



## IN THIS ISSUE:

- Prevention and Management of Radiation-induced Bowel Toxicity
- What's the Latest on RADICALS?
- 8th BUG Annual Meeting
- STAR Trial Coming Soon
- Where are We Going with Advanced Prostate Cancer?
- Society Column

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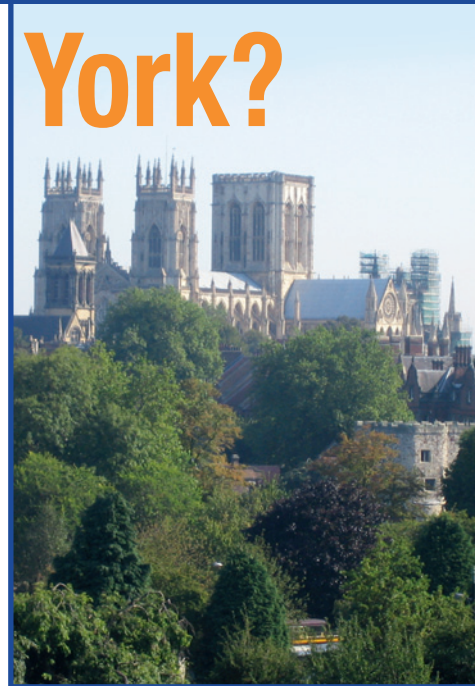
Specialist Trainee in Clinical Oncology, Northern Centre for Cancer Care, Newcastle upon Tyne

## All Set for York?

By popular demand we are returning to York this year for the Annual Meeting - the Meeting Programme with our speakers is featured in this issue. A big thank you in advance to all our speakers and supporters - it's an exciting and varied line up of sessions. Although focussing now on this year's event we have included a final highlights piece from the 2010 Meeting in this issue of *BUG Bytes*.

Since last September, we've been working hard on analysing and writing up the surveys conducted on Advanced Prostate Cancer and the NICE Prostate Cancer Guideline and we hope these will be published before the end of the year. Please do submit your interest if you have ideas for surveys at this year's meeting - there is still time!

Our 8th year of success is down to the hard work of everyone within our BUG community, but all work and no play...? You will find in this *BUG Bytes* we have introduced the new Society Column through which to share adventures; ventures; general out of clinic activities and achievements. Thank you to Simon Hughes who has got the ball rolling and has probably set a tough act to follow.



Please don't be shy - share a story big or small, quirky or not and we'll publish as many as possible. Otherwise, we look forward to hearing them during the social session in York!

We look forward to seeing you in September.

**Dr Heather Payne**

Chair, British Uro-oncology Group

## NEW Roles

We are delighted to have Carys Thomas and Mark Beresford join the Executive Committee and support us in the overall planning of BUG and developing new initiatives. Carys and Mark may choose to apply for a Trustee position in the future.

Welcome to James Wilson from Newcastle who has been nominated and voted to be the Registrar Representative on the BUG Committee to focus on activities aimed specifically at our Registrar and Junior Consultant colleagues.



**Carys Thomas**  
Kent



**Mark Beresford**  
Bristol/Bath



**James Wilson**  
Newcastle

# Prevention and Management of Radiation-induced Bowel Toxicity

**Ten years after radiotherapy, 9% of men with localised prostate cancer experience  $\geq$  Grade 2 late anorectal toxicity. At a seminar at the 2010 Annual Meeting, chaired by Sharon Beesley, BUG members had the opportunity to discuss this issue with gastroenterologists: Alastair Forbes from London and Clare Donnellan from Leeds.**

Radiation enteritis begins histologically with acute inflammation, but later changes include obliterative endarteritis of small vessels, lymphoid atrophy, lymphatic dilatation and fibrosis of submucosal tissue. The result is loss of normal elasticity and capacity in the rectum. Symptoms include diarrhoea, bleeding, constipation, incontinence and pain.

“It is astonishing how often I talk to patients about incontinence and they say you are the first doctor who has ever asked. If you do not ask, you will not hear about these symptoms,” said Alastair.

Colonocytes are dependent on butyrate, a short-chain fatty acid. Although there is little randomised trial evidence, a low-fibre diet has been recommended to reduce bowel symptoms after pelvic radiotherapy. But this deprives the gut microflora of non-absorbed carbohydrate, the main source of butyrate. So, when patients do need to reduce their fibre consumption, it is important to avoid butyrate deficiency.

