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In this issue

Ki-67 labeling index may be a promising indicator to identify "very high-risk" gastrointestinal stromal tumor: a multicenter retrospective study of 1022 patients☆,☆☆

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Summary We sought to determine whether Ki-67 labeling index (LI) was an independent prognostic factor for gastrointestinal stromal tumor (GIST). A multicenter cohort of 1022 patients undergoing surgical resection of primary GIST between August 2004 and October 2015 was retrospectively analyzed. Immunohistochemical analysis was performed to evaluate expression of Ki-67 in their paraffin-embedded tissue samples. The optimal cutoff value of Ki-67 LI was determined as 6% by receiver operating characteristics curve analysis. Multivariate analysis showed that Ki-67 LI was a significant predictor of overall survival (OS) (hazard ratio: 1.793; 95% confidence interval, 1.240-2.593; $P = .002$). When stratified by modified National Institutes of Health classification, it was still independently associated with OS in high-risk and non–high-risk patients ($P = .001$ and $P = .055$, respectively). Of note, the prognostic significance of Ki-67 LI was also maintained when stratified by tumor size, mitotic index, tumor site, and histological subtype (all Ps $< .05$). In addition, high-risk patients with Ki-67 LI >6% exhibited a significantly poorer OS rate than those with Ki-67 LI ≤6% (53.6% versus 88.7%, respectively; $P = .001$). The area under the receiver operating characteristics curve for Ki-67 LI was higher than that of modified National Institutes of Health

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classification component in high-risk patients ($P = .029$). Therefore, Ki-67 LI is a promising predictor of outcome in GIST, especially in high-risk patients, and it may have important clinical utility in identifying "very high-risk" patients for rational targeted therapy.
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1. Introduction

Gastrointestinal stromal tumors (GISTs) are the commonest mesenchymal tumors in the gastrointestinal tract, resulting most commonly from *KIT* or platelet-derived growth factor receptor α activating mutations [1-3]. Because of KIT activation that occurs in the majority of cases of GISTs, KIT inhibition has emerged as the primary therapeutic approach along with surgery [4,5]. Imatinib mesylate, a selective inhibitor of the KIT protein tyrosine kinase, has received considerable attention and produced durable clinical benefit in most patients with GIST [6,7]. Unfortunately, acquired resistance to imatinib is a frequent event in metastatic GIST, which usually occurs at a median overall treatment duration of less than 2 years [8]. Therefore, the high recurrence rate still remains an unsettling problem [9].

In many malignancies, independent prognostic factors are useful for identifying high-risk patients and tailoring treatment. However, in terms of GISTs, only tumor size, mitotic index, tumor site, and tumor rupture are well-established risk factors [9,10]. The rarity of the tumor and the relatively recent recognition as a distinct disease entity have limited the identification of prognostic factors and the establishment of staging systems. Several of the most widely used risk stratification tools, for example, the Armed Forces Institute of Pathology classification and the modified National Institutes of Health (NIH) classification, are still worth further improving [11,12]. Over the past decades, Ki-67, a nuclear protein universally expressed on proliferating cells, has received considerable attention in a variety of malignancies, including GISTs [13-15]. Although previous studies have revealed that Ki-67 labeling index (LI) is useful in predicting the malignant potential of GISTs, its prognostic utility and criterion in GISTs remain unclear [16-18].

In this study, we performed a large-scale multicenter retrospective cohort analysis to investigate the prognostic value of Ki-67 LI in patients undergoing surgical resection of primary GIST.

2. Materials and methods

2.1. Ethics statement

The Research Ethics Committee at the Cancer Center of Sun Yat-sen University approved the study. No informed consent (written or verbal) was obtained for the use of retrospective tissue samples from patients, some of whom were deceased. Informed consent was deemed unnecessary by the Ethical Committee, and all tissue samples were anonymous.

2.2. Patient selection

The 1022 enrolled GIST patients underwent surgical resection between August 2004 and October 2015 at the following 4 hospitals in China: Sun Yat-sen University Cancer Center, the Union Hospital Huazhong University of Science and Technology, Southern Medical University Nanfang Hospital, and Guangdong General Hospital. All patients had histologically confirmed GIST depending on postoperative histological specimens. Clinicopathological data including age, sex, postoperative tumor characteristics, and tumor rupture (before or during surgery) were obtained by review of the medical records.

The inclusion criteria were as follows: (1) adequate paraffin-embedded tumor tissue sample for Ki-67 LI analysis, (2) no other synchronous malignancy, (2) no preoperative imatinib, (3) no chemotherapy or radiotherapy, and (4) complete set of clinicopathological and follow-up data.

2.3. Immunohistochemistry

The expression level of Ki-67 was measured by immunohistochemistry. Ki-67 antibodies (rabbit polyclonal to proliferation marker; 1:1000; Abcam, Cambridge, UK) were studied with the streptavidin-biotin indirect immunoperoxidase technique on the representative 4-μm–thick tissue sections obtained from formalin-fixed paraffin blocks. The sections were finally visualized using diaminobenzidine substrate–chromogen solution, washed in distilled water, and counterstained with hematoxylin. The expression level of Ki-67 was determined by counting at least 500 tumor cells in the representative high-power (×40 objective) fields. Ki-67 labeled the nucleus of cells in all active phases of cell cycle. The Ki-67 LI was defined by the percentage of positively stained cells with varying intensity of nuclear staining among total counted cells in the fields. All tissue slides were examined for histology independently by 2 expert pathologists in each center, and discordant cases were discussed to reach a final decision. The mitotic index was determined by counting the number of mitotic cells per 50 high-power fields (HPFs).

2.4. Follow-up

The follow-up schedule was routinely performed annually for very low– or low-risk patients and every 6 months for

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