Chronic GI effects of radiotherapy

Jervoise Andreyev
Consultant Gastroenterologist in Pelvic Radiation Disease
The Royal Marsden

Treating cancer is expensive

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate radiotherapy</td>
<td>£6,000-9,000</td>
</tr>
<tr>
<td>Right hemicolecotomy + adjuvant capecitabine</td>
<td>£8,300</td>
</tr>
<tr>
<td>Anterior resection</td>
<td>£10,800</td>
</tr>
<tr>
<td>ChemoRT cervix</td>
<td>£14,800</td>
</tr>
<tr>
<td>Whipple + adjuvant chemoRT</td>
<td>£15,900</td>
</tr>
<tr>
<td>Neoadj chemoRT + rectal surgery + adj chemo</td>
<td>&gt;£45,000</td>
</tr>
</tbody>
</table>

**Question:**
How much should we spend dealing with collateral damage caused by the cancer therapy?
The Royal Marsden

Changes in 10 year survival 1971-72 to 2010-11

All cancers

Incidence

- Testis
- Malignant Melanoma
- Prostate
- Breast
- Uterus
- NHL
- Cervix
- Bowel
- Bladder
- Kidney
- Leukaemia
- Stomach
- Brain
- Oesophagus
- Lung
- Pancreas

CRUK - Cancer Survival Statistics December 2014
SEER database USA Survival figures after cancer

1 year survival
2 year survival
5 year survival
10 year survival
15 year survival
A fundamental truth:

Success story

But at what price?
Mrs F

- 68 years old
- Cervical cancer - radiotherapy 1986
- Bilateral ureteric stents - 15 years
- 2008 left nephrectomy and re-implantation of right ureter
- Gall stones

- Borborygmi
- Bowels 5-10/ day since RT
- Diarrhoea / steatorrhoea
- Urgency+++ 
- Regular faecal incontinence for years
- Flatulence +++
- Tenesmus
- Frightened to eat
- 25% body weight loss
Mrs F

2 previous gastroenterologists

Investigations
• Colonoscopy x 3
• CT virtual colonoscopy x 1
• Blood tests
• Glucose hydrogen breath test
• Stool for faecal elastase

Treatments
• Trial of rifaximin
• Trial of colestyramine 4g od
• Many anti-diarrhoeals

c £3,500  ->  No benefit
Mrs F

“nothing can be done....

........you will have to live with it...

......... but at least you do not have any cancer”
Symptoms | Surgery alone | Preoperative radiotherapy | Post operative radiotherapy
--- | --- | --- | ---
Any incontinence | 5-38% | 51-72% | 49-60%
Toilet dependency | 6% | 30% | 53%
Excellent function | 32% | 14% | N/A
Original Article

Substantial Improvement in UK Cervical Cancer Survival with Chemoradiotherapy: Results of a Royal College of Radiologists’ Audit

C.L. Vale *, J.F. Tierney *, S.E. Davidson †, K.J. Drinkwater ‡, P. Symonds §

* Meta-analysis Group, MRC Clinical Trials Unit, London, UK
† The Christie NHS Foundation Trust, Manchester, UK
‡ The Royal College of Radiologists, London, UK
§ Department of Cancer Studies & Molecular Medicine, University of Leicester, Leicester Royal Infirmary, Leicester, UK

Received 21 January 2010; received in revised form 7 April 2010; accepted 26 April 2010

5-year survival:
• 56% any radical treatment
• 44% radical radiotherapy
• 55% chemo-radiotherapy
• 71% surgery & postop radiotherapy

Late toxicity
• 47% grade 1-2
• 10% grade 3-4
  • 5% vaginal
  • 7% GI
  • 2% bladder
Grade 2=
- Increase of 4-6 bowel movements /day over baseline
- Moderate cramping
- Nocturnal stools
Globally 1 million people are treated with pelvic radiotherapy annually

After Pelvic Radiation - patient focused scoring

• 90% permanent change in bowel habit
• 50% bowel dysfunction affects QOL
• 30-40% change in QOL is moderate or severe

A truth?

It is no-one’s job to manage quality of life
Why the lack of interest in chronic toxicity?

not a real disease

it becomes legitimate to ignore it
The solution?

Define a “real disease”
Comment

Defining pelvic-radiation disease for the survivorship era

Progress in complex disorders requires clear thinking facilitated by clear language. \(^1\) Radiation is used to treat pelvic cancer more than any other tumour site. Of the toxic effects experienced after pelvic irradiation, gastrointestinal symptoms have the greatest effect on quality of life. \(^2\) 50% of patients say that quality of life is affected by gastrointestinal symptoms and 20–40% rate the effect as moderate or severe. \(^3, 4\) Some argue that toxicity. Radiation-induced bowel toxicity is assessed by scoring scales that are based on clinical symptoms, an approach that ignores the nature of gastrointestinal symptoms. Apoptotic, inflammatory, ischaemic, or fibrotic pathological changes do not cause symptoms in their own right—only when they affect gastrointestinal physiological processes.

