Original research

Gastrointestinal consequences of cancer treatment: evaluation of 10 years' experience at a tertiary UK centre

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ABSTRACT

Objective Up to 90% of patients treated for pelvic cancers experience chronic gastrointestinal (GI) symptoms. This study characterises this patient cohort at a single centre, addressing a paucity of publications reporting 'real-world' experiences.

Method Outpatient referrals, from oncology to the gastroenterology and nutrition services, at a tertiary London hospital from 2006 to 2016, were retrospectively identified. Patient characteristics, reported symptoms, investigations, diagnoses, response to therapeutics and follow-up were recorded.

Results Of 269 patients referred, 81% were within the latter 5 years. A total of 260 patients had diagnoses of pelvic cancers (prostatic (52%), cervical (19%) and endometrial (19%)). Among 247 treated with radiotherapy, the median time from radiotherapy to symptom onset was 8 months. Common symptoms were rectal bleeding (51%), diarrhoea (32%), faecal urgency (19%) and pain (19%). Patients underwent a median of three investigations including lower GI endoscopy (86%), thyroid function tests (33%) and glucose hydrogen breath test (30%). Diagnoses included radiation proctopathy (39%), colonic polyps (16%), pelvic floor dysfunction (12%), bile acid malabsorption (BAM) (8%), small intestinal bacterial overgrowth (SIBO) (8%), vitamin D deficiency (7%) and iron deficiency (7%). Among 164 discharged patients, the time to discharge was 7 months, after a median of two appointments.

Conclusions This unique patient group reports a complex mix of symptoms and requires specialist review and consideration of often uninvestigated diagnoses (pelvic dysfunction, BAM, SIBO and nutritional deficiencies). Such patients are often overlooked, compared with those suffering many other chronic GI disorders.

Significance of this study

What is already known on this topic

- ▶ Pelvic radiation disease (PRD) is a complex, multifactorial disease, which is under-recognised and under-resourced. The majority of published work in the UK in this field has come from a single internationally renowned centre with a dedicated PRD service.

What this study adds

- ▶ This study provides a clinical description of patients with PRD from a large centre without a dedicated PRD service, which may approximate clinical experience in other UK hospitals.

How might it impact on clinical practice in the foreseeable future

- ▶ Understanding clinical needs and practice across a number of UK centres will aid service planning nationally and locally, and inform future strategies for education, training and awareness of PRD.

Further reports from non-dedicated centres treating patients with pelvic radiation disease will aid in understanding of secondary GI diagnoses and variation in practice.

INTRODUCTION

Half of the UK population born after 1960 will develop cancer, requiring treatments including radiotherapy.¹⁻⁴ Although cancer outcomes improve (with 4 million survivors projected by 2030^{5 6}), 25% of patients face poor health from treatment toxicity. In 2011, 35% of new UK cancers were pelvic (including bladder, rectum and reproductive organ cancers),⁷ these carrying the highest gastrointestinal (GI)

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toxicity risks. Despite suspected under-reporting,⁸ up to 90% of patients report chronic gut symptoms after radiotherapy with quality of life affected in 50%.^{9–14} This compares with inflammatory bowel disease where 76% of patients report symptoms impacting leisure activities and 69% report impact on functioning at work.^{15,16}

'Pelvic radiation disease' (PRD) describes a constellation of consequences including genitourinary, bowel, oncological, dermatological pathologies, bone damage, neuropathy and psychological trauma. Among GI manifestations, 23 reported symptoms represent a spectrum of pathologies.¹⁷ This wide range makes diagnosis and management challenging.¹⁸ The Royal Marsden group has published on secondary syndromes in this cohort^{19–23} but reports from elsewhere are limited. The largest of four published studies^{23–26} identified barriers in developing services, including referrer awareness and confidence among gastroenterologists in managing PRD.²³ Suggestions to meet demand for accessible, appropriate care include establishing supra-regional centres, algorithm-based pathways, nurse-led services and a specific National Health Service Tariff.^{14,26,27} Developing such proposals requires exploration of current practice. This study describes the clinical characteristics, GI diagnoses and outcomes of the second-largest reported cohort of patients with PRD.

METHODS

University College London Hospital (UCLH) has tertiary oncology and clinical nutrition services. Although patients with PRD symptoms are referred to the nutrition clinic, there is currently no dedicated service. Referred patients are assessed in the clinic by a gastroenterologist. GI investigations are requested based on presenting symptoms (as per clinical assessment rather than questionnaire) with subsequent follow-up to discuss results and management.

