ISAAC TRIAL

Initial Surgery in Advanced Asymptomatic Colorectal cancer patients receiving chemotherapy for metastatic disease)

Austin Obichere MD, FRCS
Consultant Laparoscopic Colorectal Surgeon
University College London Hospital

Heidelberg October 2011

Background

? Standard of Care

(synchronous unresectable liver mets & asymptomatic colorectal primary)

Current Treatment Options

Palliative resection + systemic chemotherapy

versus

Systemic chemotherapy alone

Case for Systemic Chemotherapy

Non operative management of primary colorectal cancer in patients with stage IV disease
Scoggins et al; Ann Surg Oncol 1999

Few (9-25%) asymptomatic pts will develop symptoms

Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases

N C Tebbutt, A R Norman, D Cunningham, M E Hill, D Tait, J Oates, S Livingston and J Andreyev

Gut 2003;52:568-573

Obstruction / abdominal complications:
Chemo 13.4% vs Surgery 13.2%

Annals of Surgical Oncology **14**(2):766–770
DOI: 10.1245/s10434-006-9146-1

Asymptomatic Colorectal Cancer with Un-Resectable Liver Metastases: Immediate Colorectal Resection or Up-Front Systemic Chemotherapy?

Andrea Muratore, MD,[1] Daria Zorzi, MD,[1] Hedayat Bouzari, MD,[1] Marco Amisano, MD,[1] Paolo Massucco, MD,[1] Elisa Sperti, MD,[2] and Lorenzo Capussotti, MD[1]

Non operative management is a safe approach

Case for Resection of the Primary

Emergency surgery for colon cancer
Smothers et al; Dis Colon Rectum 2003

Higher mortality in emergency surgery

20-40% vs 3-6%

Surgical Resection of Primary Tumors in Patients Who Present With Stage IV Colorectal Cancer: An Analysis of Surveillance, Epidemiology, and End Results Data, 1988 to 2000

Alan D. Cook, MD,[1] Richard Single, PhD,[2] and Laurence E. McCahill, MD, FACS[1]

Median and 1 year survival benefit with primary resection

The role of primary tumour resection in patients with stage IV colorectal cancer

V. R. Konyalian*, D. K. Rosing*, J. S. Haukoos†, M. R. Dixon*, R. Sinow‡, S. Bhaheetharan*, M. J. Stamos§ and R. R. Kumar*

*Division of Colon and Rectal Surgery, Harbor-UCLA Medical Center, Torrance, California, †Department of Preventive Medicine & Biometrics and Emergency Medicine, Denver Health Medical Center, University of Colorado Health Sciences Center, Denver Colorado, ‡Department of Radiology, Harbor-UCLA Medical Center, Torrance, California and §Division of Colon and Rectal Surgery, University of California, Irvine, Orange, California, USA

Primary resection improves survival

Case for Resection UCLH Data

Variable	Odds Ratio	OR 95% CI	P Value
Surgery	0.26	0.13-0.52	0.0001
Primary Response to Chemotherapy	0.53	0.32-0.87	0.01
Proximal Tumours	2.61	1.29-5.28	0.0075
>1 Primary	3.37	1.21-9.38	0.02

