

STUDY OF THE INCIDENCE OF GASTRO-INTESTINAL STROMAL TUMOURS (GISTs) IN SCOTLAND



Dr Jeff White
Beatson Oncology Centre
Glasgow

Study Team



- **Writing committee:**
 - Dr Shaun Walsh, Consultant Pathologist, Ninewells Hospital, Dundee
 - Dr Jeff White, Consultant Medical Oncologist, Beatson Oncology Centre, Glasgow
- **Principle Investigator:**
 - Dr Jeff White
- **Research Nurse/Data Manager:**
 - Gillian Dunbar, Beatson Oncology Centre, Glasgow
- **Pathology Centre:**
 - Department of Pathology, Ninewells Hospital, Dundee
- **Financial support:**
 - Novartis Pharmaceuticals UK- unrestricted educational grant

Introduction

- Nearly all GISTs are characterized by the expression of the c-kit receptor (CD117)
- Detection of c-kit by IHC is the gold standard for the diagnosis of GIST
- Main treatment remains surgical as standard anti-cancer therapies have been shown to be ineffective
- Glivec™ has significantly changed the management and prognosis of patients with advanced disease, with a median survival of over 18 months
- This major therapeutic advance means it is important to establish the correct diagnosis of GIST

Background



- Prior to the development of IHC assays for c-kit, GISTs may have been classified as e.g. leiomyoma, leiomyoblastoma, epitheloid leiomyosarcoma, leiomyosarcoma
- An estimate of the US incidence is 150 per year (Licht, J.D. 1988)
- German study based on archival blocks from single institution showed that the use of CD117 IHC increased the proportion of GISTs from 22 to 47 %
- Western Sweden population based study estimated the incidence of GISTs to be 14.5/ million (Kindblom, L.G 2003)
- Low incidence (10-20 cases per million (Miettinen, M. 2002) means there is uncertainty about the true prevalence of disease within the Scottish population
- Registration based US study showed an age-adjusted yearly incidence rate of 0.68/100 000 (Tran et al. Am J Gastro ;100:162-168)

Background



- We are examining all archived mesenchymal tumours arising along the GI tract, which could potentially be GIST, with an IHC for CD 117 diagnosed in Scotland over 5 years
- The allocation of the appropriate diagnostic code using CD-117 will allow these patients access to potentially useful therapy with Glivec if they relapse
- The lack of information of the true incidence of this condition is a problem with regard to planning drug budgets, etc

End-points

- Primary end-point is to establish the incidence of GISTs in the Scottish population
- Secondary endpoints will be:
 - to establish prognostic factors in GIST
 - to establish the survival of patients with GISTs in the Scotland
 - to confirm the c-kit expression status of patients already diagnosed with GIST
 - to establish a register of GIST patients in Scotland

Patient Selection Criteria



Inclusion criteria:

- Any patient identified from Scottish hospital pathology department records with a potential or actual diagnosis of GISTs, including all patients with leiomyoma, leiomyosarcoma, epitheloid leiomyosarcoma, leiomyoblastoma, gastrointestinal autonomic nerve tumour, stromal sarcoma, sarcoma NOS, schwannoma occurring within any part of the gastrointestinal tract
- Informed consent will be obtained from surviving patients

Exclusion criteria:

- Any patient with a sarcoma metastatic to the gastrointestinal tract
- Any patient whose tumour was referred to a Scottish pathology department for diagnosis but who was resident outside Scotland
- Any patient with a recurrence of a GIST but whose primary diagnosis was made outside the study period

