Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts

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Summary
Background The risk of recurrence of gastrointestinal stromal tumour (GIST) after surgery needs to be estimated when considering adjuvant systemic therapy. We assessed prognostic factors of patients with operable GIST, to compare widely used risk-stratification schemes and to develop a new method for risk estimation.

Methods Population-based cohorts of patients diagnosed with operable GIST, who were not given adjuvant therapy, were identified from the literature. Data from ten series and 2560 patients were pooled. Risk of tumour recurrence was stratified using the National Institute of Health (NIH) consensus criteria, the modified consensus criteria, and the Armed Forces Institute of Pathology (AFIP) criteria. Prognostic factors were examined using proportional hazards and non-linear models. The results were validated in an independent centre-based cohort consisting of 920 patients with GIST.

Findings Estimated 15-year recurrence-free survival (RFS) after surgery was 59.9% (95% CI 56.2–63.6); few recurrences occurred after the first 10 years of follow-up. Large tumour size, high mitosis count, non-gastric location, presence of rupture, and male sex were independent adverse prognostic factors. In receiver operating characteristics curve analysis of 10-year RFS, the NIH consensus criteria, modified consensus criteria, and AFIP criteria resulted in an area under the curve (AUC) of 0.79 (95% CI 0.76–0.81), 0.78 (0.75–0.80), and 0.82 (0.80–0.85), respectively. The modified consensus criteria identified a single high-risk group. Since tumour size and mitosis count had a non-linear association with the risk of GIST recurrence, novel prognostic contour maps were generated using non-linear modelling of tumour size and mitosis count, and taking into account tumour site and rupture. The non-linear model accurately predicted the risk of recurrence (AUC 0.88, 0.86–0.90).

Interpretation The risk-stratification schemes assessed identify patients who are likely to be cured by surgery alone. Although the modified NIH classification is the best criteria to identify a single high-risk group for consideration of adjuvant therapy, the prognostic contour maps resulting from non-linear modelling are appropriate for estimation of individualised outcomes.

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Introduction Gastrointestinal stromal tumours (GIST) have varying malignancy potential. Micro-GISTS, with a diameter of less than 1 cm, occur in roughly 30% of the middle-aged and elderly general population.14 Micro-GISTS have almost no malignancy potential, even though many of these tumours harbour an activating mutation in KIT or PDGFRA, which are considered the key drivers of GIST molecular pathogenesis.1 Large GISTS and GISTs with a high mitosis count have a high recurrence rate, with metastases typically in the liver and abdominal cavity. Metastatic GISTS are often lethal despite treatment with tyrosine kinase inhibitors.5

Estimation of the risk of recurrence is important in the management of operable GIST. Adjuvant imatinib increases the time to GIST recurrence,14 and patients with a high risk of recurrence have longer survival with 3 years of adjuvant imatinib therapy than with 1 year.6 Although adjuvant imatinib is generally well tolerated, nearly all patients report some adverse effects.7 Since many GIST patients are likely cured by surgery and might not benefit further from adjuvant treatment, risk stratification is one of the challenges in the management of operable GIST.

A few risk-stratification schemes are available for operable GIST.8-10 Tumour size, mitosis count, and tumour site are considered established risk factors for recurrence. Patients with gastric GIST generally have more favourable prognosis than those with intestinal GIST.10 Tumour rupture either spontaneously or at surgery is associated with a high risk of recurrence,10,11 but whether rupture is an independent risk factor is controversial. Some mutations, such as deletions involving KIT exon 11 at codons 557–558, and many tumour biological factors, are associated with unfavourable outcome, but they are not considered established independent risk factors and are not included in the current risk-stratification schemes.8