Studies have investigated probiotics, but lack of standardisation and the need for a cold chain has led to increasing interest in prebiotics. These selectively fermented ingredients allow specific changes in the composition and/or activity in the gastrointestinal microbiota that confer well-being and health on the host.

Alastair and gastroenterology and oncology colleagues have begun two randomised, double-blind studies of prebiotics. Patients undergoing pelvic radiotherapy are assigned to either placebo or fructose oligosaccharide (FOS) 15 mg/day. This natural sugar is a butyrate donor that is fermented by gut bacteria, and sustains the effects of probiotics. The aim is to reduce the frequency and severity of acute radiation toxicity, and chronic damage.

Claire Donnellan emphasised a structured approach to diagnosis. “It is absolutely key to get a very clear history, especially what the patient means by diarrhoea or constipation,” she said.

Initial blood tests include full blood count, C-reactive protein, thyroid function tests, haematinics and celiac serology. Endoscopy with or without duodenal biopsy checks for celiac disease or ulcers in patients with dyspepsia and vomiting. Colonoscopy is recommended in patients with diarrhoea, and flexible sigmoidoscopy in rectal bleeding. Abdominal computed tomography (CT) investigates non-specific symptoms such as weight loss or abdominal pain that suggest stricture.

A breath test for small bowel bacterial overgrowth or direct culture at endoscopy rules out malabsorption in the jejeunum. SeHACT is recommended for bile salt malabsorption, and faecal elastase for pancreatic insufficiency. Capsule endoscopy is the second-line investigation for anaemia after colonoscopy or endoscopy, though radiotherapy patients are at risk of capsule retention due to fibrosis.

“Treatment depends on the investigation results, but radiotherapy patients often have multiple pathologies. If you just do one test that finds their celiac disease, but do not test for malabsorption you will not improve their symptoms,” continued Clare.

Nutritional advice is important in weight loss. Anti-diarrhoeals provide good symptomatic treatment. Antibiotics are used in bacterial overgrowth, but there is a discrepancy between improvements on breath testing and reduced diarrhoea.

Cholestyramine binds bile salts if the terminal ileum is damaged, but half of patients experience unacceptable nausea and bloating. Colesevelam is an alternative. Antioxidants should help fibrosis, but although LENT-SOMA scores improve, there is little functional benefit.

Because of the high risk of complications, surgery should be avoided, but one third of patients will need treatment for obstruction, perforation or fistulae. Endoscopic argon plasma coagulation is used to treat proctitis, colonic telangiectasia and haemorrhagic duodenitis. There have been good responses to hyperbaric oxygen in patients with rectal bleeding. Formalin enemas are also used, but they have significant side effects and should be avoided in patients with incontinence because of the risk of further reducing rectal compliance.

Throughout the session Alastair and Clare welcomed the opportunity for a dialogue with BUG members. Clare concluded: “We all agree that bowel toxicity is a significant problem. As gastroenterologists, I think we can make a significant improvement in patients’ symptoms. I recommend you find a friendly gastroenterologist!”

## Common Toxicity Criteria (CTC) v2.0: Late anorectal toxicity grading

Grade 1	Increased stool frequency, occasional blood-streaked stools or rectal discomfort (including haemorrhoids) not requiring medication
Grade 2	Increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure
Grade 3	Increased stool frequency/diarrhoea requiring parenteral support, rectal bleeding requiring transfusion; or persistent mucus discharge, necessitating pads
Grade 4	Perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (eg colostomy)

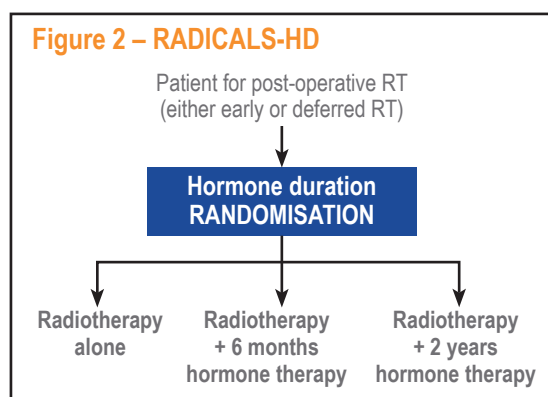
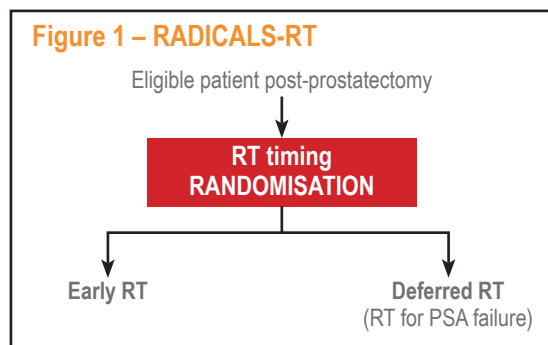


