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# Small bowel bacterial overgrowth and lactose intolerance during radical pelvic radiotherapy: An observational study

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ABSTRACT

*Introduction:* Loose stool affects up to 80% of all patients during pelvic radiotherapy and faecal incontinence may occur. Several causes for diarrhoea have been defined, though few oncologists target these causes in affected patients and most treat symptomatically only. It is not known whether small bowel bacterial overgrowth, a frequent cause of gastrointestinal symptoms in other contexts, occurs during radiotherapy. The frequency of new-onset lactose intolerance during pelvic radiotherapy is also not clear.

*Aims and methods:* To perform an observational pilot study to estimate the incidence of small bowel bacterial overgrowth and lactose intolerance during radical pelvic radiotherapy. Before treatment started and at weeks 4–5 of pelvic radiotherapy, a glucose hydrogen breath test and lactose tolerance test were performed. Gastrointestinal symptoms were assessed using the Vaizey incontinence questionnaire and the Radiation Therapy Oncology Group scoring system.

*Results:* Twenty two men and 17 women (median age 61, range 42–81) were recruited, four were treated for gastrointestinal, 17 were treated for gynaecological and 18 for urological cancers. Thirty-eight patients underwent glucose hydrogen breath tests and 26 patients underwent lactose breath tests at both time points. Ten patients (26%) were positive for the glucose hydrogen breath test: 60% of these developed new or worsening faecal incontinence during treatment and 60% had worsening bowel frequency. Four patients (15%) developed lactose intolerance. Of these 1 developed worsening faecal incontinence during treatment, 2 (50%) developed new-onset increase in bowel frequency or a change in the quality of bowel habit.

*Conclusion:* Small bowel bacterial overgrowth and lactose intolerance may occur during radical pelvic radiotherapy and are likely to contribute to gastrointestinal symptoms in some patients.



## 1. Introduction

Radical pelvic radiotherapy is used to treat approximately 300,000 patients annually in the Western world.[1] Historically, the acute toxicity of pelvic radiotherapy affecting the gastrointestinal tract has only been really considered of importance in that it limits the dose of radiotherapy that can be delivered to pelvic tumours. However, prospective patient centred data

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suggest that the gastrointestinal side-effects of radical treatment significantly affect quality of life in a higher proportion of patients than clinician scored data suggest.[2] In addition, it has been recently suggested that severe acute toxicity increases the risk of severe late toxicity (the consequential effect).[3–5]

The proven causes for diarrhoea during radiotherapy include accelerated small bowel transit,[6–9] the development of lactose intolerance (the risk increases with the amount of small bowel irradiated),[6,10,11] and bile salt malabsorption.[12–15] Postulated but unproven causes of diarrhoea include the degree and the extent of inflammation occurring in the gastrointestinal tract during radiotherapy, prostaglandin release from inflamed mucosa and changes in the bacterial flora of the large bowel induced by the radiotherapy.

Small bowel bacterial overgrowth is a cause for chronic diarrhoea in up to 15% of patients after radiotherapy[16] and is not an infrequent cause for a variety of gastrointestinal symptoms in non-irradiated patients.[17] However, there are no published data as to whether small bowel bacterial overgrowth develops during radiotherapy or contributes to symptoms at this time.

In this pilot study, we aimed to determine the frequency with which glucose hydrogen breath test suggests the development of small bowel bacterial overgrowth. Limited data suggest that *de novo* lactose intolerance occurs during pelvic radiotherapy in as many as 44–50% of patients, but a controlled trial of lactose restriction showed no benefit. As testing for lactose intolerance uses a similar technique to the glucose hydrogen breath test, we also performed a lactose tolerance test.

## 2. Materials and methods

### 2.1. Study design

The study was approved by the Research and Ethics committees of the Royal Marsden NHS Foundation Trust, London. Patients with a histologically proven malignancy of the lower gastrointestinal (rectal, anal), gynaecological (endometrial, cervical) or urological (prostate, bladder) tracts, for whom radical or adjuvant pelvic radiotherapy was planned were recruited prospectively following provision of signed, informed consent.

