The epidemiology, clinicopathological characteristics and outcomes of GISTs in Durham and Tees Valley

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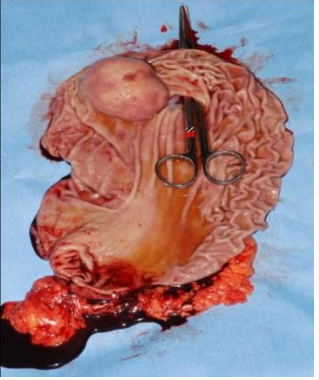
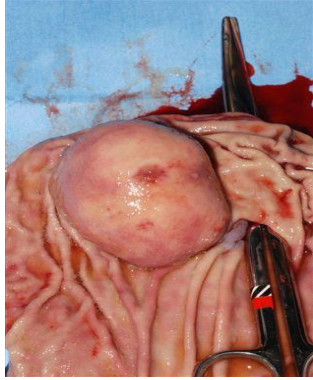
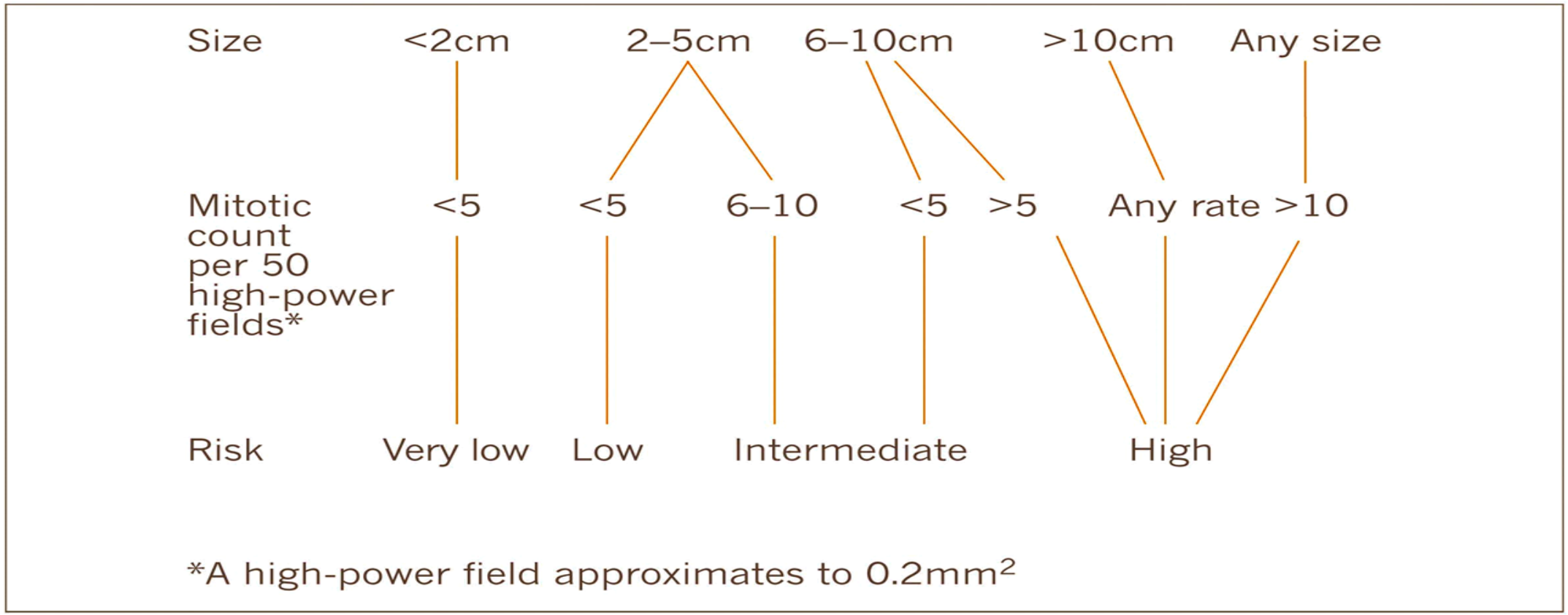


Introduction



- Gastrointestinal stromal tumours (GISTs):
  - 0.1-3% of all GI neoplasms (predicted incidence of 900 cases/yr in UK and 50 in NCN)
  - result most commonly from KIT (CD117) or platelet-derived growth factor receptor α (PDGFRα)-activating mutations.
- Clinical presentation:
  - variable depending on the site and size of the tumour
  - metastases at presentation being a generally uncommon occurrence.
- Treatment strategies depend on site, size, malignant potential and metastases.
  - surgery
  - use of tyrosine kinase inhibitors
- Long term follow recommended
  - high risk of local recurrence and metastases