Pathology Problems: case retrieval

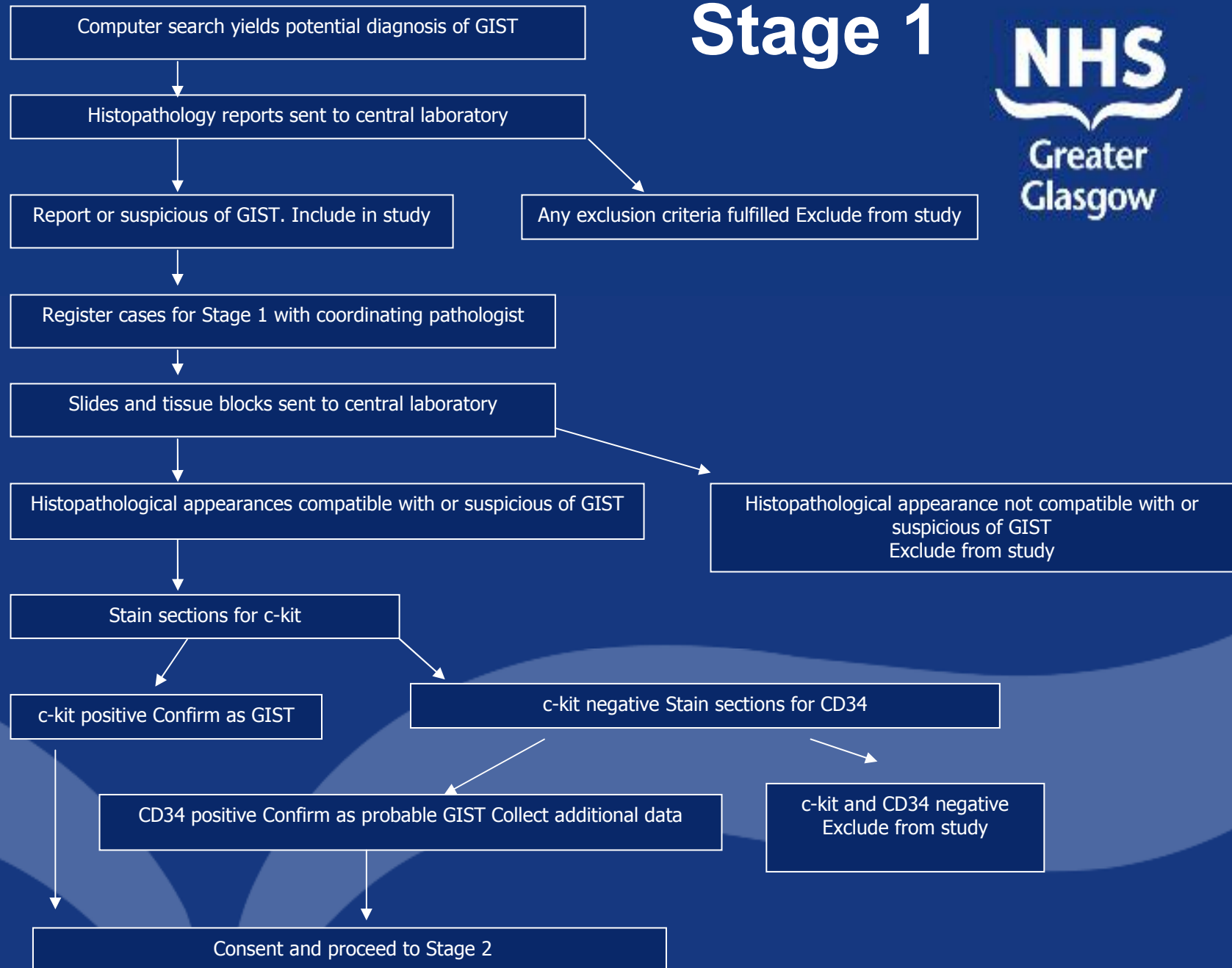


- Time: Pathology staffing crisis prohibits research activity
- Costs: Overtime compensation for MLA to retrieve cases from the archives
- Concerns: Does reclassification mean misdiagnosis?

