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## Short Communication

# Mitotic Count and Estimation of the Risk of GIST Recurrence in Patients Treated with Preoperative Imatinib

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ABSTRACT

Preoperative imatinib is used frequently in the treatment of large localized GISTs to shrink the tumor prior to surgery. This approach may lead to challenges in the estimation of the risk of recurrence and the need of adjuvant imatinib, because the diagnosis is usually made from a needle biopsy with scant tissue for the assessment of GIST mitotic activity, a key prognostic factor. We propose a mitosis count multiplication method as a proxy for estimating the tumor mitotic count in select cases.



Many gastrointestinal stromal tumours (GISTs) recur despite macroscopically complete surgery. Adjuvant imatinib decreases the risk of GIST recurrence, and when administered for three years also the risk of death [1-3]. The methods developed to estimate the risk of recurrence often rely on tumour mitotic count, size, site, and rupture [4]. The most important single prognostic factor may be the mitotic rate, which is often expressed as the number of mitotic figures within 50 high power fields (HPFs) of the microscope, or per 5 $mm^2$. Most risk stratification schemes consider mitotic counts >10 per 50 HPFs suggestive for a high-risk GIST. Adjuvant imatinib for three years is recommended for patients with a high risk of GIST recurrence and an imatinib-sensitive mutation [5]. Two ongoing randomised trials are evaluating longer than 3-year adjuvant imatinib treatments (NCT02413736 and NCT02260505).

Preoperative (neoadjuvant) treatment with imatinib may shrink the tumour and may facilitate surgery, making organ-sparing surgery feasible in some patients with rectal, duodenal, or gastric GIST. Preoperative imatinib often decreases tumour mitotic count dramatically, and thus makes GIST risk assessment with the standard criteria uncertain or impossible from the surgically excised residual tumour tissue [6]. Patients treated with preoperative imatinib usually have the GIST diagnosis made from a needle core biopsy taken at endoscopy or percutaneously. Such a biopsy will rarely allow counting mitoses from 50 HPFs or an area of 5 $mm^2$ due to scant tumour tissue available.

In the authors' experience, administration of preoperative imatinib has recently become increasingly popular. The downside of this trend is that the selection of patients for adjuvant imatinib has become more problematic, since in the absence of a reliable mitotic count there is now a greater risk for both undertreatment and overtreatment of patients with adjuvant imatinib. The former may result in an increased risk for recurrence and death, and the latter in unnecessary side effects and cost. This problem, faced by most GIST-treating oncologists, has not been extensively discussed, and there are no suggested solutions.

When mitotic counting is done from a surgically excised tumour specimen, mitotically active areas ("hot spots") are usually first identified, and the mitotic counting is usually done from these areas. On the other hand, when only limited tumour tissue from a needle core biopsy is available from an untreated tumour, mitotically most active areas may not be available for counting, which could result in underestimation of the mitotic count and the risk of recurrence.

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To the best of our knowledge, mitotic counts obtained from needle core biopsies have not been compared with counts from surgically excised tissue of the same GISTs. Data from other types of sarcoma may not be directly applicable to GISTs, but, for example, mitotic counts in needle core biopsies taken from leiomyosarcoma are frequently smaller than counts obtained from excised tumour tissue [7]. Overestimation of the mitotic count from a needle core sample is rare, and needle core biopsy tissue assessment tends to underestimate also soft tissue sarcoma grade [7, 8]. The risk for mitotic count underestimation might be the smaller the greater the number of needle biopsies taken, but this may not always be the case and taking of many needle core biopsies may not be feasible due to the anatomical localization of the tumour and the potential risks for tumour cell seeding and bleeding [7].

Since the risk for overestimating the mitotic count from a needle core biopsy seems small, accepting a mitotic count obtained from fewer than 50 needle core biopsy HPFs for GIST risk assessment is appealing when multiplying the count to correspond 50 HPFs or 5 $mm^2$ exceeds 10 mitotic figures. For example, a patient with 2 mitotic figures in a diagnostic biopsy in an area corresponding to 5 HPFs might have at least 20 mitoses per 50 HPFs had the tumour been excised without administering preoperative imatinib, and a patient with 4 mitotic figures within 17 HPFs could have at least 12 mitoses in 50 HPFs, each suggesting high-risk GIST. On the other hand, a small mitotic count in a needle core biopsy does not exclude high-risk GIST due to tumour heterogeneity and possibly incidentally missing the mitotically most active parts of the tumour at biopsy.

Therefore, we suggest that multiplying of the mitotic count obtained from a needle core biopsy sample and using this figure in the estimation of GIST recurrence risk helps in identifying some patients who may benefit from adjuvant imatinib, provided that the multiplication exercise results in an estimate that exceeds 10 mitoses per 50 HPFs or per 5 $mm^2$. The multiplication method should be used with caution, since robust research data are currently not available to support this strategy. Moreover, the estimates of the tumour mitotic count obtained by the multiplication method are particularly sensitive to chance findings when the needle tissue sample consists of only few HPFs and only few mitotic figures are present. Some of the needle core tissue should be spared for mutation analysis to exclude GIST genotypes that are not sensitive to imatinib. The potential benefits of preoperative imatinib (organ sparing, reducing the risk of tumour rupture and bleeding at surgery) need to be weighed against suboptimal risk evaluation and inaccurate selection of patients for adjuvant therapy.

**Conflicts of Interest**

The authors declare no conflicts of interest.

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