Malignant potential of GIST – NIH stratification[1]



1. Fletcher CDM *et al.* Human Pathol 2002.

Immunohistochemical markers for GIST[1]

	CD117 (c-KIT)	CD34	SMA	Desmin	S-100
GIST	+ Around 90%	+ 60–70%	+ 30–40%	Very Rare	+ 5%
Smooth muscle tumour	–	+ 10–15%	+	+	Rare
Schwannoma	–	+	–	–	+

1. Fletcher CDM *et al.* Hum Pathol 2002.

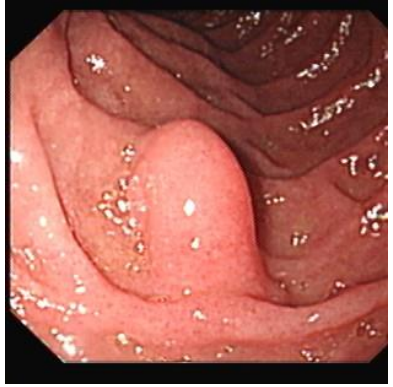
Retrospective analysis of GISTs in Durham and Tees Valley, 2007-12

- Review clinical presentations
- Pathological characteristics
- Treatment outcomes over a five year follow-up period
- Analysing prognostic factors associated with adverse outcomes.

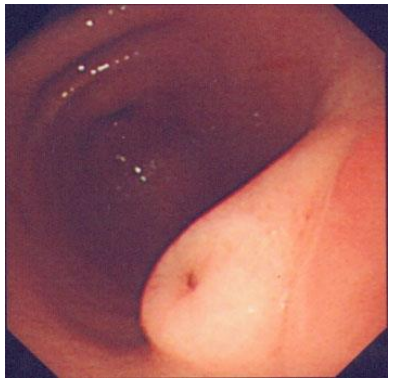
Methods

- Patients identified from the Regional Tumour Registry Database at James Cook University Hospital, between Jan 2007 and Dec 2012.
- Data recorded:
  - baseline demographics
  - tumour characteristics
  - tumour size
  - mitotic index
  - immunohistochemical markers and other pathological parameters
- Patients were risk-stratified according to NIH and AFIP risk-stratification systems.
- Overall survival assessed using Kaplan–Meier survival analysis.
- Prognostic factors analysed using stepwise Cox proportional hazard analysis.

Results



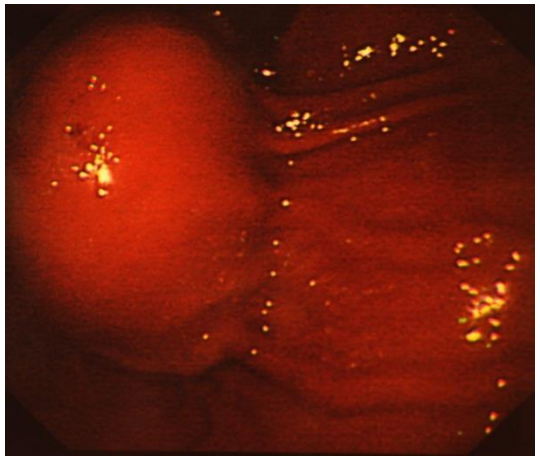
- 42 patients with GISTs.
- Tumour size: 1.0 - 12.7cm.
- 9 (21.4%) tumours were incidental. (Identified during scanning for other conditions
- 8 (19.0%) patients had concurrent tumour diagnoses
- 2 (4.8%) patients had multiple primaries at diagnosis
- Of those with metastases at diagnosis, 7 loco-regional and 12 distant
  - liver most commonly affected metastatic site.