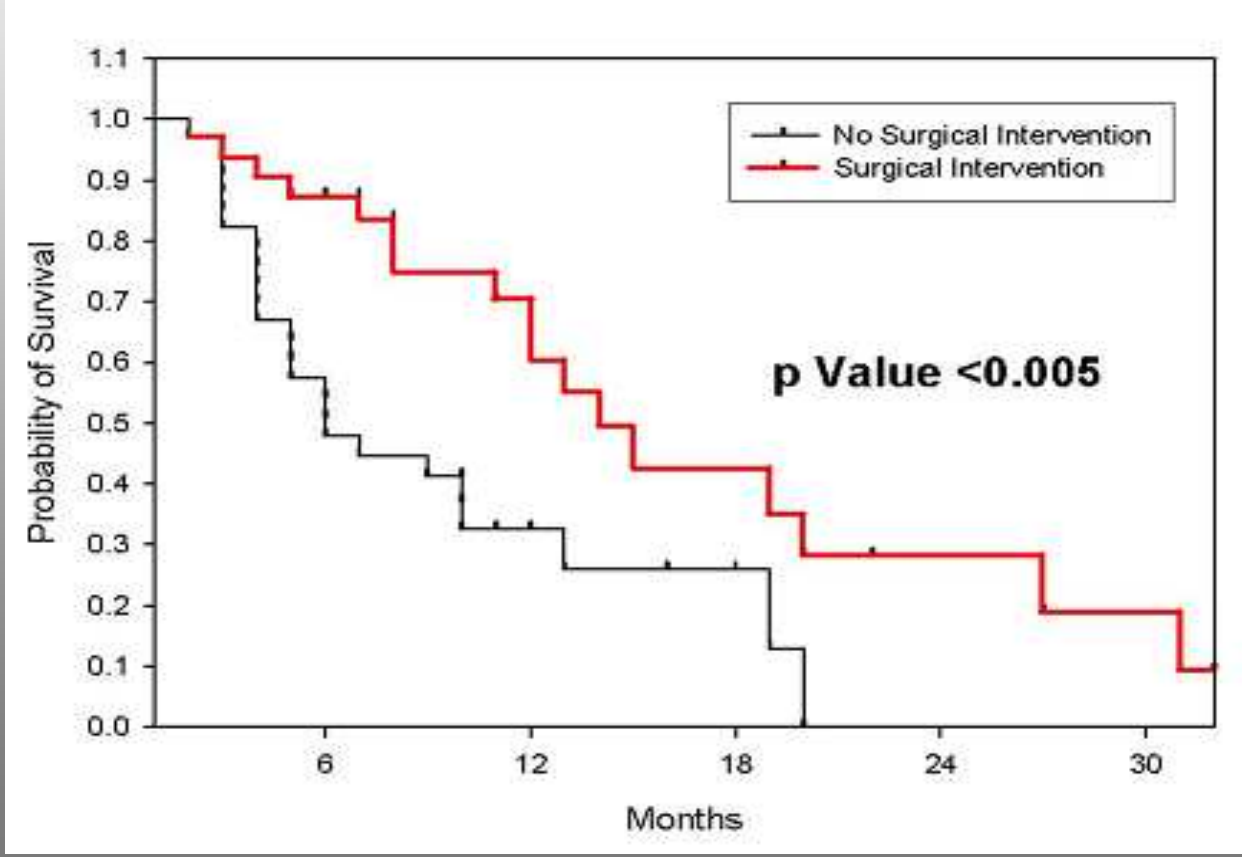
Bajwa et al; *Eur J Surg Oncol.* 2009

Case for Resection UCLH Data

Estimated median survival from Kaplan Meier curve

Chemotherapy only = 8 months

Chemotherapy + Surgery = 14 months



Bajwa et al; *Eur J Surg Oncol.* 2009

ACPGBI Postal Survey

139 colorectal surgeons completed the questionnaire (58% response)

For office use only: Ref:

IN CONFIDENCE

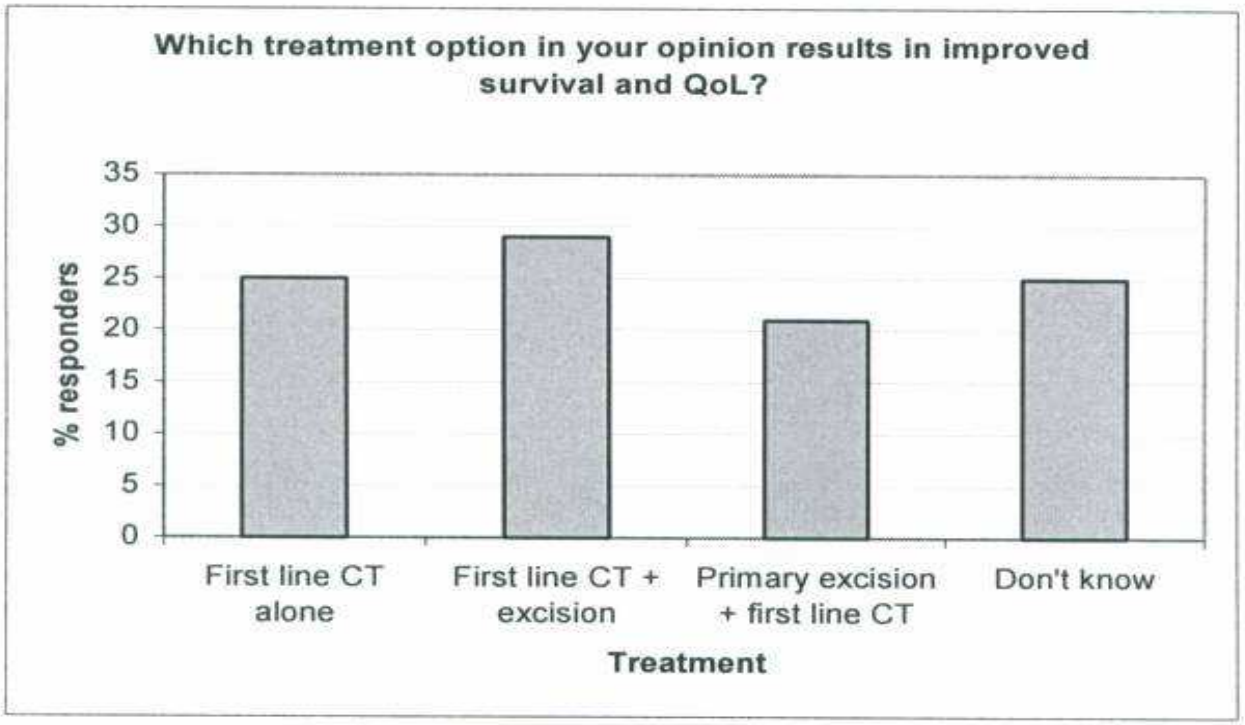


Figure 4

Figure 4 shows that there was no consensus among responding surgeons as to the most effective treatment for this group of patients.

Summary

- The standard of care for patients presenting with asymptomatic metastatic colorectal cancer is uncertain.

- No consensus in the literature or from a poll of ACPGBI members whether we should resect or leave the asymptomatic primary in stage IV colorectcal cancer

Other evidence in support of a randomised trial

- Combination chemotherapy
  - improved response rates
  - tumour control
  - survival