Trial Design

- Retrospective
- Based on archived pathological records and material from patients with an actual or suspected diagnosis of GIST identified from pathological records of Scottish Hospital pathology departments between Jan. 1st 1995 and Dec. 31st 1999
- The study is divided in to two stages:
 - identification of GIST cases
 - collection of patient information of genuine GIST cases

Stage 1



Stage 2



Informed consent obtained from live patients



Register cases for Stage 1 with Research nurse

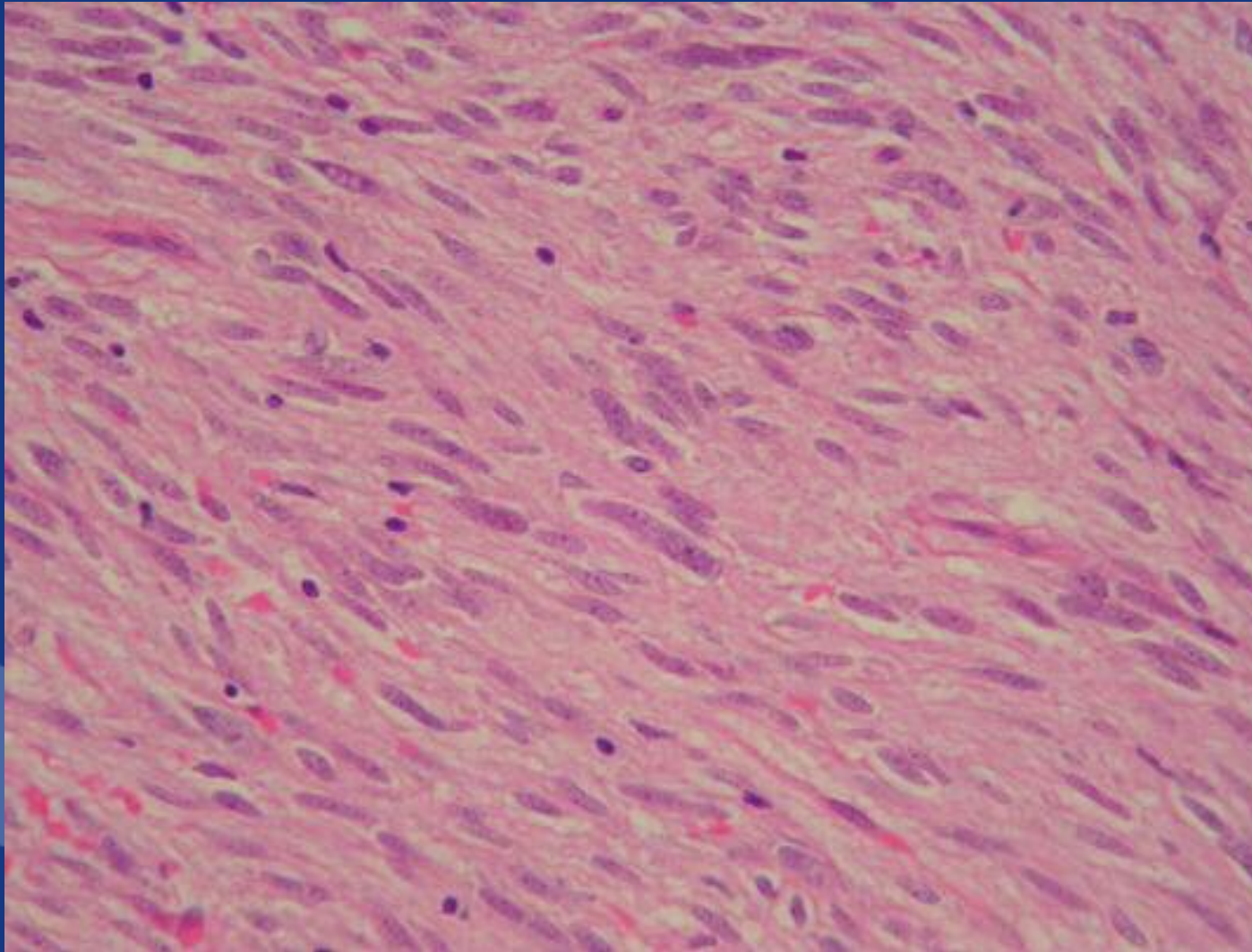


Collect additional data



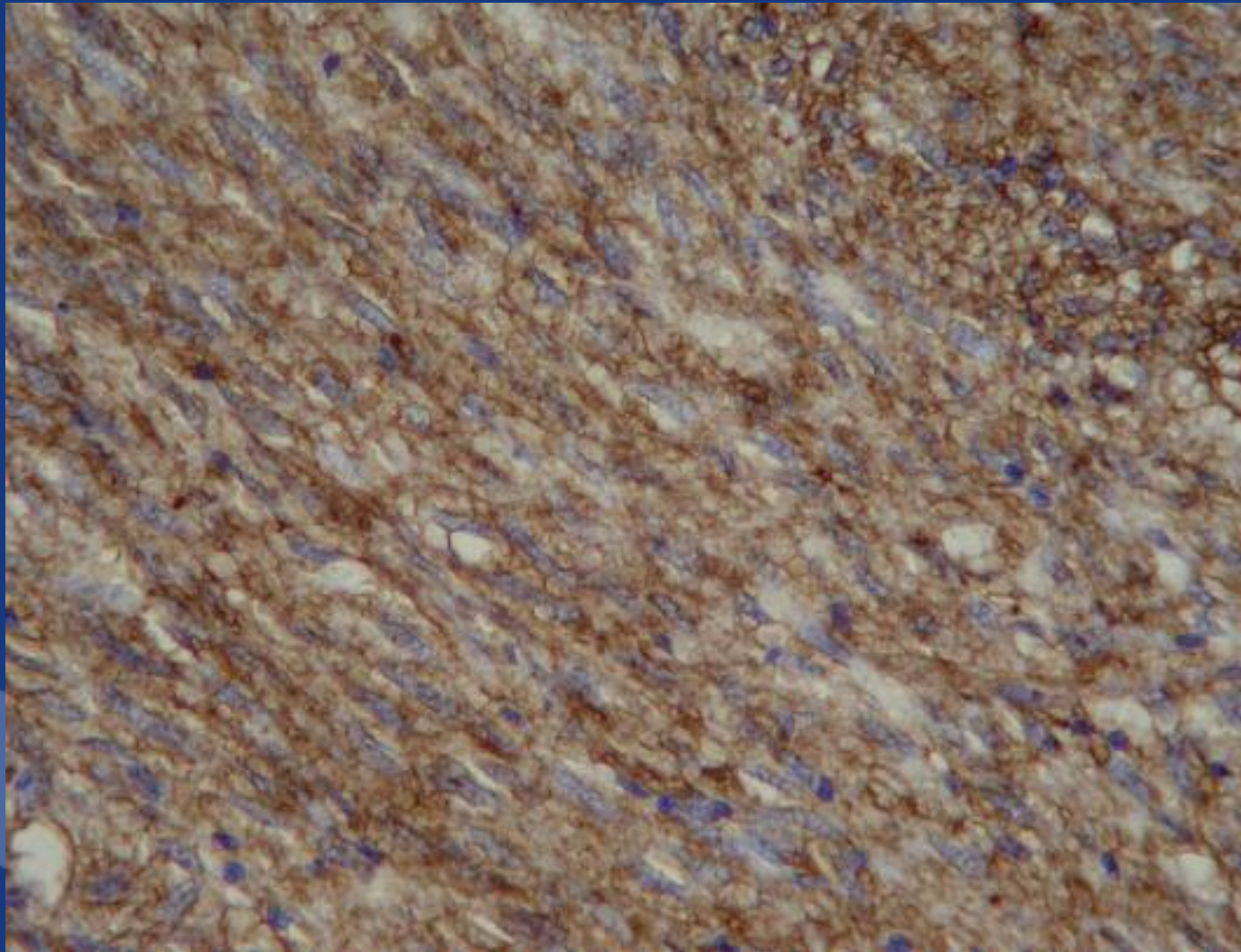
Enter data on to database and analysis