Symptoms scored as manifestations of radiation.

Andreyev, Wotherspoon, Denham, Hauer-Jensen
Lancet Oncology 2010
Scandinavian J Gastroenterology 2011
“Pelvic Radiation Disease”

Defined by

- symptoms
- patho-physiology
- affects non-cancerous tissues
- occurs after radiotherapy to a pelvic tumour
- transient or chronic
- mild to very severe

and it should be properly diagnosed & treated

Andreyev, Wotherspoon, Denham, Hauer-Jensen

Lancet Oncology 2010
Scandinavian J Gastroenterology 2011
Colorectal Diseases 2015
3 principles of management of PRD

1. An holistic, multidisciplinary, systematic approach is needed
It's time to meet
The Royal Marsden GIANTS
(GI and Nutrition Team)
Dr Clare Shaw
Consultant Dietitian

Ann Muls
Macmillan Nurse Consultant
GI Consequences of Treatment
### Holistic Needs Assessment: Concerns Thermometer (over 25yrs)

**Prefered Name:**  
**Patient Identifier:**  
**Pathway Point:**  
**Date:**  

**“I am coping well?”**  
**YES □ NO □**

#### Practial Concerns

<table>
<thead>
<tr>
<th>Description</th>
<th>YES</th>
<th>NO</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caring responsibilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housing or Finances</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transport or parking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work or Further Information needs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Physical Concerns

<table>
<thead>
<tr>
<th>Description</th>
<th>YES</th>
<th>NO</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>My appearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bathing or dressing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathing difficulties</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passing urine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Relationship Concerns

<table>
<thead>
<tr>
<th>Description</th>
<th>YES</th>
<th>NO</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relationship with my children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationship with my family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationships</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling swollen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High temperature or fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Emotional Concerns

<table>
<thead>
<tr>
<th>Description</th>
<th>YES</th>
<th>NO</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loneliness or isolation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadness or depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worry, fear or anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger or frustration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guilt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indigestion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual concerns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry, itchy or sore skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tingling in hands or feet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in how things taste</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Spiritual/Religious Concerns

<table>
<thead>
<tr>
<th>Description</th>
<th>YES</th>
<th>NO</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of faith or other spiritual concern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of meaning of purpose in life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling regret about the past</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flushes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory or concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Other concerns:**  
**YES □ NO □**

---

**Firstly**, please circle the number (0-10) that best describes how much distress you have been experiencing in the past week (including today).

**Secondly**, using the concerns list opposite, for each item please tick YES or NO to indicate if it has been a concern for you during the past week (including today). Please tick DISCUSS if you wish to speak further about your concern.
Holistic Needs Assessment 2013-2014

Proportion of patients with moderate to severe issues other than GI

- GI problems
- Fatigue
- Urinary problems
- Nutritional problems
- Sexual problems
- Emotional concerns
- Skin problems
# Modified GI Symptom Rating Scale

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain, bloating</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td></td>
</tr>
<tr>
<td>Flatus</td>
<td></td>
</tr>
</tbody>
</table>

### Bristol Stool Chart

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Separated hard lumps, like nuts</td>
</tr>
<tr>
<td>Type 2</td>
<td>Shapeless, mushy, like apples</td>
</tr>
<tr>
<td>Type 3</td>
<td>Rarely or no stools, no lumps or shape</td>
</tr>
<tr>
<td>Type 4</td>
<td>Soft, semi-liquid, watery dispersive</td>
</tr>
<tr>
<td>Type 5</td>
<td>Hard stools, no lumps, no shape</td>
</tr>
<tr>
<td>Type 6</td>
<td>Liquefied stools, no lumps or shape</td>
</tr>
</tbody>
</table>

### Quality of Life Rating Scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Perfect</td>
</tr>
<tr>
<td>8</td>
<td>Excellent</td>
</tr>
<tr>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>6</td>
<td>Satisfactory</td>
</tr>
<tr>
<td>5</td>
<td>Fair</td>
</tr>
<tr>
<td>4</td>
<td>Poor</td>
</tr>
<tr>
<td>3</td>
<td>Very Poor</td>
</tr>
<tr>
<td>2</td>
<td>Very Poor</td>
</tr>
<tr>
<td>1</td>
<td>Worst</td>
</tr>
</tbody>
</table>

### Additional Notes

- Please record any other symptoms not listed.
- Use the Bristol Stool Chart to assess stool consistency.