### 2.2. Biological tests

To define the development of new small bowel bacterial overgrowth, glucose hydrogen breath tests were performed at baseline and at 4–5 weeks of treatment. Patients undergoing a glucose hydrogen breath test were asked to avoid high fibre cereals and pulses in the evening meal before the test, and then to fast overnight. They were also asked to avoid strenuous exercise and cigarette smoking two hours before the breath test.

A basal breath sample was taken (Bedfont Scientific Limited, Gastrolyzer) and patients subsequently drank a solution containing 50 g glucose (Unichem, Chessington) dissolved in 200 ml water. Breath samples were then taken every 15 min for 2 h. Any rise in breath hydrogen above 16 ppm was considered abnormal.

Lactose breath tests were performed in the same way, substituting 50 g lactose (JML, Southampton) instead of the glucose. The lactose breath test was not performed in those patients who were already known or suspected to be lactose intolerant. A positive result was recorded if there was an increase of 20 ppm above baseline or an end reading of >24 ppm.

Patients were treated with a range of radiotherapy protocols according to disease site as summarised elsewhere.[18] In brief, these predominantly used a three-field technique, with fraction size between 1.8 and 2 Gy (Table 1). Conformal RT was done for patients with urological malignancy or those with rectal carcinoma, and patients with gynaecological malignancy also received brachytherapy at either a high dose rate or a low dose rate where clinically indicated.

### 2.3. Assessment of bowel toxicity

Gastrointestinal symptoms were assessed at baseline (start of radiotherapy) and following 4 or 5 weeks of radiotherapy. The Vaizey Incontinence Questionnaire (VIQ) was used to assess changes in continence for stool during pelvic radiotherapy, a score of '0' indicating complete continence and '24' total incontinence. The physician-assessed Radiation Therapy Oncology Group (RTOG) toxicity scoring tool was used to identify the change in bowel habit during radiotherapy.

### 2.4. Statistical tests and study powering

The study was designed as an observational pilot study. No previous data were available to power the study. It was considered that 25 paired (i.e. baseline and 4/5 weeks) glucose and/or lactose breath tests would comprise a representative sample.

## 3. Results

Thirty-nine patients were recruited. Thirty-eight provided glucose breath tests ('glucose group') and 26 patients underwent lactose breath tests ('lactose group') at both time points. Twenty-five patients underwent glucose and lactose breath tests at both time points. Baseline characteristics for the glucose and lactose groups are shown in Table 1. In contrast to the glucose group, the lactose group contained almost twice as many males as females. These were predominantly men with prostate cancer and nodal involvement receiving pelvic and prostate radiotherapy.

### 3.1. Glucose hydrogen breath tests (Table 2)

Twenty seven patients (71%) underwent normal tests at both time points, 10 patients (26%) were positive for breath test at 4/5 weeks and 1 patient (positive for test at baseline) underwent a normal breath test at 4/5 weeks .

### 3.2. Change in glucose hydrogen breath tests and continence

In the 27 patients who underwent normal breath tests throughout, 7 (26%) remained fully continent, 11 (41%)

**Table 1 – Study population Baseline characteristics**

| Characteristic | | Glucose group | Lactose group |
|---|---|---|---|
| *n* | | 38 | 26 |
| Sex (M:F) | | 21:17 | 17:9 |
| Age median (range) | | 61 (42–81) | 59(42–79) |
| *Disease site category and number of patients per site of disease within each group* | | | |
| Gynaecological | Ovary | 2 | 0 |
| | Cervix | 5 | 4 |
| | Endometrium | 9 | 4 |
| | Vagina | 1 | 1 |
| Lower gastrointestinal | Rectum | 3 | 2 |
| Urological | Prostate | 15 | 12 |
| | Bladder | 3 | 3 |
| *Number of patients receiving chemotherapy within each group* | | | |
| Gynaecological | No CT | 8 | 4 |
| | Pre-RT | 2 | – |
| | Concomitant (CT-RT) | 6 | 5 |
| | CT within previous year | 1 | – |
| Lower gastrointestinal | Pre-RT + concomitant | 1 | 2 |
| | Concomitant | 2 | 0 |
| Urological | None | 16 | 13 |
| | Pre-RT | 2 | 2 |
| *Radiotherapy dose (Gy) Median (range)* | | | |
| Lower GI | | 52.2 (50–54) | |
| Gynaecological | | 45 (45–68) | |
| Urological | | 70 (61–70) | |

*Key*: CT: Chemotherapy, RT: Radiotherapy, Gy: Gray.