Tumour classified GIST '99



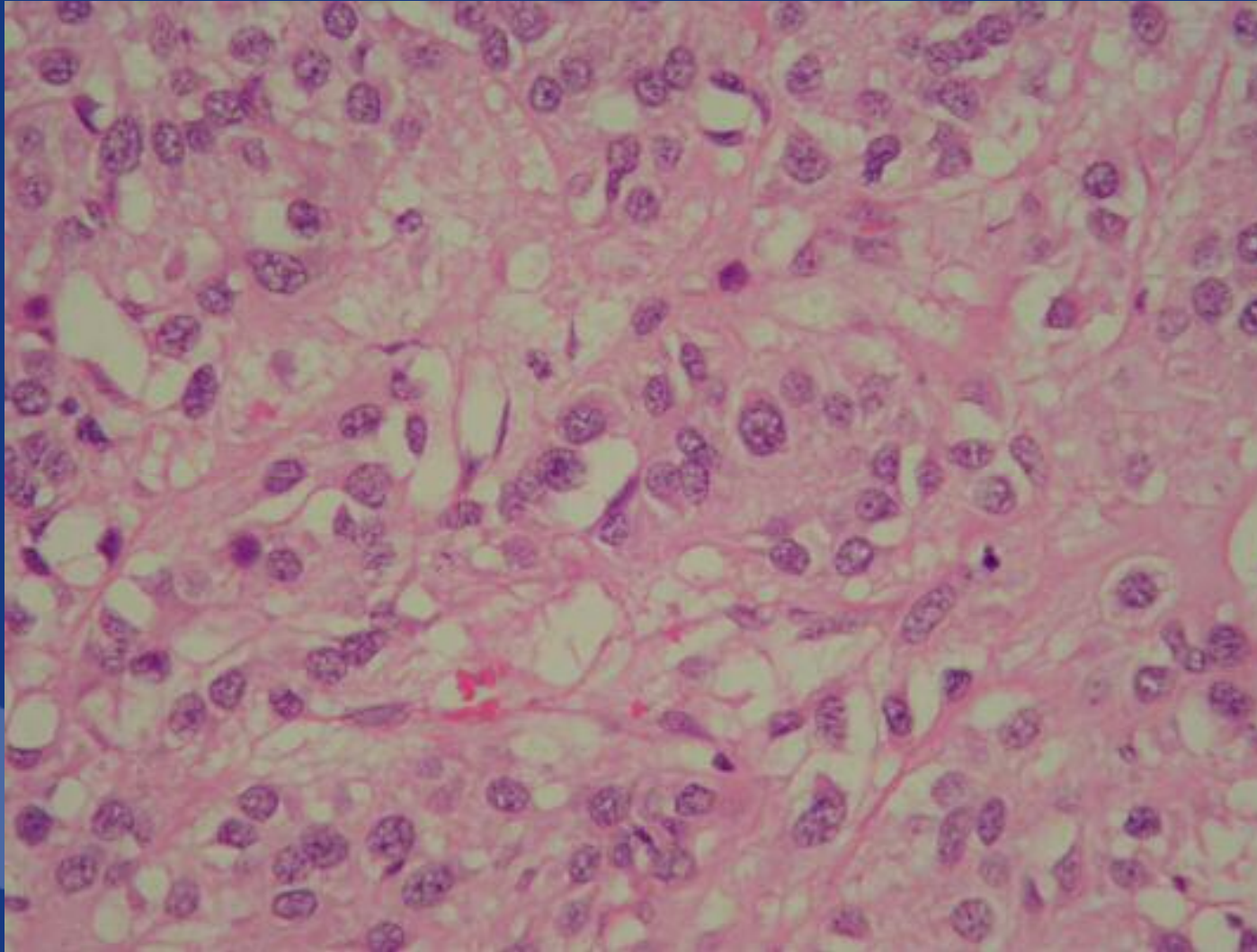
H&E: Spindle cell gastric tumour

Tumour classified GIST '05



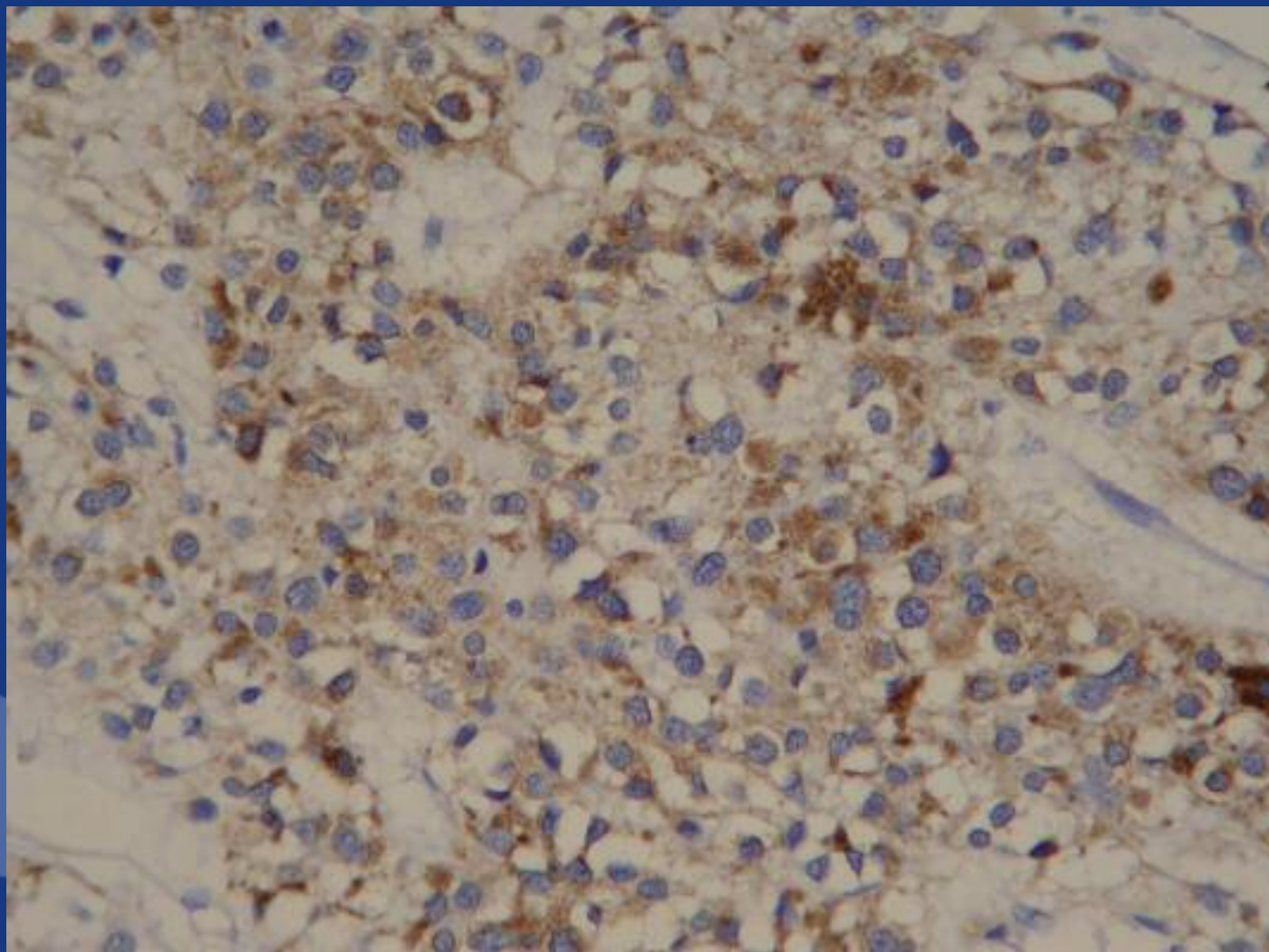
KIT IHC: Diffuse membranous and cytoplasmic expression