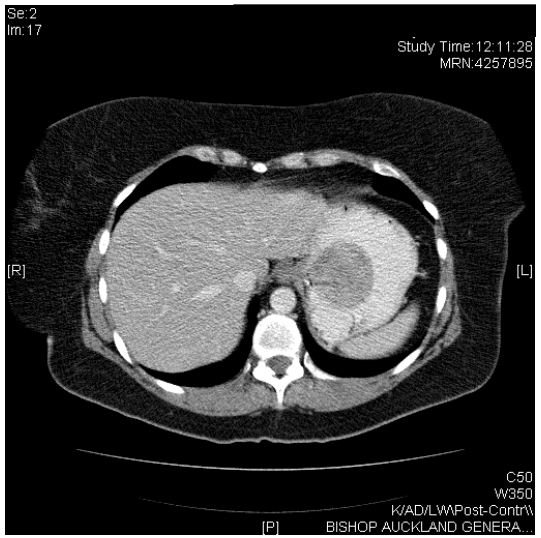


- Adjuvant Imatinib therapy given to 4 patients (combination therapy)
  - in 2, the tumour converted from unresectable to removable.
  - 2 patients were given palliative chemotherapy, the remainder were managed conservatively.
- Recurrence was confirmed in 5 (11.9%) patients at a median of 597 (range 402-943) days
- Of these, 2 were deemed low risk by all three classification systems.

Clinical characteristics

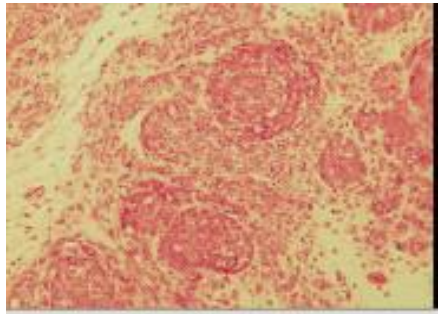
Baseline Clinical Variables	Outcome
Age, n (%)	
<50 years	5 (11.9)
≥50 years	37 (88.1)
Gender, n (%)	
Male	18 (42.9)
Female	**24 (57.1)**
Tumour site, n (%)	
Stomach	**36 (85.7)**
Small intestine	5 (11.9)
Oesophagus	1 (2.4)
Tumour size, mean (SD)	5.46 (3.7)
Metastases at Dx , n (%)	**19 (45.2)**



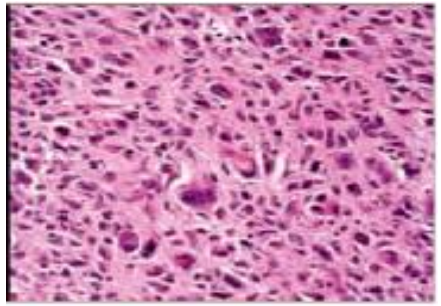


Histopathological features

Histopathological Variables (n=32)	Number of patients (%)
Histology	
Epitheloid	10 (33.1)
Spindle	17 (53.1)
Mixed	5 (15.6)
Immunohistochemistry	
CD117	29 (90.6)
CD34	24 (75.0)
DOG1 (n=18)	18 (100)
Mitotic index	
<5/50 HPF	15 (46.9)
>5/50 HPF	17 (53.1)