**Table 2 – Results of glucose breath test (n = 38) and change in Vaizey and RTOG scores**

| | Glucose breath test: (Baseline to 4/5 weeks) | | |
|---|---|---|---|
| | Negative to negative | Negative to positive | Positive to negative |
| *Vaizey score: (Baseline to 4/5 weeks)* | | | |
| 0–0 | 7 | 3 | |
| 0 to ⩾1 Median (Baseline) (4/5 weeks) (Range 4/5 weeks) | 11<br>(0) (5)<br>(2–10) | 2<br>(0) (8.5)<br>(2–15) | |
| ⩾1 to >1 Median (Baseline) (4/5 weeks) Range (Baseline) (4/5 weeks) | 8<br>(2) (8.5)<br>(1–9) (2–15) | 4<br>(2.5) (8)<br>(2–3) (6–11) | 1<br>(1) (5) |
| 1–1 | | 1 | |
| ⩾1 to 0 Median (Baseline) (4/5 weeks) | 1<br>(1) (0) | | |
| Any increase (% of totals) (95% CI) | 19 (70%)<br>(50%, 85%) | 6 (60%)<br>(26%, 88%) | 1 (100%)<br>(3%, 100%) |
| Totals (% of all) (95% CI) | 27 (71%)<br>(54%, 86%) | 10 (26%)<br>(13%, 43%) | 1 (3%)<br>(0%, 14%) |
| *RTOG score: (Baseline to 4/5 weeks)* | | | |
| 0 to 0 | 4 | 2 | |
| 0 to ⩾1 (% patients scoring 1 : 2) | 19<br>(47:53) | 5<br>(40:60) | 1 |
| 1 to >1 | | 1 | |
| 1 to 1 | 4 | 1 | |
| 1 to 0 | | 1 | |
| Totals | 27 | 10 | 1 |

*Key*: Negative glucose breath test result indicates glucose-tolerant; Positive test result indicates glucose intolerant; Vaizey Incontinence questionnaire: Minimum score (asymptomatic) = 0, maximal score (most symptomatic) = 24; RTOG (radiotherapy toxicity oncology group: Minimum score (asymptomatic) = 0, maximal score (death) = 5.

developed new-onset incontinence and 8 (30%) who were incontinent to some degree at baseline developed worsening incontinence during treatment. One patient with faecal incontinence at baseline had no incontinence by the end of radiotherapy.

In the 10 patients who were positive for breath tests, 3 (30%) remained fully continent, 2 (20%) developed new-onset incontinence and 4 (40%) who were incontinent to some degree at baseline developed worsening incontinence during treatment. One patient had faecal incontinence at baseline, the severity of which remained unchanged at week 4/5.

### 3.3. *Change in glucose hydrogen breath tests and bowel habit*

In the 27 patients who were negative for glucose hydrogen breath test, 4 (15%) were scored as RTOG grade 0 at baseline and at 4/5 weeks, 19 (70%) developed an increase in bowel frequency or a change in the quality of bowel habit (RTOG 1 or 2), and 4 (15%) who had some disturbance in bowel habit before the radiotherapy (RTOG 1) experienced no worsening of the symptoms during treatment.

In the 10 patients who were positive for breath test, 2 (20%) had normal bowel movements at baseline and at 4/5 weeks and 6 (60%) developed new-onset increase in bowel frequency or a change in the quality of bowel habit. The remaining 2 had existing bowel problems at baseline, which either remained stable or improved.

### 3.4. *Lactose tolerance (Table 3)*

Three patients were lactose intolerant at baseline. 19 patients (73%) were lactose tolerant at both time points, 4 patients (15%) became lactose intolerant at 4/5 weeks.

### 3.5. *Changes in lactose tolerance and continence*

In the 19 patients who remained lactose tolerant, 2 (11%) remained fully continent, 9 (35%) developed new-onset incontinence and 7 (27%) who were incontinent at baseline developed worsening incontinence during treatment. One patient with incontinence at baseline had unchanged Vaizey scores by the end of the treatment (but with RTOG score which increased from 0 to 2). In the 4 patients who became lactose-intolerant, 3 (75%) remained fully continent and 1 patient who was incontinent at baseline developed worsening symptoms during treatment.