# What's the Latest on RADICALS?

Chris Parker provides the latest news from RADICALS – the large-scale randomised controlled trial to assess the role of radiotherapy and hormone therapy following radical prostatectomy. The trial is now open in over 100 centres in the UK and 14 centres across Canada where the trial is run through the NCIC Clinical Trials Group. The first centre in Denmark opened in March 2011 and already 3 Copenhagen patients have been randomised; a further centre in Galway, Ireland will open next month.

The trial has two randomisations:

- RADICALS-RT** (see Figure 1) assesses whether adjuvant treatment with radiotherapy following radical prostatectomy leads to better freedom-from-distant metastases than regular observation with early salvage treatment given if there is a rising PSA
- RADICALS-HD** (see Figure 2) assesses whether the addition of short term hormone therapy to post-operative radiotherapy given to the prostate bed at any time leads to better disease-specific survival; and whether two years hormone therapy is better than six months.

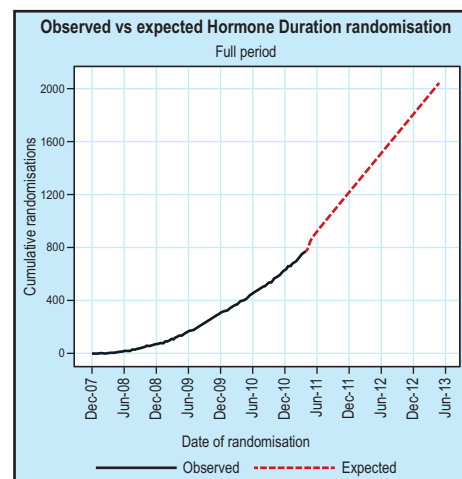
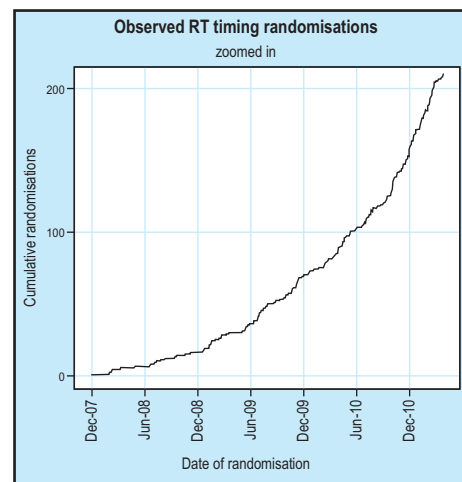


The main inclusion criteria for the trial are broad and simple. The trial may include almost any man who has undergone radical prostatectomy.

**RADICALS-RT:** Up to 22 weeks after radical prostatectomy, men with post-operative PSA <0.2ng/ml and one or more of: pT3/4, Gleason 7-10, pre-operative PSA >10ng/ml, positive margins (or a combination of these factors) can join RADICALS-RT.

**RADICALS-HD:** Any man due to be having post-operative radiotherapy to the prostate bed with a PSA <5ng/ml can join RADICALS-HD. This can be in the early or deferred setting.

Recruitment rates have been increasing recently and we are pleased to say that there are now 221 men in RADICALS-RT and 822 men in RADICALS-HD. Anecdotally, highlighting the trial to men before surgery improves randomisation rates.



Amit Bahl, RADICALS Principal Investigator in Bristol has a top tip for helping recruit patients into RADICALS-RT:

*I provide the information for RADICALS-RT at the time of the consultation prior to surgery. I explain to patients that radical prostatectomy for prostate cancer is a treatment that can result in 3 outcomes after the final histology is available:*

- 1st:** No further treatment needed
- 2nd:** Role of further treatment like radiotherapy uncertain and is being addressed in RADICALS-RT
- 3rd:** Radiotherapy would be strongly recommended.