Epithelioid

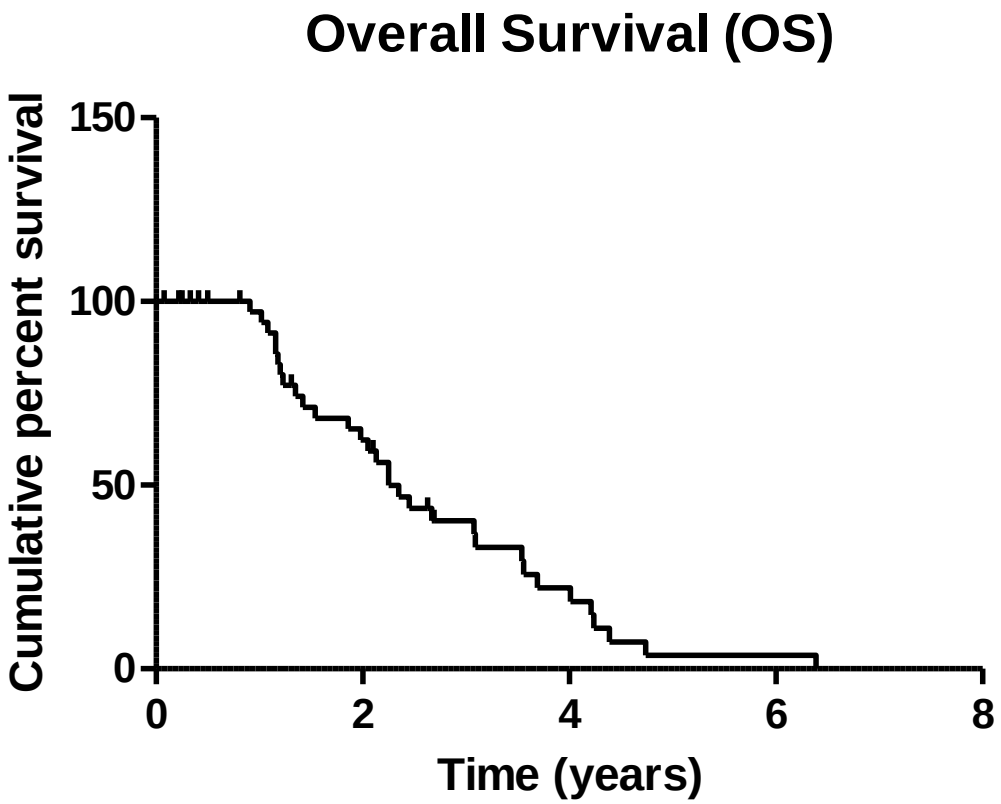

Spindle

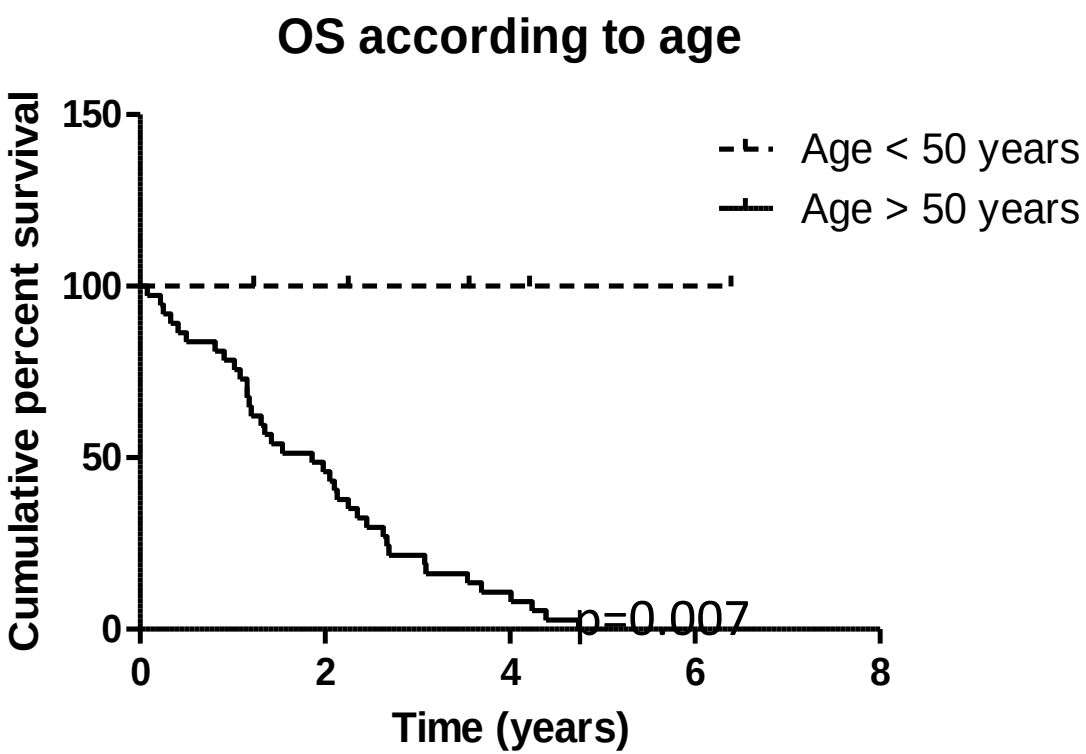

Pleomorphic

Treatment and outcomes

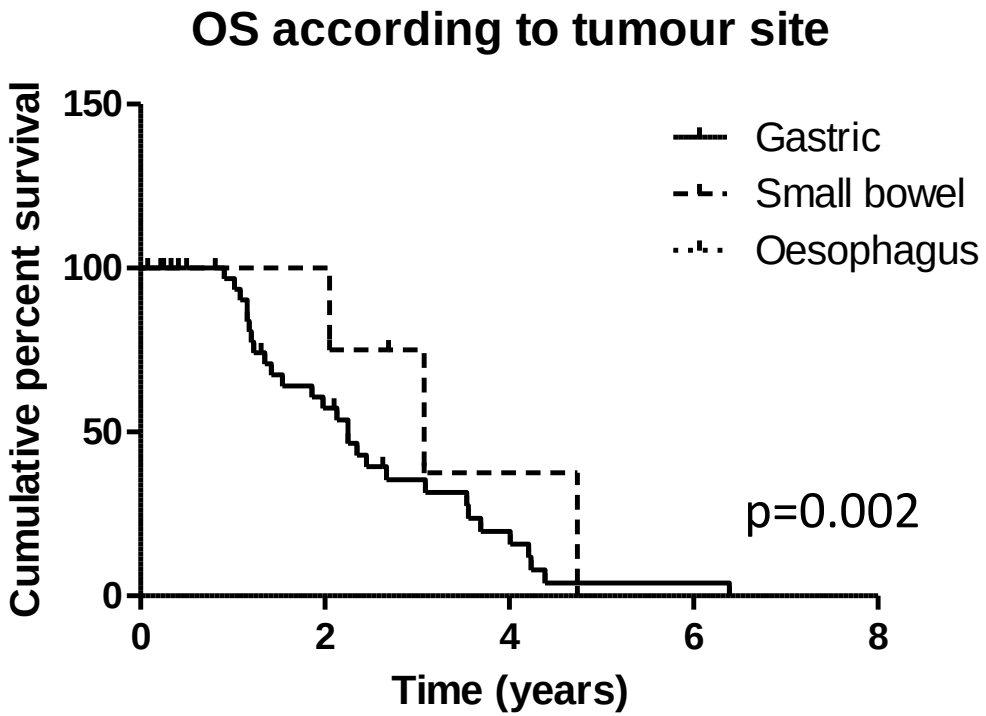
Treatment outcomes	Number of patients (%)
AFIP score (n=32)	
Very low risk	3 (9.4)
Low risk	10 (31.3)
Intermediate risk	8 (25.0)
High risk	11 (34.8)
Treatment (n=42)	
Surgery	**23 (54.8)**
Imatinib	10 (28.3)
Combination	5 (11.9)
Recurrence	5 (11.9)
Survival (months), med (IQR)	24.2 (13.9-35.8)