*Please turn over page*
Prospective audit of severity of GI symptoms

- nocturnal
- steatorrhoea
- rectal bleeding
- heartburn
- nausea
- leakage
- tenesmus
- diarrhoea
- frequency
- urgency
- borborygmi
- belching
- flatulence
- bloating
- abdo pain

% of affected patients
3 principles of management of PRD

1. An holistic, multidisciplinary, systematic approach is needed
2. Symptoms do not reliably predict their cause
What do GI symptoms mean?

- very little!
Patients referred to a gastroenterologist “typical radiation-induced symptoms”

After systematic investigation

- 38% diagnoses unrelated to radiotherapy

Gastrointestinal symptoms after pelvic radiotherapy: is there any role for the gastroenterologist?
Andreyev et al  IJROBP 2005; 62: 5: 1464-1471
Mr. H

• 76 year old, normal bowel function pre-RT
• Prostate cancer, 1 year after conformal RT
• Normal PSA
• Bowels open x4 per day
• Urgency
• Often loose stool
• Faecal incontinence weekly
• Tenesmus
• Perianal soreness

Mr. J

• 64 year old, normal bowel function pre-RT
• Prostate cancer, 1 year after IMRT
• Bowels open 3-6 per day
• Urgency
• Often loose stool
• x2 faecal incontinence / month
• Tenesmus
• Perianal soreness

Too much fibre

Giardia
&
2cm sigmoid polyp
Why GI symptoms?

Any insult

Pathological change

- Cell death
- Atrophy
- Ischaemia
- Oedema
- Inflammation
- Fibrosis

Affects specific GI physiological functions depending on the affected site

Symptoms
# Physiological causes for diarrhoea after pelvic RT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose intolerance</td>
<td>50%</td>
<td>5-7%</td>
</tr>
<tr>
<td>Malabsorption of other disaccharides</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Bile acid malabsorption</td>
<td>50%</td>
<td>1-83%</td>
</tr>
<tr>
<td>Small bowel bacterial overgrowth</td>
<td>25%</td>
<td>8-45%</td>
</tr>
<tr>
<td>Rapid transit</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Viral infection</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>C.Difficile</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Drug related</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

RMH algorithm version 10

For each of 22 symptoms:

- defined list of tests
- defined sequence of treatments
Identify each symptom accurately
Management of symptoms becomes straightforward
Using the concept of physiological algorithmic approach
Arranging appropriate tests to identify which physiological deficits are present
- obvious treatment options
Workload in GI consequences clinic at The Royal Marsden Hospital
The Royal Marsden

**Tumour types**

- **Urology**: 43%
- **Gynaecology**: 21%
- **Colorectal**: 12%
- **Upper GI**: 10%
- **Haematology**: 7%
- **Breast**: 3%
- **Head & neck**: 1%
- **Other**: 3%
Investigations required
- according to the algorithm

- 86% blood tests
- 58% OGD+ duodenal aspirate
- 53% breath tests
- 51% SeHCAT scanning
- 48% flexible sigmoidoscopy
- 45% stool faecal elastase
- 20% colonoscopy
- 3% radiological imaging.

- Six investigations (median 0-10) were requested.
New diagnoses made

62% had 3 or more diagnoses

3 visits were required (median, 1-16)

- 46% small bowel bacterial overgrowth
- 38% vitamin D deficiency
- 28% bile acid malabsorption
- 22% gastritis
- 20% radiation-induced bleeding
- 17% vitamin B12 deficiency
- 17% weak pelvic floor
- 13% polyps
- 5% pancreatic insufficiency.
Other referrals:

- 36% referred to dietitians
- 4% psychological support
- 2% urology
- 1% psychosexual counselling
- 1% physiotherapy
- 1% endocrinology
Top 10 symptoms (moderate/severe)
- at presentation and at discharge

- Steatorrhoea
- Perianal pain
- Nocturnal defaecation
- Borborygmi
- Abdominal pain
- Flatulence
- Tenesmus
- Bloating
- Faecal incontinence
- Urgency
Treating cancer is expensive

Question:
How much should we spend dealing with collateral damage caused by the cancer therapy?