*This way when the patients are approached for RADICALS-RT after the results of RP, it is put to them that the good news is that the results of surgery are favourable and there is no definite need for radiotherapy and they should consider randomisation in the trial. I have noted that this takes away the perceived disappointment felt by some patients and this results in effective team working with the urologists and oncologists and in my opinion is a factual representation of where we are with the role of radiotherapy in post-RP setting. For some patients who like to discuss the possibility of the three options post-RP, I put a rough estimate of 25-30%, 40-50% and 25-30% respectively and highlight that the commonest group is the 2nd option and reiterate the uncertainty which RADICALS is trying to address.*

Much more information about the trial, including the up to date accrual figures, information videos and all the latest news, can be found on the RADICALS website: [www.radicals-trial.org](http://www.radicals-trial.org).

RADICALS references: MRC PR10, NCIC PR13, ISRCTN40814031, NCT00541047.

# STOP PRESS: Revisions to RADICALS sample sizes

The sample sizes required for RADICALS-RT and RADICALS-HD are in the process of being revised to take into account new outcome data from the EORTC trial 22911 and the SWOG trial 8794. There will be more details to follow, but, in summary, patients in the EORTC and SWOG trials have done better than we assumed when we designed the RADICALS trial. This is good news, not just for them but also for RADICALS, because it means that we need fewer patients in order to target the same absolute benefit in long-term outcome.

RADICALS-RT will now aim to recruit around 1000 patients to detect a 5% absolute improvement in freedom from distant metastasis at 10 years. Disease-specific survival will also be analysed as part of a meta-analysis with the RAVES (NCT00860652) and GETUG-17 (NCT00667069) trials.

RADICALS-HD will now aim to recruit around 2000 patients to detect a 6% absolute improvement in disease-specific survival. The more patients that are randomized 3 ways (0 versus 6m versus 24m) rather than 2 ways, the fewer patients that will be needed overall.

These changes mean that accrual to RADICALS-RT is almost 25% complete, and accrual to RADICALS-HD is over 40% complete. Well done, and keep up the good work!

# 8<sup>th</sup> BUG Annual Meeting



BRITISH URO-ONCOLOGY GROUP

Friday 9th and Saturday 10th September 2011

The Royal York Hotel & Events Centre, Station Road, York, YO24 1AA

Our 8th Annual Meeting will cover the main tumour types, but will also have a keen focus on advanced prostate cancer, recognising the rapidly emerging developments in this field, particularly in metastatic Castration Resistant Prostate Cancer (mCRPC).

The regular Breaking News plenary will review key publications and International meeting summaries and new on the programme this year will be The Dragon's Den Session. We are requesting information on trials in development from the NCR1 groups to be presented to The Dragons at the Meeting for the Dragons then to give advice on how each trial could be most successfully moved forward. This will also allow the BUG membership to have some input into forthcoming national studies and those that they would be keen to support.

## Friday 9th September

11.00am Exhibition

Poster Viewing

Lunch

12.30pm Introduction – Heather Payne

12.45pm Main Session: Advances in the Management of Castration Resistant Prostate Cancer

(Supported by an educational grant from sanofi-aventis) Chair: Johann de Bono; Eric Small; Amit Bahl

2.00pm Seminar Session 1\*:

- Advanced Prostate Cancer – Lessons from the Past for Success in the Future

(Supported by an educational grant from Janssen) Karim Fizazi; Gerhardt Attard

- PET Imaging in Urological Cancer

Simon Hughes; Gary Cook

- Testicular Cancer - Poor Prognosis, Salvage Therapy, and High Dose Chemotherapy

Robert Huddart; Tom Powles

3.15pm Tea/Coffee and Exhibition

4.00pm Seminar Session 2\*:

- Hot Topics for Debate in Prostate Cancer (Takeda educational seminar)

Chris Parker; David Deamaley; Noel Clarke

- Chemoradiosensitization – What Next? Jim Barber; Anthony Chalmers; Ananya Choudhury

- Challenging Cases in Renal Cancer Lisa Pickering; Janet Brown

5.15pm Main Session: Breaking News Chair: John Logue

Malcolm Mason; Rhona McMenemin; Rob Jones; Stephen Harland

6.45pm Drinks Reception (non sponsored)

Poster Viewing

7.30pm Non Sponsored Social Session – Conference Dinner

## Saturday 10th September

8.00am Poster Viewing

8.30am BUG AGM: Review of 2010/2011 Activity Heather Payne and Executive Committee

9.00am Main Session: Registrar Presentations

9.45am Seminar Session 3\*:

- An Update in Bladder Chemotherapy (Supported by an educational grant from Pierre Fabre)

James Green; Ben Lamb; Carys Thomas; Ludwig Fischer von Weikersthal

- The Life-Cycle of a Clinical Trial John Chester; Alison Birtle

- The Way Forward with Radioisotopes Chris Parker; Joe O'Sullivan

11.00am Tea/Coffee and Exhibition

11.25am Main Session: Prize-giving of Registrar Presentations

11.30am Main Session: The Dragon's Den Chair: Peter Kirkbride

Malcolm Mason; Gareth Griffiths; Kate Law; David Sebag-Montefiore

12.45pm Lunch

2.00pm Meeting Close



\*Participants will be asked to select one seminar option for each of the three seminar sessions in advance of the meeting.