This retrospective study aimed to improve understanding of service requirements for this population, add to published work and inform service planning. Electronic, outpatient and nutrition service clinic lists were screened from 1 July 2006 to 30 June 2016, identifying patients referred with GI symptoms following cancer treatment. The censoring date of data collection was 1 January 2017. Each record was interrogated for demographic data, oncological diagnoses, investigations, management and outcomes of treatment as determined by the responsible physician.

Following UK National Research Ethics Service guidance, this service analysis did not require ethical approval.

Data analysis

Statistical analyses were conducted using SPSS 26. The independent samples median test tested for differences between group medians, log-rank Mantel-Cox test for

Figure 1 Number of patients referred over the study period and the ages of patients. Histograms showing: (A) the number of referrals received grouped into 12-month periods over the course of the study (figures above column denote % of the total population, n=269); (B) the number of referrals received grouped by the age of patients at the time of referral (figures above column denote % of the total population, n=269).

differences between groups in time intervals, and χ^2 test (with Fisher exact test) for differences in proportion.

RESULTS

A total of 269 patients were identified, 218 (81%) within the latter half of the study (figure 1A). Patients were referred by 7 oncologists (from a pool of 13) and reviewed by 4 gastroenterologists. One hundred and forty-six (54%) patients were men. The median age of patients was 67 (IQR 58–75) years (figure 1B). The median time from referral to the consultation was 36 (17–70) days.

Oncological characteristics

Oncological diagnoses were prostate (n=141, 52.4%), endometrial/ovarian (61, 22.7%) and lower

Figure 2 Original oncological diagnoses and treatment modalities. (A) Pie chart showing the original oncological diagnoses of referred patients (figures on chart denote the number of patients, total $n=269$); other cancers (5, 1.9%) included biliary, bladder, gastric and cancer of unknown primary. (B) Bar chart showing the percentage of patients receiving each modality of treatment for their primary cancer diagnosis (figures above columns denote the number of patients, $n=269$) and (C) a table showing the number of patients undergoing combination therapy ($n=265$, with 4 patients in whom previous treatment was not documented).

gynaecological tract cancers (58, 21.6%) (figure 2A). The most common treatment was radiotherapy ($n=247$ (91.8%)) such that 22 patients did not receive radiotherapy (figure 2B,C). Patients presented with a median of 2.1 symptoms (IQR 1–3, range 0–7), reporting 18 symptoms collectively (figure 3). These included rectal bleeding ($n=137$, 50.9%), diarrhoea ($n=85$, 31.6%), pain ($n=50$, 18.6%) and faecal urgency ($n=50$, 18.6%). Patients who had received radiotherapy presented with a higher median number of symptoms than those who had not (2 (IQR 1–3),

$n=247$ vs 1 (IQR 0–1), $n=22$; $p=0.01$). Patients who had received radiotherapy reported higher rates of diarrhoea (83/247 (33.6%) vs 2/22 (9.1), $p=0.02$) and rectal bleeding (135/247 (54.7%) vs 2/22 (9.1 %), $p<0.01$).

The median time from radiotherapy to symptom onset was 8 months (IQR 0–24, $n=216$). The median time from symptom onset to referral was 40 months (17–106, $n=216$). This was shorter among those presenting with bleeding versus without (35 months (IQR 16–89) $n=121$, vs 52 months (18–128) $n=95$, $p=0.03$).

Figure 3 Symptom frequency. Bar chart showing the frequency of reporting of a range of symptoms at presentation (figures above columns denote number of patients, $n=269$); 'other symptoms' included high stoma output, dysphagia, abnormal imaging findings and symptoms of small bowel obstruction.

GI investigations and diagnoses

Investigations were requested based on the clinical suspicion of specific diagnoses, for example, a constellation of abdominal bloating, diarrhoea and post-prandial symptoms might lead to a suspicion of SIBO, whereas nocturnal symptoms might raise a suspicion of BAM; and rectal bleeding almost always led to lower GI endoscopy to exclude polyps/malignancy/proctopathy.

Patients underwent a median of three investigations (IQR 1–6). These included colonoscopy ($n=169$, 62.8%), blood tests ($n=93$, 34.6%), glucose hydrogen breath tests (BTs) ($n=81$, 30.1%) and flexible sigmoidoscopy ($n=63$, 23.4%) (figure 4).

