Nationwide trends in the incidence and outcome of patients with gastrointestinal stromal tumour in the imatinib era

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Background: The incidence, treatment and outcome of patients with newly diagnosed gastrointestinal stromal tumour (GIST) were studied in an era known for advances in diagnosis and treatment.

Methods: Nationwide population-based data were retrieved from the Netherlands Cancer Registry. All patients with GIST diagnosed between 2001 and 2012 were included. Primary treatment, defined as any treatment within the first 6–9 months after diagnosis, was studied. Age-standardized incidence was calculated according to the European standard population. Changes in incidence were evaluated by calculating the estimated annual percentage change (EAPC). Relative survival was used for survival calculations with follow-up available to January 2017.

Results: A total of 1749 patients (54.0 per cent male and median age 66 years) were diagnosed with a GIST. The incidence of non-metastatic GIST increased from 3.1 per million person-years in 2001 to 7.0 per million person-years in 2012; the EAPC was 7.1 (95 per cent c.i. 4.1 to 10.2) per cent (P < 0.001). The incidence of primary metastatic GIST was 1.3 per million person-years, in both 2001 and 2012. The 5-year relative survival rate increased from 71.0 per cent in 2001–2004 to 81.4 per cent in 2009–2012. Women had a better outcome than men. Overall, patients with primary metastatic GIST had a 5-year relative survival rate of 48.2 (95 per cent c.i. 42.0 to 54.2) per cent compared with 88.8 (86.0 to 91.4) per cent in those with non-metastatic GIST.

Conclusion: This population-based nationwide study found an incidence of GIST in the Netherlands of approximately 8 per million person-years. One in five patients presented with metastatic disease, but relative survival improved significantly over time for all patients with GIST in the imatinib era.

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Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms in the gastrointestinal (GI) tract, affecting 10–15 people per million per year in Western countries¹–³. The incidence is estimated to be higher for the Asian population at 16–20 per million per year⁴,⁵, whereas it is estimated to be 6.8 per million per year in the USA⁶. There are no studies available with data on global incidence and prevalence.

The identification of GIST originating from the interstitial cells of Cajal and gain-of-function mutations in KIT and PDGFRA genes was pivotal in defining a specific sarcoma subtype⁷–⁹. Validated immunohistochemical analysis of KIT and DOG1 facilitates the diagnosis of GIST¹⁰,¹¹. The more widely available mutation testing of KIT and PDGFRA genes has led to a better understanding of the clinical application of registered tyrosine kinase inhibitors (TKIs) imatinib, sunitinib and regorafenib.

Wild-type GISTs are nowadays divided into succinate dehydrogenase (SDH)-competent and SDH-deficient tumours, with different oncogenic driver mutations in the SDH-competent group⁹,¹²–¹⁴. It has become increasingly important to genotype GISTs, as not all genotypes respond equally to TKIs. These advances in the diagnosis and treatment of GIST have changed rapidly and dramatically over the past decade¹⁵,¹⁶–¹⁷.

The present study analysed the incidence and treatment of GIST in an era with gradual advances in diagnosis, imaging and systemic therapy. In addition, the long-term
outcomes of patients with GIST were analysed in comparison with a nationwide population-based database.

**Methods**

Data were retrieved from the nationwide population-based Netherlands Cancer Registry (NCR). Data from the NCR are used both in clinical practice and for research purposes. The NCR regularly receives overviews of patients with newly diagnosed cancer from a nationwide pathology network, in which pathology departments of all Dutch hospitals participate. In addition, the medical records services of hospitals provide overviews of diagnoses of cancer in patients treated within outpatient and hospital settings. Trained data managers extract data on patient and tumour characteristics, and on primary treatment from the medical and pathology records. Data on survival were retrieved by linkage to the nationwide population registers network. Survival time was defined as time from diagnosis to death, or until 1 January 2017 for patients who were still alive.

Different from a recent pathology study from the Netherlands, all patients with a malignant GIST (as defined in ICD-O-3, morphology code 8936/3) in 2001–2012 were included for analysis in the study and micro-GIST were excluded. As the NCR has been using the ICD-O-3 morphology code for GISTs from 2001 onwards, this was chosen as a starting point. In previous versions of the ICD-O, which were used by the NCR until 2000, no specific morphology code for GIST was available.

