gastrointestinal stromal tumours: A clinicopathological and immunohistochemical study of 108 resected cases of the stomach. Histopathology 43: 118‑126, 2003.
56. Kramer K, Knipschild U, Mayer B, Bügelspacher K, Spatz H, Henne‑Bruns D, Agaimy A, Schwab M and Schmieder M: Impact of age and gender on tumor related prognosis in gastrointestinal stromal tumors (GIST). BMC Cancer 15: 57, 2015.
57. Hohenberger P, Ronellenfitsch U, Oladjeji O, Pink D, Ströbel P, Wardelmann E and Reichardt P: Pattern of recurrence in patients with ruptured primary gastrointestinal stromal tumour. Br J Surg 97: 1854‑1859, 2010.

This work is licensed under a Creative Commons Attribution‑NonCommercial‑NoDerivatives 4.0 International (CC BY‑NC‑ND 4.0) License.