Tumour classified leiomyoblastoma '97



H&E: Epithelioid gastric tumour

Tumour reclassified GIST '05



KIT IHC: Dot like cytoplasmic expression

Data Flow

- Once cases are proven to be genuine GISTs our research nurse will contact the responsible clinician and arrange a mutually convenient meeting with the patient
- At this point the patient will be asked to give their consent for collection of relevant clinical information
- Patients will also be offered information and support for their “new diagnosis”

Scottish GIST Registration Study Data Collection Form



- Referring Hospital Number
- Original Hospital
- Responsible Clinician
- Date of Birth
- Age at Diagnosis
- Sex
- Date of Original Diagnosis
- Original Diagnosis
- Survival Date
- Status
- Primary Site
- Symptomatic
- Type of Symptom
- Staging Endoscopy
- Staging CT
- Staging MRI
- Date of surgery
- Type of Surgery
- Emergency Surgery
- Lymph Nodes Involved
- Lymph Nodes Retrieved
- Lympho-vascular invasion
- Site of Metastases
- Metastasis at Presentation
- Size (cm)
- Tumour Type
- Haemorrhage
- Necrosis
- Other Histological Features
- Grade
- Invasion of Other Structures
- Mitotic rate/ 50 hpf
- Margin
- Prognostic index
- Relapse
- Relapse Date
- Site of Recurrence
- Cause of Death

Status



- Ethical approval (MREC Reference Number 04/S0709/62 West Glasgow Ethics Committee 2)
- R and D approval from North Glasgow Hospitals Division of NHS Glasgow Late 2004
- Awaiting R and D approval for further 11 Health Boards
- Research Nurse in post from Feb 2005

Progress



- Started Feb 2005
- Study Pathologist has liaised with pathology departments re generating list of potential cases
- Autumn 2005 first two Health Board GIST cases confirmed with IHC and estimated incidence
- Ongoing collection of clinical information
- Estimated duration 1 year

Pathology Problems



- Report and slides available but no tissue blocks
- Not possible to confirm or refute diagnosis of GIST
- Methodology for KIT IHC not standardised
- Some protocols use antigen retrieval (HIER) using heat to unmask KIT protein
- Many pathologists feel that this will yield false positives and over diagnosis
- For our study no HIER was not used unless internal positive controls absent

Study Management Problems



- Pathologists concerns over “ misdiagnosis” and potential legal implications
- Multiple R and D applications
- Misinterpretation by some Health Boards as a commercially driven exercise and the financial implications on them of confirmation of “ new cases”
- Lack of follow-up information notes destroyed, etc

Scottish GIST

Incidence Results 1995-99



- Health Board A
 - 14 cases had already a diagnosis of GIST, were confirmed with IHC and a further case was “re-classified”
 - Incidence 7/ million
- Health Board B
 - 6 cases had already a diagnosis of GIST, these and a further 5 were “re-classified”
 - Incidence 10.5 / million

Conclusions



- The incidence figures obtained so far are in keeping¹ or somewhat lower² than those quoted in other studies
- ¹ Tran, T., et al., Am J Gastro 2005;100: p. 162-168
- ² Nilsson, B., et al., Cancer, 2005. 103(4): p. 821-9. 2
- ² Miettinen, M., et al., Hum Pathol, 2002. 33(5): p. 478-83