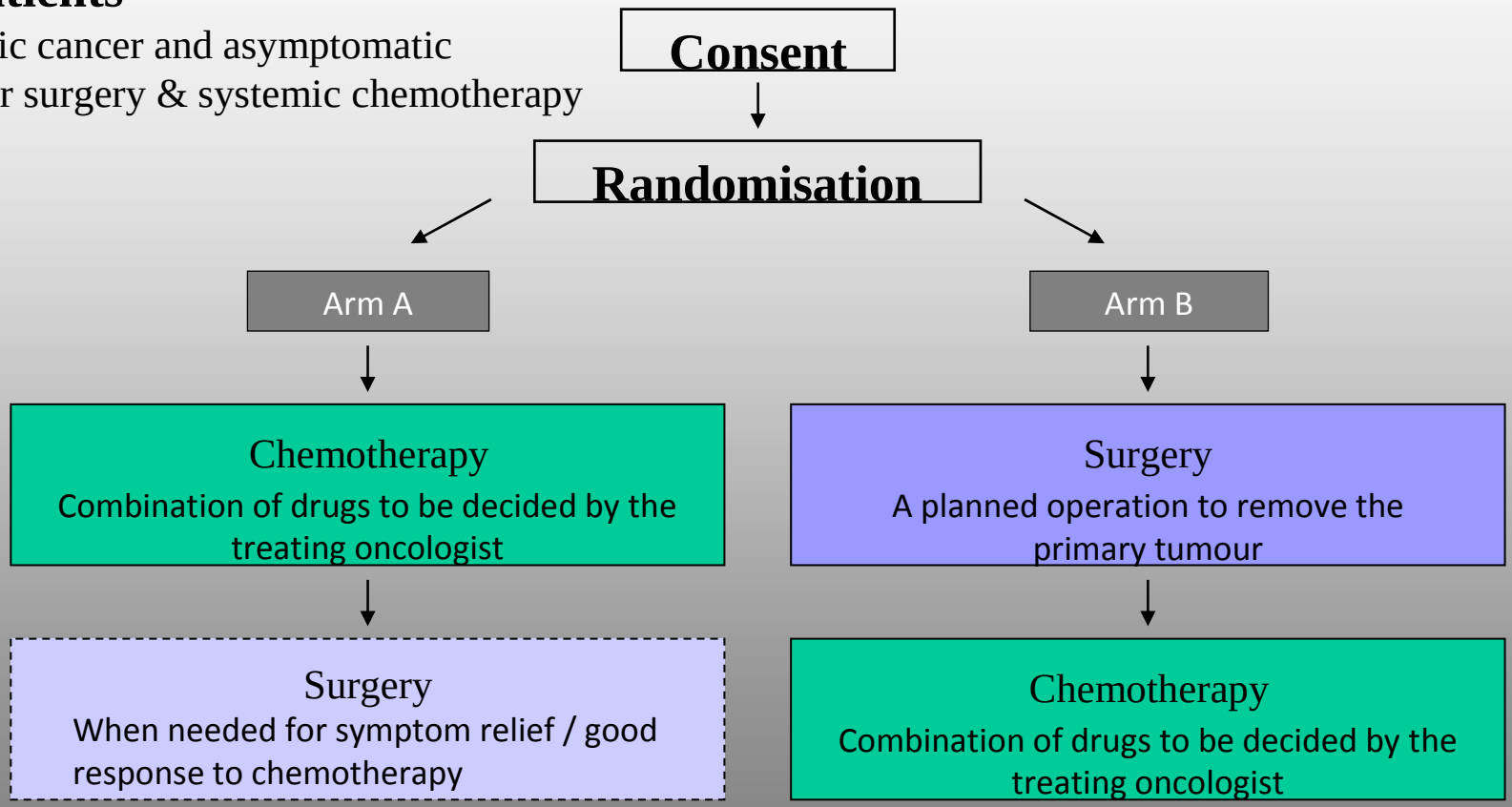
Zampino et al; Cancer 2007

- Survival benefit demonstrated after resection of primary for other stage IV malignancies (breast, ovarian, renal, gastric)

ISAAC TRIAL DESIGN

Eligible Patients

With metastatic cancer and asymptomatic primary, fit for surgery & systemic chemotherapy



Primary end point: Survival

Secondary end points: Morbidity of primary / subsequent planned or unplanned surgery
Quality of life
Economic evaluation

ISAAC SAMPLE SIZE

- **80% power / 5% significance (logrank)**
- **4 month survival difference ***
- **440 (500) patients for 376 events over 4 years and 2 years follow-up**

*The trial was designed to detect an increase of 4 months (or more) in the average length of survival, from 12 months in patients receiving chemotherapy alone to 16 months in those receiving surgery plus chemotherapy.

ISAAC Trial

- Funding approved by CRUK
- Trial Launched in Jan 2010
- 40-50 U.K sites proposed
- 2 International sites:
  - Naples Cancer Institute (Italy)
  - Australia (2 sites opened)