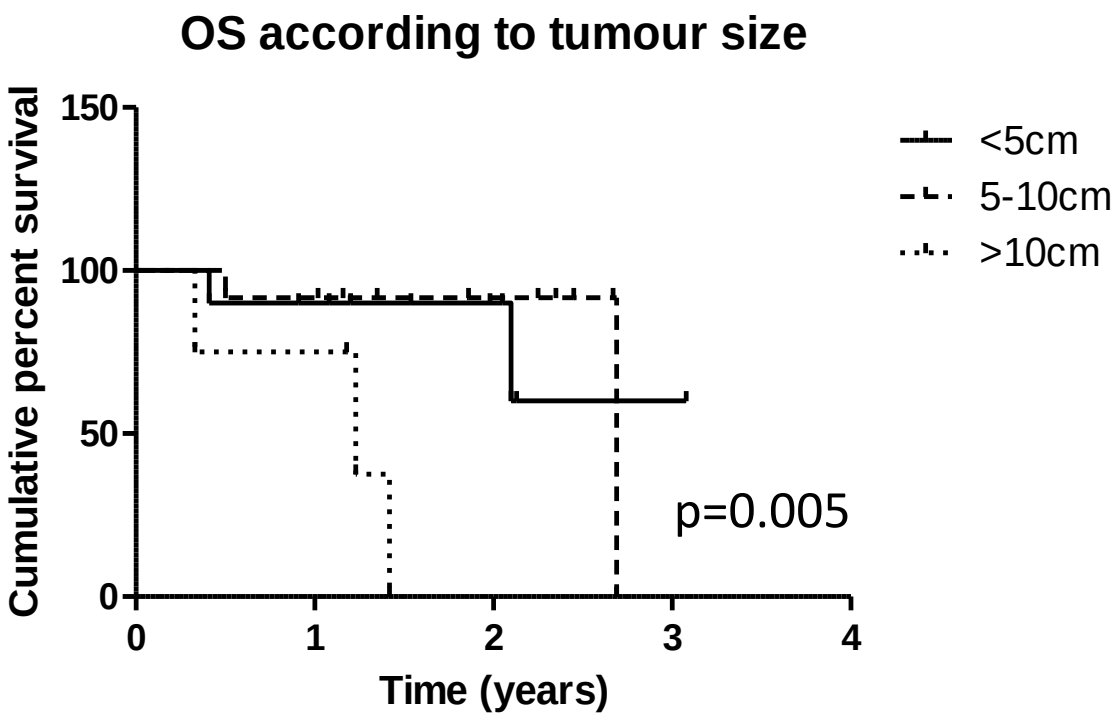
Survival curves





Survival statistics