As there was no specific TNM classification for GISTs until TNM-7, stage of disease at diagnosis was categorized as localized or metastatic (including both lymph nodes and/or distant metastases). The pathological stage was used if available; otherwise, the clinical stage was used to categorize patients. Data on mitotic rate are not registered in the NCR. Data on completeness of surgery (R status) and tumour size (T category) were available only from 2010. Data in the NCR encompass primary treatment, defined as the treatment a patient receives within the first 6–9 months after primary diagnosis, and categorized as surgery with or without systemic treatment. No data on diagnosis and treatment of recurrent disease are available in the NCR.

The incidence of GIST was calculated by dividing the annual number of patients with GIST by the number of inhabitants in the Netherlands in that particular year, and

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**Table 1** Patient demographics and disease stage at diagnosis

| Age at diagnosis (years) | 2001–2004 (n = 446) | 2005–2008 (n = 610) | 2009–2012 (n = 693) | Total (n = 1749) |
|-------------------------|---------------------|---------------------|---------------------|-----------------|
| Median                  | 66                  | 67                  | 66                  | 66              |
| 0–44                    | 36 (8·1)            | 51 (8·4)            | 50 (7·2)            | 137 (7·8)       |
| 45–60                   | 135 (30·3)          | 168 (27·5)          | 182 (26·3)          | 485 (27·7)      |
| 61–74                   | 153 (34·3)          | 209 (34·3)          | 262 (37·8)          | 624 (35·7)      |
| ≥ 75                    | 122 (27·4)          | 182 (29·8)          | 199 (28·7)          | 503 (28·8)      |
| Sex ratio (M:F)         | 229:217             | 348:262             | 368:325             | 945:804         |
| Tumour stage            |                     |                     |                     |                 |
| Localized GIST          | 283 (63·5)          | 464 (76·1)          | 539 (77·8)          | 1286 (73·5)     |
| Metastatic GIST         | 90 (20·2)           | 109 (17·9)          | 124 (17·9)          | 323 (18·5)      |
| Unknown                 | 73 (16·4)           | 37 (6·1)            | 30 (4·3)            | 140 (8·0)       |

Values in parentheses are percentages. *Data available only for 407 patients resected in 2010–2012. GIST, gastrointestinal stromal tumour.

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**Fig. 1** Incidence of gastrointestinal stromal tumour (GIST) in the Netherlands, according to stage at diagnosis.
age-standardized according to the European standard population. Changes in incidence were evaluated by calculating the estimated annual percentage change (EAPC) with its corresponding 95 per cent c.i.19. 

The Cochran–Armitage trend test was used to assess for differences over time. Three time frames of 4 years each were used for analyses, thereby accounting for improvements in diagnosis and application of TKIs.

Relative survival (RS), an internationally accepted method that approaches disease-specific survival, was used for survival calculations. As survival of certain subgroups of patients with GIST can be very good, the RS rate can exceed 100 per cent if it is greater than the survival of the general population. RS is calculated by dividing the absolute survival in the patient population by the expected survival based on overall mortality of the Dutch population matched for age and sex.10 The estimation of RS becomes unreliable when the group size is less than ten patients, in which case the results are not presented.

### Results

#### Incidence

A total of 1749 patients, 945 male and 804 female patients, were diagnosed with GIST between January 2001 and December 2012. At diagnosis, 1286 patients (73.5 per cent) were diagnosed with non-metastatic GIST, 323 (18.5 per cent) with metastatic GIST, and for 140 patients (8.0 per cent) the disease stage was unknown. The specific distributions of patient sex, age and disease stage are shown in Table 1. The incidence of non-metastatic GIST increased from 3·1 per million person-years in 2001 to 7·0 per million person-years in 2012 (Fig. 1), and the EAPC was 7·1 (95 per cent c.i. 4·1 to 10·2) per cent (P < 0·001). After 2006, the incidence remained relatively stable. The incidence for unknown disease stage decreased from 1·0 to 0·3 per million person-years between 2001 and 2012, with an EAPC of −12·1 (−20·0 to −4·3) per cent (P = 0·004). For primary metastatic GIST, the incidence was 1·3 per million person-years in both 2001 and 2012 (P = 0·175). The EAPC for all patients was 4·2 (2·3 to 6·2) per cent (P = 0·001). The majority of GISTs were located in the stomach (1020 patients, 58.3 per cent), followed by the small intestine and duodenum (411 patients, 23·5 per cent), and rectum (69 patients, 3·9 per cent). In 249 patients (14·2 per cent) the location was unknown or overlapping.