### 3.6. *Changes in lactose tolerance and bowel habit*

In the 19 patients who remained lactose tolerant, 1 had normal bowel movements at baseline and at 4/5 weeks, 15 (79%) developed new-onset increase in bowel frequency or a change in the quality of bowel habit, 60% of whom (9 patients) required medication to control their symptoms (RTOG grade 2). Three patients (16%) had some disturbance of bowel habit before radiotherapy and experienced no worsening of the symptoms during treatment. In the 4 patients who became lactose-intolerant at 4/5 weeks, 2 (50%) developed new onset-increase in bowel frequency or a change in the quality of bowel habit, 50% of whom (1 patient) required medication to control their symptoms.

### 3.7. *Combined positive glucose hydrogen breath test and lactose intolerance (Table 4)*

Twenty five patients provided breath samples using glucose and lactose at both time points. Both breath tests were negative in 21 patients at baseline. Fourteen remained negative at

**Table 3 – Results of lactose breath test (n = 26) and change in Vaizey and RTOG scores**

| | Lactose breath test: (Baseline to 4/5 weeks) | | |
|---|---|---|---|
| | Negative to Negative | Negative to positive | Positive at baseline |
| *Vaizey score: (Baseline to 4/5 weeks)* | | | |
| 0–0 | 2 | 3 | 1 |
| 0 to ⩾1 Median (Baseline) (4/5 weeks) (Range 4/5 weeks) | 9 (0) (6) (2–15) | | |
| ⩾1 to >1 Median (Baseline) (4/5 weeks) Range: (Baseline) (4/5 weeks) | 7 (2) (8) (1–9) (2–15) | 1 (1) (5) | 2 (2-2) |
| 1 to 1 | 1 | | |
| ⩾1 to 0 | | | |
| Any increase (% of totals) (95% CI) | 16 (84%) (60%, 97%) | 1 (25%) (1%, 81%) | |
| Totals (% of all) (95% CI) | 19 (73%) (52%, 88%) | 4 (15%) (4%, 35%) | 3 (12%) |
| *RTOG score: (Baseline to 4/5 weeks)* | | | |
| 0–0 | 1 | 1 | |
| 0 to ⩾1 (% patients scoring 1:2) | 15 (40:60) | 2 (50:50) | 2(50:50) |
| 1 to >1 | | | 1 |
| 1 to 1 | 3 | | |
| 1 to 0 | | 1 | |
| Totals | 19 | 4 | 3 |

*Key:* Negative lactose breath test result indicates lactose tolerant; Positive test result indicates lactose intolerant; Vaizey incontinence questionnaire: minimum score (asymptomatic) = 0, maximal score (most symptomatic) = 24; RTOG (radiotherapy toxicity oncology group: minimum score (asymptomatic) = 0, maximal score (death) = 5.

**Table 4 – Change in glucose and lactose tolerance at both time points (n = 16)**

| | Lactose breath test | | | |
|---|---|---|---|---|
| | Negative to negative | | Negative to positive | |
| | Baseline | Week 4/5 | Baseline | Week 4/5 |
| *Glucose breath test (Baseline to 4/5 weeks)* | | | | |
| Negative to negative | 14 patients | | | |
| Vaizey | 0 (0–9) | 5.5 (0–15) | | |
| RTOG grade 0 | 86% | 8% | | |
| Grade 1 | 14% | 50% | | |
| Grade 2 | 0% | 42% | | |
| Negative to positive | | | 2 patients | |
| Vaizey | | | 0 | 0 |
| RTOG grade 0 | | | 50% | 100% |
| Grade 1 | | | 50% | 0% |

4/5 weeks, 5 had developed either lactose or glucose intolerance (but not both) at 4/5 weeks, and 2 patients developed new onset-glucose and lactose intolerance by 4/5 weeks. Of the remaining 4 patients, 2 were lactose intolerant at baseline and were positive for glucose hydrogen breath test by 4/5 weeks, 1 was lactose intolerant at baseline, but was negative for the glucose breath test at both time points, and 1 was negative for lactose and positive for glucose breath test at baseline, with lactose test resulting positive and glucose breath test resulting negative at 4/5 weeks.