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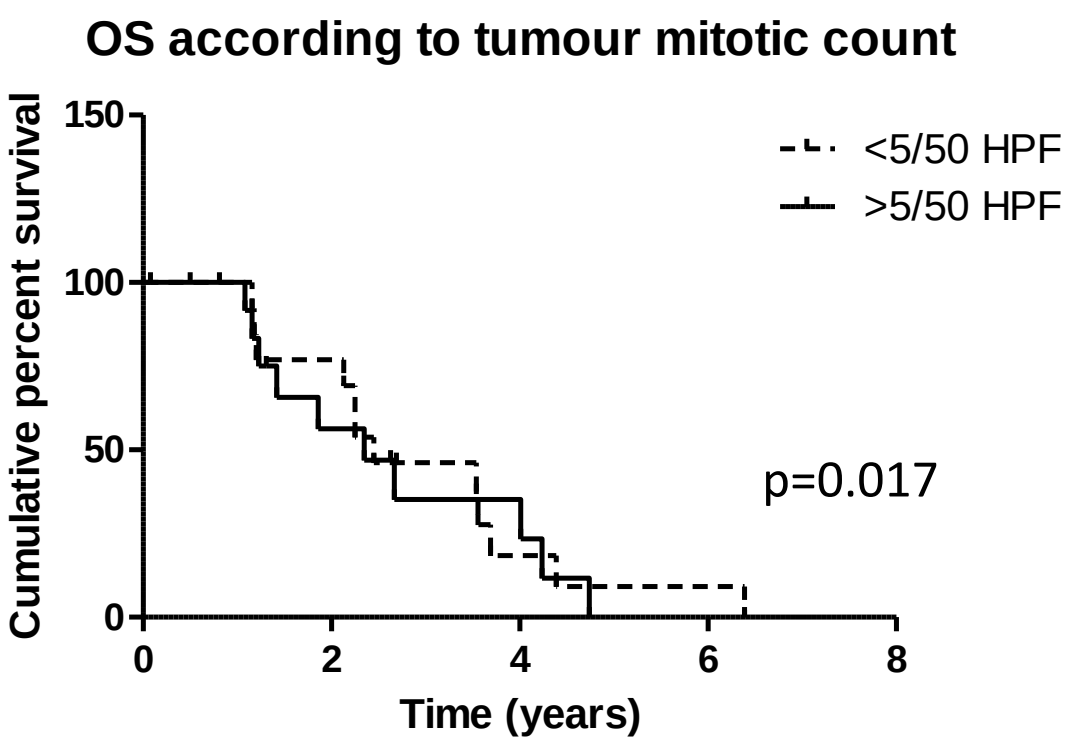
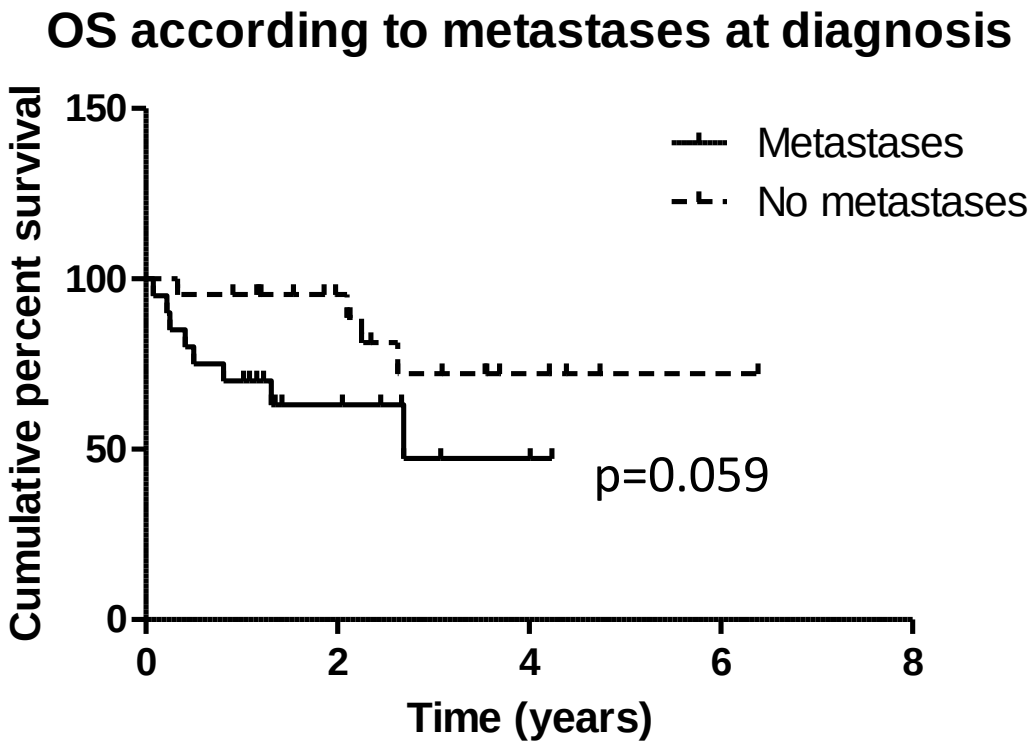