### Treatment

The various treatment options undertaken in the 1286 patients (73.5 per cent) with non-metastatic GIST are reported in Table 2. Only a small number of patients were treated for very small (pT1) GIST lesions (3·9 per cent). The majority of patients (922, 71·7 per cent) were operated on without receiving any systemic therapy. In the first period (2001–2004), 16 patients (5·7 per cent) were treated with some form of preoperative and/or postoperative systemic treatment. This increased to 79 (17·0 per cent) and 103 (19·1 per cent) respectively in the subsequent time periods of 2005–2008 and 2009–2012. Of all 57

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### Table 2  Treatment of patients with a localized gastrointestinal stromal tumour in the first 6–9 months after diagnosis

|                          | 2001–2004 (n = 283) | 2005–2008 (n = 464) | 2009–2012 (n = 539) | Total (n = 1286) |
|--------------------------|---------------------|---------------------|---------------------|------------------|
| Surgery, no systemic therapy | 229 (80·9)         | 335 (72·2)          | 358 (66·4)          | 922 (71·7)       |
| Surgery and preoperative systemic therapy | 10 (3·5)           | 36 (7·8)            | 40 (7·4)            | 86 (6·7)         |
| Surgery and postoperative systemic therapy | 6 (2·1)           | 39 (8·4)            | 49 (9·1)            | 94 (7·3)         |
| Surgery and preoperative and postoperative systemic therapy | 0 (0)              | 4 (0·9)             | 14 (2·6)            | 18 (1·4)         |
| Systemic therapy, no surgery | 21 (7·4)           | 36 (7·8)            | 48 (8·9)            | 105 (8·2)        |
| Other or no treatment | 17 (6·0)            | 14 (3·0)            | 30 (5·6)            | 61 (4·7)         |

Values in parentheses are percentages.

### Table 3  Treatment of patients with metastatic gastrointestinal stromal tumour in the first 6–9 months after diagnosis

|                          | 2001–2004 (n = 90) | 2005–2008 (n = 109) | 2009–2012 (n = 124) | Total (n = 333) |
|--------------------------|---------------------|---------------------|---------------------|------------------|
| Surgery, no systemic therapy | 21 (23)            | 10 (9·2)            | 14 (11·3)           | 45 (13·9)        |
| Surgery and preoperative systemic therapy | 4 (4)              | 8 (7·3)             | 5 (4·0)             | 17 (5·3)         |
| Surgery and postoperative systemic therapy | 6 (7)              | 16 (14·7)           | 16 (12·9)           | 38 (11·8)        |
| Surgery and preoperative and postoperative systemic therapy | 1 (1)              | 1 (0·9)             | 7 (5·6)             | 9 (2·8)          |
| Systemic therapy, no surgery | 29 (32)            | 61 (56·0)           | 71 (57·3)           | 161 (49·8)       |
| Other or no treatment | 29 (32)            | 13 (11·9)           | 11 (8·9)            | 53 (16·4)        |

Values in parentheses are percentages.
patients treated with preoperative imatinib in 2010–2012 who underwent surgery within 6–9 months after diagnosis, three patients had a complete pathological response after resection. From 2010 onwards, the NCR contained data on completeness of resection; 323 (79.4 per cent) of the 407 resected patients had an R0 resection and 39 (9.6 per cent) an R1–R2 resection.

The different treatment modalities for the 323 patients (18.5 per cent) with a primary metastatic GIST are shown in Table 3. The proportion of patients who received systemic treatment with no surgery in the 6–9-month interval after diagnosis increased from 32 per cent in 2001–2004 to 57.3 per cent in 2009–2012, and presumably included patients treated with neoadjuvant imatinib who had not yet undergone surgery.