Patient Recruitment by Sites

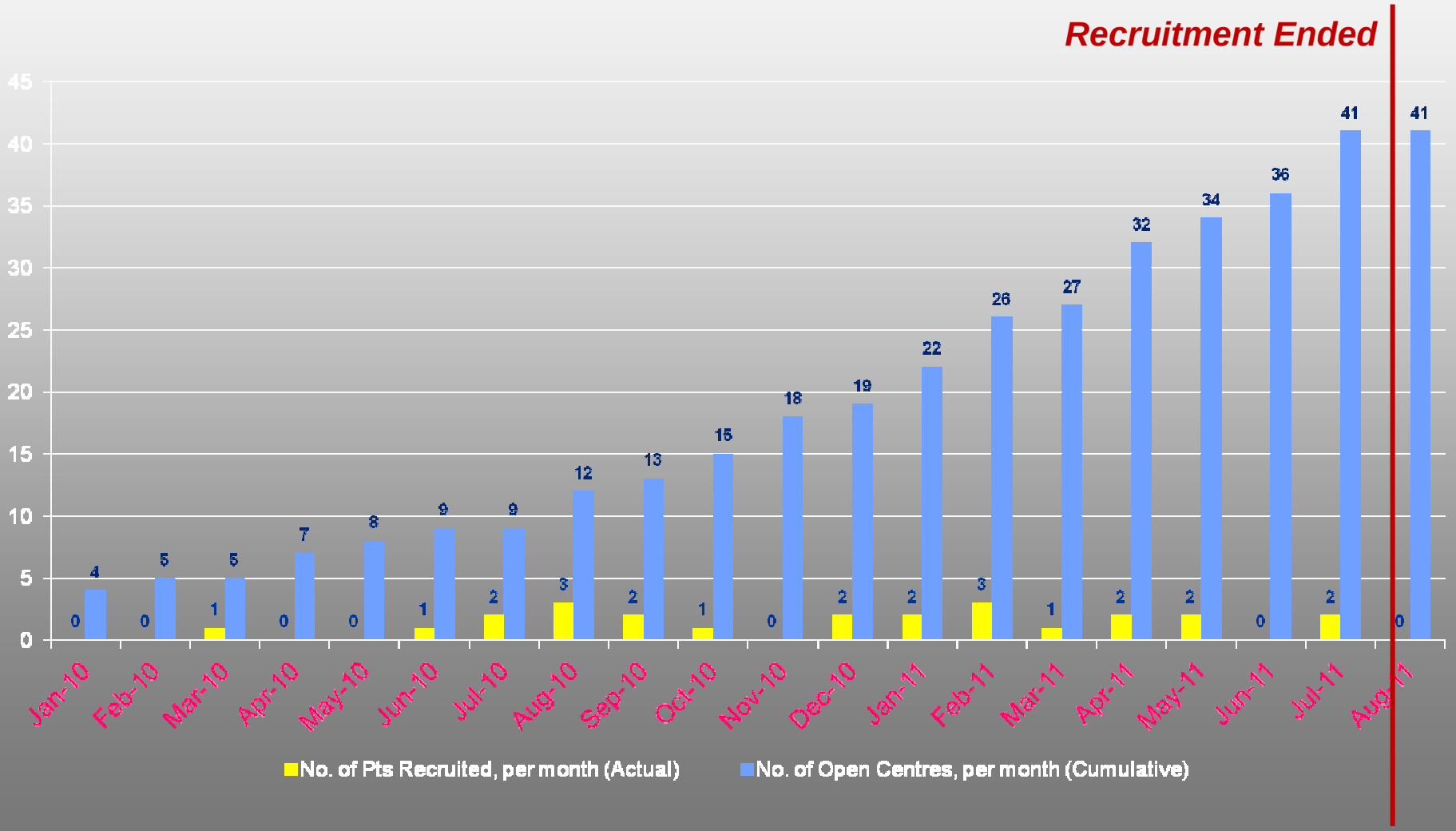
(between January 2010 – July 2011)

Site/Centre	No. of Patients
Luton and Dunstable Hospital	4
University College Hospital London	3
Istituto Nazionale dei Tumori di Napoli (Italy)	3
Royal Derby Hospital	3
Imperial Coillege Healthcare	3
Sheffield Teaching Hospitals NHS Trust	2
St Marks Hospital (Harrow)	1
Queens Medical Centre, Nottingham	1
Salisbury District Hospital	1
Ysbyty Gwynedd (Bangor)	1
Bristol Royal Infirmary	1
Medway Maritime Hospital(Kent & Medway)	1