Answer:
Mean episode of care / patient = £1,500

Muls et al Clinical Medicine in press
Mrs F

- 68 years old
- Cervical cancer - radiotherapy 1986
- Bilateral ureteric stents - 15 years
- 2008 left nephrectomy and reinsertion right ureter
- Gall stones

- Borborygmi
- Bowels 5-10/ day since RT
- Diarrhoea / steatorrhoea
- Urgency+++ 
- Incontinence for years
- Flatulence +++
- Tenesmus
- Frightened to eat
- 25% body weight los
Mrs F

Holistic needs assessment
• Depressed - psychological support (citalopram)
• Vaginal bleeding - gynaecology (topical hormone therapy)

Gastroenterological evaluation
• Faecal elastase - pancreatic insufficiency (pancreatic supplements)
• SeHCAT scan - severe bile acid malabsorption (colesevelam and low fat diet)
• Breath test and duodenal aspirate confirm SIBO (ciprofloxacin)
• Severe biliary gastritis (mucaine)
• Vit B12 and vitamin D deficiency (replaced)

Outcome
• Thriving
• Weight gain
Anecdote is not enough
You are making it up

Your approach is naive

You are bringing your hospital into disrepute!

What you do is not important

You live in an Ivory Tower
“Pay no attention to what the critics say; no statue has ever been erected to a critic”

Jean Sibelius
Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial

H Jervoise, N Andreyev, Barbara E Benton, Amyn Lalji, Christine Norton, Kabir Mohammed, Heather Gage, Kjell Pennert, James O Lindsay

Summary
Background Chronic gastrointestinal symptoms after pelvic radiotherapy are common, multifactorial in cause, and affect patients’ quality of life. We assessed whether such patients could be helped if a practitioner followed an investigative and management algorithm, and whether outcomes differed by whether a nurse or a gastroenterologist led this algorithm-based care.

Funded by: “Research for Patient’s Benefit”, a programme of the National Institute for Health Research

December 2013
Aims of this RCT (n=218):

1. Is a comprehensive management algorithm for new onset GI symptoms after pelvic radiotherapy effective?  
   Yes  p=0.006

2. Outcomes when patients are managed by a specialist nurse are not inferior to those managed by a gastroenterologist?  
   Yes  p=0.2
Simply managing symptoms is not good enough in IBD...........

So why should it be good enough for PRD...........?
Priorities in managing PRD

1. Predicting
2. Preventing
3. Modifying
Radiotherapy for pelvic cancer

Acute phase during radiotherapy
• Acute inflammatory response
• At its peak by 2nd week
• Resolved within 3 months
• Fibrosis seen in rectal biopsies by 2nd week

Chronic phase
• Chronic cytokine activation
• Characterised by ischaemia & fibrosis
• Progressive

Denham & Hauer-Jensen 2001, 2002
The consequential effect

Severe acute response

-> worse chronic toxicity

-> independent of the radiotherapy dose

Manipulating the consequential effect

Microbiota

HOT2 v HORTIS

Clarke IJROBP 2008
Submitted 2015

Haydont IJROBP 2007
Wedlake EJC 2009

Covington Sensors 2012
Ferreira Lancet Oncol 2014

Jackson 1959, Sullivan 1962, Archambeau 1965
The PPALM study: gamma-tocotrienol (GT3) in combination with pentoxifylline (PTX)
Vitamin E + Pentoxifylline
Treatment of Intestinal Radiation Fibrosis?

- “Open label study”
- 30 patients
- RTOG grade I-II toxicity
- Post-RT interval 12-48 weeks

Hille et al., Strahlenther Onkol 2005;181:606-14
GT3 Ameliorates Intestinal Radiation Injury

**Intestinal Crypt Survival**

- **Vehicle**
- **GT3**

**Mucosal Surface Area**

- **Vehicle**
- **GT3**

**Mucosal Permeability (day 4)**

- **Vehicle**
- **GT3**

**Bacterial Translocation**

- **Vehicle**: 80 ng bacterial DNA/g
- **GT3**: 20 ng bacterial DNA/g

*Note: All graphs display statistical significance with p-values.*

Berbée Radiat Res. 2011
Study design

- Double blind placebo controlled RCT
- Tocovid Suprabio 200mg + pentoxifylline 400mg BD
- GI symptoms despite optimal treatment
Endpoints

- GI symptoms
- Quality of life
- Urinary and sexual symptoms
- Change in fibrosis

Powering

- 115 patients, 85% power
Conclusion

Patients need us to be more intelligent about side effects of cancer therapies.

Symptoms are important and they determine who needs assessment and treatment.

Prediction/prevention/reduction of toxicity are possible.

Each cancer unit needs to reconsider fundamentally how it will provide supportive care in general but especially in gastroenterology.
GI and nutritional consequences of cancer treatment, 4th conference.

Thursday 26 & Friday 27 November 2015

www.gi-conference.com