### Relative survival

Median follow-up was 69.9 (range 0–192.7) months for all patients. The 5-year RS rate for all patients increased from 71.0 (95 per cent CI 65.6 to 76.0) per cent in 2001–2004 to 81.4 (77.3 to 85.1) per cent in 2009–2012 (Table 4). Women had a better 5-year RS rate than men: 81.3 (77.6 to 84.7) versus 74.9 (71.2 to 78.4) per cent respectively. As the survival of patients with small tumours (pT1–2) was better than that of the general population, the RS rate exceeded

| Time interval | No. of patients | 1 year survival | 3 years survival | 5 years survival |
|---------------|----------------|----------------|-----------------|----------------|
| 2001–2004     | 446            | 85.4 (81.5, 88.7) | 77.8 (73.0, 82.1) | 71.0 (65.6, 76.0) |
| 2005–2008     | 610            | 90.3 (87.4, 92.8) | 84.0 (80.1, 87.4) | 79.0 (74.5, 83.1) |
| 2009–2012     | 693            | 93.2 (90.7, 95.2) | 85.1 (81.5, 88.2) | 81.4 (77.3, 85.1) |

Table 4: Relative survival of patients with gastrointestinal stromal tumour according to Netherlands Cancer Registry standards.
100 per cent. Patients with a gastric GIST had a 5-year RS rate of 84-5 per cent versus 78-2, 76-1 and approximately 50 per cent for GISTs of the small intestine/duodenum, rectum and other GI locations respectively. Patients with a non-metastatic GIST had a 5-year RS rate of 88-8 (86-0 to 91-4) per cent. Of patients with a localized GIST, those who received surgery only had a better RS than patients who had systemic therapy alone or a combination of surgery and systemic therapy. For patients with a primary metastatic GIST, the 5-year RS rate was 48-2 (42-0 to 54-2) per cent. Patients who received systemic therapy before and/or after surgery for primary metastatic GIST had a better RS rate than those who had surgery or systemic therapy alone: 77-4 versus 67-0 and 39-7 per cent respectively.

Discussion

Since the introduction of imatinib in 2001 and the improved diagnosis of GIST as a distinct histopathological entity, both diagnosis and treatment of patients with GIST have changed dramatically. The present study showed the current incidence of GIST to be approximately 8 per million population annually in the Netherlands, comparable to data from other Western countries1–3,21. There is considerable variation in the incidence of GIST reported from different countries, which can be explained by a number of factors. The diagnostic criteria have improved over time as GISTs were commonly misdiagnosed before 2001, and the immunohistochemical identification of KIT and DOG1 expression has made the reliable diagnosis of GIST possible7,10,11,22. Therefore, patients with a GIST or GIST-like tumour diagnosed before 2001 were excluded from the present study, but will have been included in some international reports4,5. Not all countries have established cancer registries that register all GISTs, with the consequence that smaller, low-risk tumours may not have been reported11,23,24. Another reason for the difference in incidence might be the lack of registries that score GISTs as separate entities.

Patients with non-metastatic GIST demonstrated an increased incidence from 3-1 in 2001 to 7-0 in 2012 per million person-years, with a significant increase in the EAPC of 7-1 per cent. However, the number of patients with unknown stage presentation decreased during the same period owing to better staging and registration; this might partly explain the increased EAPC for localized GIST. From 2006 onwards, the incidence remained stable.

Risk classification of GIST has developed over time, including not only tumour size, but also location and mitotic rate. More recently, tumour rupture and GIST genotype have been added to risk classifications25–29. High tumour mitotic count, non-gastric location, large tumour size, rupture during surgery, and adjuvant imatinib for 12 rather than 36 months, were independently associated with a lower recurrence-free survival rate in patients with GIST29,30.