## 4. Discussion

In this prospective pilot study of patients undergoing radical pelvic radiotherapy, we found that one quarter of patients were positive for glucose hydrogen breath test, which is suggestive of small bowel bacterial overgrowth, and that 15% developed lactose intolerance during radiotherapy treatment.

Although this study recorded changes in bowel symptoms, it was not powered to determine whether significant differences in symptoms exist between those who were newly positive for breath test. Indeed as there are a large variety of causes for gastrointestinal symptoms occurring acutely during radiotherapy, it would require a very large study to show whether small bowel bacterial overgrowth or lactose intolerance was an independent predictor of gastrointestinal symptoms.

The accurate diagnosis of small bowel bacterial overgrowth is difficult as there is no 'gold standard' test to measure for its presence.[17] A glucose hydrogen breath test as used in this study has been reported to have a sensitivity of 36–93% and a specificity of 75–100% at detecting small bowel bacterial overgrowth.[19] False negative tests may be found in approximately 25% of patients who have non-hydrogen producing bacteria, and glucose is likely to be fully absorbed within the proximal jejunum so a glucose hydrogen breath test may be negative in patients with bacterial overgrowth affecting more distal small bowel only.

In patients with chronic gastrointestinal symptoms caused by radiotherapy, it has been shown that it is the chronic motility changes caused by radiotherapy that are the main cause for small bowel bacterial overgrowth.[20] Small bowel bacterial overgrowth particularly with gram negative bacilli has been reported in 4–45% patients with a variety of gastrointestinal symptoms after pelvic radiotherapy[16], but both in this patient group and in other patient groups, with detectable small bowel bacterial overgrowth, gastrointestinal symptoms do not always improve after antibiotics are given.[16,17] The reported clinical response rate with antibiotics varies from 35% to 100% in different studies in a variety of populations.

There is evidence that altered small bowel motility – a prerequisite for the development of small bowel bacterial overgrowth – occurs acutely in most patients undergoing radical pelvic radiotherapy. Therefore, our pilot data, which indicate that one quarter of these patients demonstrate the development of hydrogen production after several weeks of pelvic radiotherapy, which can only come from small bowel bacteria, have a plausible physiological basis.

Two previous studies reported that lactose intolerance develops in up to 45% of all patients during radiotherapy. However, a well conducted randomised clinical trial based on these data suggested no benefit from a lactose-free diet [21], suggesting that either this figure of 45% was excessive, or other physiological defects (such as small bowel bacterial overgrowth) were also contributing to symptoms in many patients. The use of conformal radiotherapy, as used in our patients, may often help reduce the exposure of the small bowel to radiation and the subsequent development of lactose intolerance [10], thus our finding of 15% of patients developing new-onset lactose intolerance also seems plausible.

Whilst on the basis of this small data set, we cannot extrapolate our data to all pelvic radiotherapy patients, our findings justify the need for a further adequately powered study to investigate new-onset glucose intolerance during pelvic radiotherapy treatment resulting from small bowel bacterial overgrowth. Such a study should be designed to record the volume of small bowel within the radiotherapy treatment field and should include additional weekly glucose tolerance tests to determine when during treatment the breath test becomes positive and if the patient is symptomatic, whether their symptoms respond to antibiotics. Since our prospective pilot sample included those with different pelvic cancers, future studies should also consider stratification of patients by site since this will influence the volume of small bowel within the treatment field.

Many patients find radical pelvic radiotherapy a very arduous treatment. Thirty four percent of this cohort developed new-onset faecal incontinence during treatment, a problem which can be extremely distressing[2,22] but which is not even measured by the RTOG scoring system. If patients are to endure fewer symptoms during treatment, it is not only technical advances in the delivery of radiotherapy which need to be addressed. There are a series of studies which show consistently that gastrointestinal symptoms during radiotherapy can often be explained by the development of one or more physiological abnormalities in the gastrointestinal tract as a direct result of the radiotherapy to which it is exposed.

This pilot study indicates for the first time, that in our patient group small bowel bacterial overgrowth is undoubtedly occurring, whilst lactose intolerance is less common than previously suggested. There exist good treatments for all the recognised gastrointestinal physiological abnormalities which can occur acutely. Patients are likely to benefit if clinicians adopted a more physiological approach to gastrointestinal symptoms occurring acutely during radiotherapy.

## Conflict of interest statement

None declared.

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