41 Sites were opened as part of the ISAAC trial, however only 12 sites entered patients into the trial*. A total of 24 patients were recruited into the ISAAC trial.*

Patient Recruitment

(between January 2010 – August 2011)



Overview of Patient Screening Logs

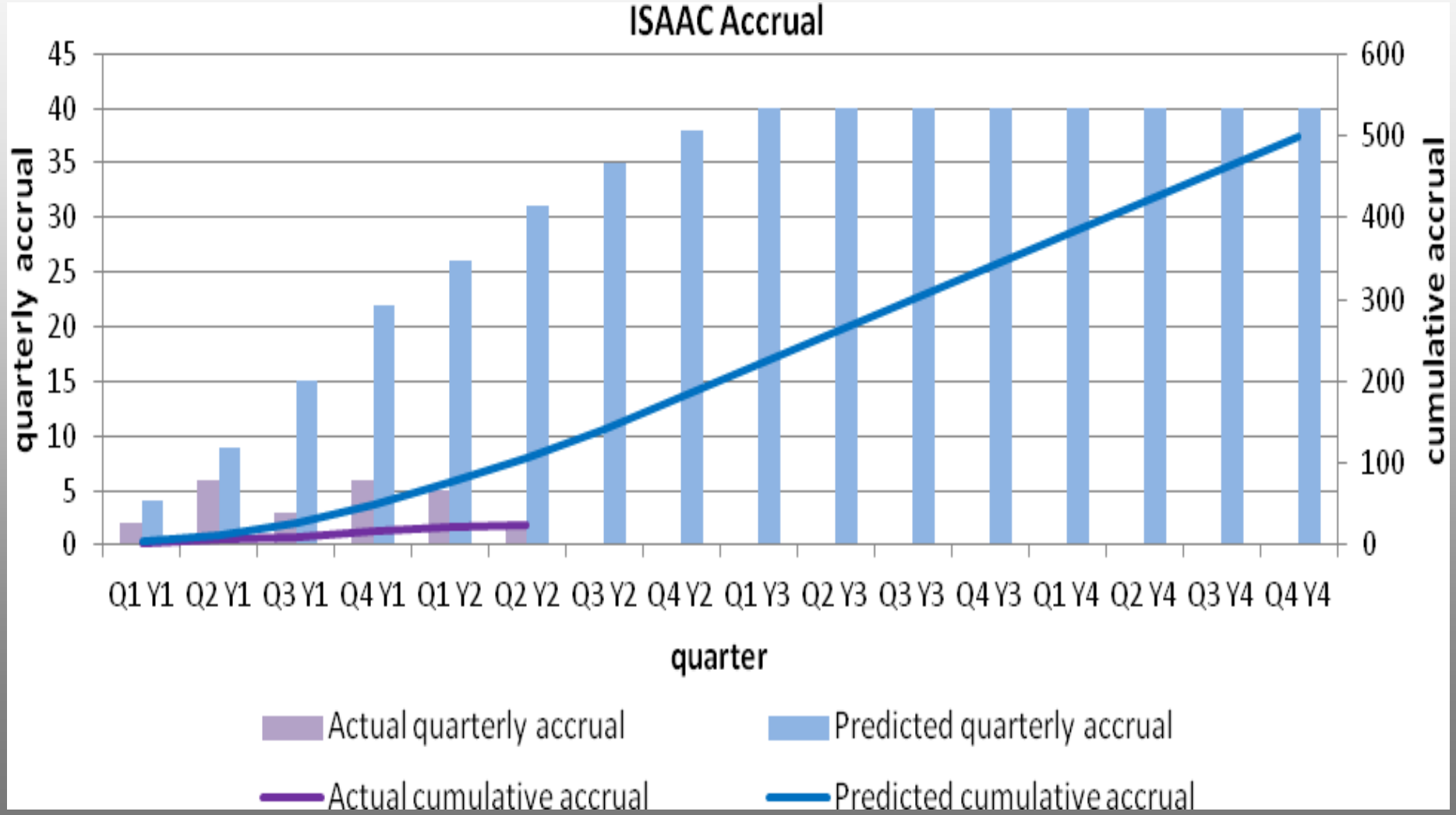
(between January 2010 – July 2011)