Sponsorship grants for this independent programme have been provided by:

sanofi-aventis Janssen Pierre Fabre Takeda

AstraZeneca Cambridge Laboratories (A division of Alliance Pharmaceuticals Limited)

Ferring Pharmaceuticals GlaxoSmithKline iba Molecular Ipsen Oncura

## The STAR Trial – Coming Soon...

**Dr Janet Brown, Chief Investigator, provides an insight into the STAR Trial - A Randomised Multi-Stage Phase II/III Trial of Sunitinib Comparing Temporary Cessation with Allowing Continuation, at the Time of Maximal Radiological Response, in the First-line Treatment of locally advanced and/or metastatic Renal Cancer.**

Developed with the full support of the UK Renal Clinical Studies Group and funded by NIHR HTA (pending final ethics approval), the STAR phase II/III trial in 1,000 patients in 38 UK centres is likely to be a landmark study in renal cancer in the NHS, when it starts recruiting in October 2011.

### Aims and Objectives

Sunitinib is now standard first line therapy in the management of locally advanced and metastatic renal cancer, but is expensive and associated with significant toxicities that cause over 40% of patients to discontinue treatment or require dose reductions. The principal aim of the STAR trial is to determine whether a sunitinib schedule with planned treatment breaks is as effective as the standard continuous sunitinib schedule, whilst delivering improved quality of life and substantial cost savings. The co-primary objectives of the study are to determine whether a sunitinib drug-free interval (DFI) approach is non-inferior with respect to the conventional continuous (CC) sunitinib approach in

- 2 year Overall Survival and
- Quality Adjusted Life Years (QALYs) averaged over study recruitment and follow up

Secondary objectives include: comparison of the DFI and CC arms for time to strategy failure, toxicity, quality of life and progression free survival; an evaluation of the cost effectiveness with sunitinib of the novel DFI compared to a CCS; exploration of patient perspectives relating to the study design; associated translational studies.

### Trial Design

The trial will be managed by Leeds Clinical Trials Research Unit. Participants will be randomised 1:1 at baseline (ie before sunitinib is commenced) into either the DFI or the CC arm and informed of their treatment arm. All participants will begin sunitinib at conventional dosing (50 mg daily for 4 weeks of a 6 week cycle) and this will continue for at least 6 months (4 cycles) and until maximal radiological response has been obtained (either complete response or stable disease between the preceding 2 radiological assessments as per RECIST). At this time point participants randomised to the CC arm will continue sunitinib as per standard practice until disease progression. Participants randomised to the DFI arm will temporarily stop sunitinib and have a planned treatment break. Clinical and radiological assessments will continue at the same time points in both arms, i.e. clinical assessments every 6 weeks and radiological assessment every 12 weeks. Participants in the DFI arm will be recommenced on sunitinib at the time of demonstrable progressive disease (as per RECIST) or on symptomatic clinical progression. In participants who begin responding again, further planned treatment breaks will be implemented on completion of a minimum 4 cycles and maximal radiological response. Participants in either arm will come off study at the time of demonstrable progressive disease while on sunitinib.

The STAR trial has 3 stages and achievement of the Phase II, stage 1 and 2 endpoints (measuring adequate recruitment rate and early efficacy) in 13 centres with 210 participants over 21 months, is required for continuation into the full Phase III study (additional 25 centres, 790 patients, 33 months).

### Translational studies

The STAR trial provides a unique opportunity to perform associated translational research aiming to identify tissue or imaging biomarkers predictive of response to sunitinib in mRCC, (CT and MRI) as well as other translational end points.

### Further information

For further information on this trial in metastatic renal cancer, please contact: Catherine Olivier, Senior Trials Manager, Leeds Clinical Trials Research Unit 0113 3431494, [c.olivier@leeds.ac.uk](mailto:c.olivier@leeds.ac.uk).