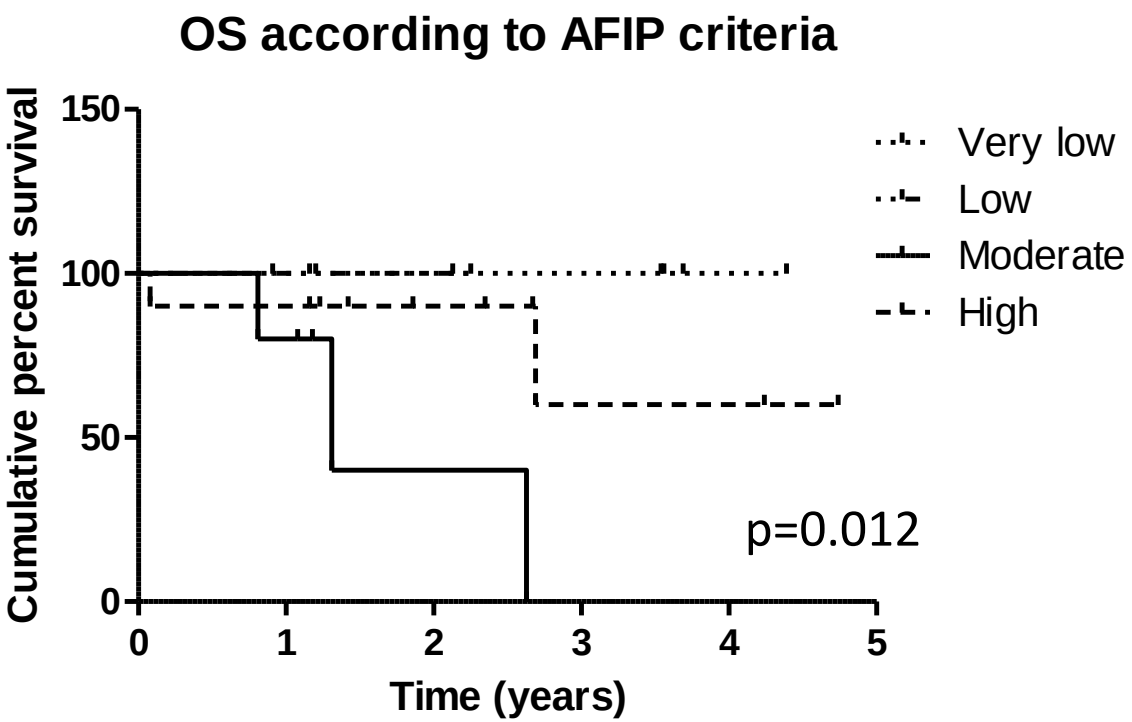
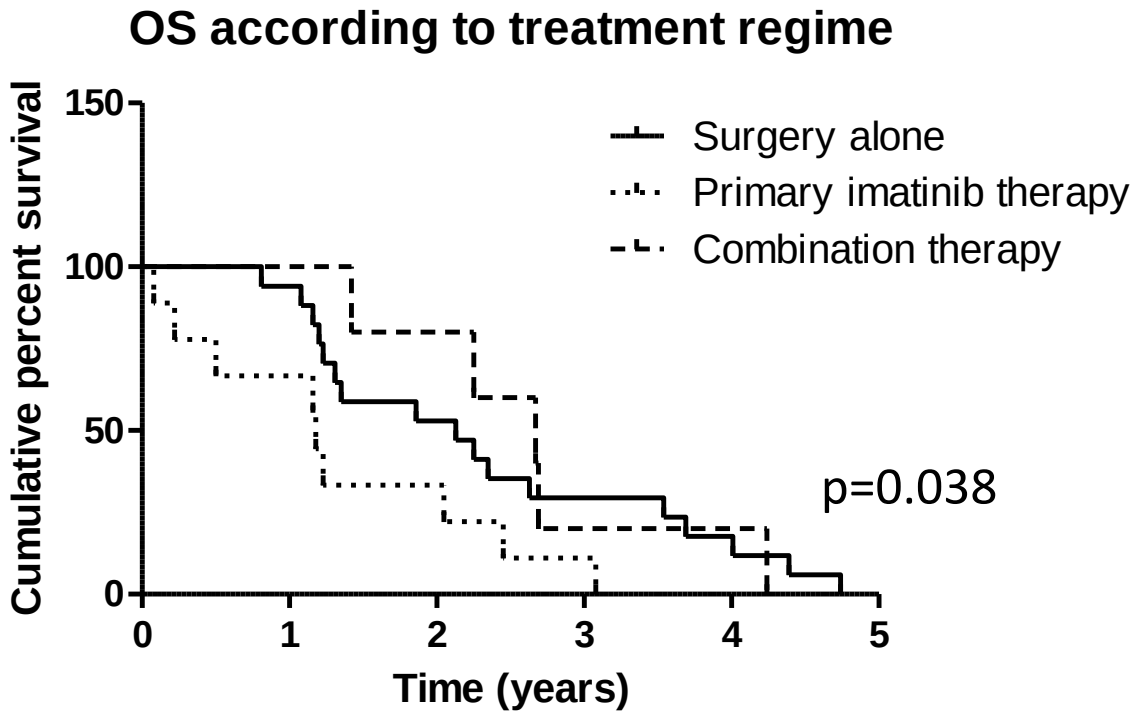