218 screened, 24=isaac and 197 excluded)

Code	Reason for Exclusion (Criteria)	No. of Patients
1	Primary tumour resectable	3
2	Primary tumour requires immediate/emergency surgery	19
3	Resectable metastases	21
4	Unequivocal extensive peritoneal metastases	15
5	Prior systemic treatment or surgery for colorectal cancer	7
6	Patient considered unfit for chemotherapy and surgery	28
7	History of malignant disease in the preceding five years	10
8	Patient refused randomisation	31
9	Randomised to another trial	1
10	Patient already offered alternative treatment	13
99	Other *(inc. patient anxious, refused any treatment, patient symptomatic, clinicians decision or preference & unknown)*	49

Reasons why patient refused randomisation were not always documented by the sites, however reasons (where specified) included patients choice for immediate treatment or preference for one form of treatment over another (i.e. chemotherapy rather than surgery or vice versa).

ISAAC Quarterly Accrual



Recruitment Challenges

General

1. Many investigators were surgeons with little experience in recruiting to randomised clinical trials (few GCP trained)
2. Support infrastructure was lacking (research nurses, data managers) and there was no understanding how to access such resources
3. Prolonged interval (from SSI and R&D approval) median time 3-6 months
4. Understanding inclusion / exclusion criteria and incorporating recruitment to site patient pathways
5. Ingrained practise
6. Patient pathways

Recruitment Challenges

Cross –speciality interests

1. *Liver surgeons*
   - *phenomena is neo-adjuvant chemotherapy*
   - *patients may be denied possible curative liver resection*
   - *NICE guidelines for the management liver metastases in stage 4 colorectal cancer*

2. *Medical oncologists*
   - *diversion of patients from phase1 chemotherapy trials*
   - *delayed opportunity for possible disease control*
   - *Trials should be confined to experienced researchers*

ISAAC Case Studies

Case 1:

67 year old man with stage 4 colorectal cancer (non-obstructing sigmoid primary) and anaemia (Hb - 9.0) attributed to intermittent episodes of rectal bleeding.

ISAAC Case Studies

Case 2:

79 year old woman with T4 N1 M1 ascending colon adenocarcinoma with localised involvement of the peritoneum overlying the primary tumour. The lung metastases is irresectable but the liver is clear.

ISAAC Case Studies

Case 3:

49 year old man with circumferential T3 rectal adenocarcinoma 1.5 cm above the dentate line, CRM clear but liver metastases irresectable.

ISAAC Case Studies

Case 4:

57 year old man presented with general fatigue, malaise and change in bowel habit with a tendency to constipation. He had a proximal transverse colon polypoidal tumour with irresectable liver but solitary lung metastases.

ISAAC Case studies

Case 5.

72 year old woman previously self caring presented with an obstructing descending colonic tumour and irresectable liver metastases. She was cachetic and dehydrated and was treated with an elective colonic stent.

ISAAC Case Studies

Case 6:

47 year old male patient with sessile 3 cm caecal polyp (adenocarcinoma Kukuchi 4) with irresectable retroperitoneal nodes and solitary resectable liver metastases.

ISAAC – What Next ?

- Premature closure of SUPER trial
- Premature closure of ISAAC trial
- Standard of care for stage 4 colorectal cancer with asymptomatic primary is still UNKNOWN
- Learn mistakes of above trials
- ? Answer German study (Synchronous trial)
- ? Collaboration
  - International centres for “Synchronous”

ISAAC - ISRCTN10963271

Contact: Rubina Begum (UCL clinical trials centre)
r.begum@ctc.ucl.ac.uk
or
ISAAC Trial Co-ordinator
Cancer Research U.K & UCL Clinical Trials Centre
90 Tottenham Court Road,
London W1T 4TJ
Tel: 0207 679 9688
Fax: 0207 679 9861
Email: ISAAC@CTC.UCL.AC.UK