## Where are we going with Advanced Prostate Cancer?

### Cabazitaxel

Cabazitaxel (JEVTANA®), in combination with prednisone/prednisolone, has now received a European Commission approval for the treatment of patients with metastatic hormone-refractory prostate cancer (mHRPC) previously treated with a docetaxel-containing regimen.

Cabazitaxel is shown to significantly extend overall survival in mHRPC patients whose disease has progressed during or after treatment containing docetaxel (15.1 months median overall survival vs 12.7 months in the mitoxantrone arm; HR=0.70 (95% CI: 0.59-0.83); P<0.0001). The approval decision is based on the results from the Phase III TROPIC clinical study involving 755 patients with mHRPC previously treated with a docetaxel-containing treatment regimen.

### Abiraterone Acetate

Abiraterone acetate (ZYTIGA™) recently received FDA approval for use in combination with prednisone for the treatment of patients with metastatic Castration Resistant Prostate Cancer (mCRPC) who have received prior chemotherapy containing docetaxel; an application for its approval in Europe has also been submitted to the European Medicines Agency.

A Phase III study, conducted in 1195 men with mCRPC who had progressed after docetaxel-based therapy, showed that abiraterone acetate plus low-dose prednisone significantly improved OS (HR 0.65, 95% CI 0.54-0.77, p<0.0001), time to PSA progression (HR 0.58, 95% CI 0.46-0.73, p<0.0001), PFS (HR 0.67, 95% CI 0.58-0.78, p<0.0001) and PSA response (p<0.0001) compared with placebo.

**The way forward in advanced prostate cancer will be a key subject of discussion at the BUG Annual Meeting.**

# Society Column

**The Adventurists: "Fighting to make the world less boring" - Simon Hughes opens up about his driving adventures....**

"In 2006 I became an Adventurist. My mum wasn't particularly happy about this but, aged 59, she was limited in her options to remedy my status of 'only child'. My conversion to Adventurism took place on Boxing Day, in Cochin, Kerala as my TukTuk crossed the startline for the inaugural, Trans-India "Rickshaw Run" (4000km Cochin to Darjeeling). Armed with only an A4 sized map of India, our navigational strategy was to head inland, perpendicular to the coast, until we reached the seaside again and then turn left and head for the Himalayas. Luckily this was a fool-proof plan...and 2 weeks later I was sat on the veranda of a former Colonial Palace eating a fried breakfast, supping a medicinal Gin and Tonic, and surveying the tea plantations.

Buoyed up by the success of my first dabbings into a less sanitised and sheltered world I instantly signed up for the 2007 Mongol Rally. The aim was to drive a 25 year old VW Polo from Hyde Park to Ulan Bataur; the reality involved finding a scrap yard in Prague and then flying home.

Towards the end of October 2009 you may have noticed that the average IQ for Europe rose sharply as 30 teams of Adventurists departed for Peru to participate in the first Trans-Andes Moto-Taxi Junket. We were joined by a handful of teams from North America - although their departure for South America resulted in a lower mean IQ for both continents. Our noble Moto-taxi was best described as the result of a drunken one-night-stand between a sofa and a lawnmower. A throbbing single cylinder 125cc engine powered just one of the beast's 3-wheels to speeds that occasionally exceed walking pace...an ideal vehicle for the adventure that lay ahead. These sentiments are no longer shared by one of my co-drivers who spent a week in a Peruvian Hospital having had his arm stitched back together under GA - although it was really his own fault for driving into the side of one of the Andes.

Last year we closed the Audit Loop of Adventurism by participating in another TukTuk race...this time traversing the Himalayas from Gangtok, Sikkim (a militarised zone near the India-China border), through Nepal and then back into India to finish in the desert fortress of Jaisalmer (near the India-Pakistan border)...I've no idea why I found it so difficult to get through passport control in Orlando for GU ASCO this year!

The Institute for Adventure Research should be announcing its next escapade within the next few weeks ([www.theadventurists.com](http://www.theadventurists.com)). Will you be joining me on the start line?"



The Rickshaw Run 2006



Locals taking an interest in the Rickshaw Run in 2006



Simon participating in the first Trans-Andes Moto-Taxi Junket

*Please submit your adventures/activities - we await your stories...*



**bug bytes**

Check out the BUG website at [www.bug.uk.com](http://www.bug.uk.com)

Easier pass-wording, latest updates and most importantly your own discussion forum