A limitation of the present study is that the NCR database lacks information on mitotic rate and tumour rupture, although data on tumour size, sex, location, stage and completeness of resection are available, and were recognized as significant prognostic factors. Other studies6,31,32 have also shown patient sex to be a prognostic factor in GIST. The BRF14 trial of the French Sarcoma Group32, which solely included patients with metastatic disease who were started on imatinib, showed a highly significant 5-year survival benefit for women of 76-5 per cent, versus 53-5 per cent in men. A clear explanation for this sex difference has not yet been found, but the present data showed a similar favourable outcome for women.

Surgery is the most important treatment modality leading to cure in low-risk tumours. In patients with low-grade GISTs, 5-year survival rates as high as 95–100 per cent have been reported in the literature29, and this was also demonstrated in the present cohort. For high-risk patients, the introduction of adjuvant imatinib has also led to improved survival rates. The stomach is the most commonly affected GI site in patients with a localized GIST, and is associated with the most favourable prognosis, with a 5-year survival rate of 84-5 per cent reported in the present study. This is comparable with survival data from other studies33, including a large cohort from Korea and Japan14. There may be a bias in these survival rates when compared to other GI locations, because gastric GISTs are generally discovered at an earlier disease stage. In the present study, only 3-9 per cent of removed tumours were smaller than 2 cm (pT1), and the majority of patients with non-metastatic GIST were treated with surgery alone. An increasing number of patients with larger tumours were treated with preoperative and/or postoperative systemic treatment. This is explained partly by adjuvant treatment with imatinib for high-risk patients, as demonstrated by Joensuu and colleagues30. Patients with locally advanced GISTs have also increasingly been treated with preoperative imatinib, leading to excellent downsizing and reduction of peroperative tumour rupture35,16. In the present study, earlier cohorts of patients with high-risk GIST treated before 2012 did not receive adjuvant imatinib, which may have had an impact on the survival results of high-risk patients in that period.

The annual incidence of patients presenting with metastatic GIST remained fairly constant over time, with
a non-significant change in the EAPC of 2.4 per cent. The increased use of TKIs in patients with metastatic GIST improved their overall survival significantly. Before TKIs were available, patients with metastatic GIST had a median survival of 10–20 months, but this has subsequently increased to more than 4 years, with further improvements in survival over time and differences dependent on molecular subtypes. The reported 5-year survival rate of 48.2 per cent for patients with primary metastasized GIST in the present study is in line with the outcome data of these clinical studies, which is remarkable as the NCR encompasses population-based data. All patients, including the elderly and patients with very advanced disease or severe co-morbidity, are included in the nationwide database, whereas such patients are usually excluded from clinical trials.

In the present population, patients with metastatic GIST who underwent surgery with or without systemic therapy had much higher 5-year RS rates than patients treated with systemic therapy alone. This could be a result of patient selection and bias, although other studies have demonstrated an indication for surgery in metastatic GIST, as long as the patient does not have progressive disease. In the NCR database, treatment data are recorded for a maximum of 9 months after diagnosis, which means information on surgery beyond 9 months is lacking, particularly after pre-operative systemic treatment. Not only patients with local recurrence or intra-abdominal metastatic lesions were operated on, but also those with hepatic metastases treated with both systemic treatment and surgery, leading to excellent long-term survival in carefully selected patients. Treatment within the context of multidisciplinary teams with expertise in GIST and in clinical studies remains crucial for further improvement in the outcome of patients with GIST.

The present study demonstrates a stable incidence of GIST in the Netherlands of approximately 8 per million person-years, with one in five patients presenting with metastatic disease. Women and patients with gastric GIST have the best prognosis. In the imatinib era, RS has improved significantly over time for all patients with GIST.

Disclosure

The authors declare no conflict of interest.

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### Snapshot quiz 18/8

**Answer:** This 40-year-old labourer presented with a 2-day history of central chest pain radiating to his back following strenuous vomiting after significant alcohol consumption. Clinical examination revealed dullness to percussion at the left lung base, and subcutaneous emphysema across the thorax consistent with Boerhaave syndrome (ruptured oesophagus). He was tachycardic and hypoxic. CT demonstrated mediastinal emphysema and a large left pleural effusion. Thoracotomy confirmed a linear perforation bridging the gastro-oesophageal junction (see figure). The defect was closed primarily. Lavage and large-bore drainage of the mediastinal cavity and thorax was performed.