Survival statistics





Predictors of survival

- Univariate analysis:
  - age, tumour site, tumour size, mitotic count, metastases at diagnosis, AFIP criteria and treatment were all independent predictors of survival.
- Multivariate analysis:
  - variables significant on univariate analysis were included.
- Stepwise Cox proportional hazards regression analysis showed age, tumour site and tumour size to be significant independent predictors of outcome in patents with GISTs (p=0.003, 0.007 and 0.048 respectively).

Conclusions

- 42 patients with GISTs diagnosed over a 5 year period
- Annual incidence 8pts/yr/1.2million population
- Stomach – commonest site.
- Patient demographics, clinical presentations and tumour characteristics are somewhat similar to those reported previously in literature.
- Age, tumour site and tumour size to be the most important predictors of overall survival in our cohort.
- AFIP risk-stratification system performed the best in relation to overall survival but recurrence was unfortunately noted in 2 patents deemed at low risk by this and other scoring systems, suggesting that further work into these prognostic models is perhaps needed

Comparison with recent literature

- A recent Japanese study:
  - 712 Japanese patients with GISTs
  - tumour size, mitotic count, tumour site, and clinical features of rupture and/or invasion to be the most important prognostic factors for GIST recurrence.
  - Comparison of the available risk-stratification systems showed Joensuu's modified NIH classification as the best identify candidates at high risk of recurrence.
  - Significant treatment benefit with combined therapy compared to surgery or imatinib alone, perhaps indicating better overall survival with composite therapy.

Limitations and key messages

- Retrospective study
- small patient numbers.
- Early diagnosis with a combination of radical surgery and targeted molecular therapy should be the standard of care where possible.
- **Rigorous follow-up over a prolonged period is necessary to prevent recurrence, even in patients deemed at low risk by current risk-stratification systems.**
- A combination of surgery and imatinib may be necessary to provide a curative treatment for GISTs and prevent recurrence.

- **Current risk-categorisation models appear to be inaccurate in estimating recurrence risk with discrepancies in predicting behaviour for many low-risk tumours.**
- A weighted scoring system, where points are allocated to identified independent factors associated with poor prognosis, according to their contribution to the model, may serve as a more accurate clinical prediction tool.

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