Endoscopic diagnoses (figure 4B) were made in 192 patients (71.4%), including proctopathy ($n=106$, 39.4%), polyps ($n=44$, 16.4%) and diverticulae ($n=41$, 15.2%). The most common non-endoscopic

Figure 4 Investigations undertaken and diagnoses made. Bar charts showing (A) the frequency and spectrum of investigations undertaken. Other investigations included: barium follow-through, BTs for lactase deficiency, abdominal CT, CT colonography, gastric emptying studies, MRI abdomen, abdominal ultrasound and videocapsule enterography. (B) The frequency and spectrum of endoscopic diagnoses made. (C) The frequency and spectrum of non-endoscopic diagnoses made. (In all charts the figures above the column denote the number of patients, n=269). BAM, bile acid malabsorption; BSS, bile salt sequestrant; BT, breath test; EAU, endoanal ultrasound; SIBO, small intestinal bacterial overgrowth; TTG, tissue transglutaminase.

diagnoses (figure 4C) included abnormal blood tests (n=46, 17.1%), abnormal GI physiology tests (n=31, 11.5%) and small intestinal bacterial overgrowth (SIBO) (n=22, 8.2%). Bile acid malabsorption (BAM) and SIBO were diagnosed by 75-selenium homocholic acid taurine (SeHCAT) scan and BT, respectively, and

by trials of therapy with bile salt sequestrants (BSS) and antibiotics, respectively.

SIBO was more frequently diagnosed in patients with cervical/vaginal/vulval cancers (19%) versus ovarian/endometrial (3.3%), prostate (6.4%) or colorectal cancer (0%, p=0.03). BAM was also more frequently diagnosed in patients with cervical/vaginal/vulval cancer (17.2% vs 4.9%, 5.7% and 0%, respectively, p=0.05) as was radiation colopathy (8.6% vs 0% in all other groups, p<0.01), radiation proctopathy (45.9% vs 27.9%, 39.7% and 0%, respectively, p=0.02) and B₁₂ deficiency (12.1% vs 3.3%, 0% and 0%, respectively, p<0.01).

Therapeutic management

Small intestinal bacterial overgrowth

SIBO was diagnosed in 13 patients by BT. Eleven patients were prescribed antibiotics, with a response in 6 (55%), no response in 3 (27%) and unknown response in 2 patients (18%). Of 64 patients with a negative BT, 10 received empirical antibiotics with 3 (30%) having a positive response and 7 (70%) no response. Of 11 patients who received empirical antibiotics (without undergoing BT), 6 patients (55%) responded, 3 (27%) did not respond and 2 (18%) had an unknown response. Overall, 32 patients were prescribed antibiotics for proven/suspected SIBO, with a response in 15 (47%) in whom only 6 had a positive BT, 3 had a negative BT and 6 were untested. Among 15 patients responding to antibiotics, the most commonly prescribed antibiotics were doxycycline (n=11), metronidazole (n=6), rifaximin (n=1) and co-amoxiclav (n=1). Three patients were documented to have received multiple courses/combinations of antibiotics.

Bile acid malabsorption

Of 14 patients diagnosed with BAM on the SeHCAT scan, 9 received BSS (with cholestyramine/colesevelam most often prescribed as first/second line, respectively). Six (67%) responded, two (22%) were non-responders and one had an unknown response. Of eight patients with negative SeHCAT scans but clinical suspicion of BAM, four received BSS, with two (50%) responders and two (50%) non-responders. BSS were prescribed empirically in 27 patients, with 6 (22%) responders, 15 (56%) non-responders and unknown response in 6 (22%). Overall, 40 patients were prescribed BSS with a positive effect in 14 patients (35%) among whom 6 had a positive SeHCAT scan, 2 had a negative scan and 6 were not tested.

Pancreatic exocrine insufficiency

Among 12 patients with pancreatic exocrine insufficiency (PEI) (faecal elastase <200 µg/g), 4 were prescribed enzyme replacement therapy and 3 were documented as responders. No patients were treated empirically.

Radiation proctopathy

Among 105 patients with proctopathy, 38 (36.2%) received treatment by argon plasma coagulation (APC). A 'clinician-judged' response was documented in 34 (89.5%) patients, 4 (10.5%) had no response and 1 unknown response. Among responders, nine patients had two treatments and one patient had four treatments. No complications were observed. Three patients were referred for hyperbaric oxygen therapy (HBOT), with one responder, one non-responder and one unknown response.

Abnormal lower GI physiology

Patients with abnormal GI physiology were referred for biofeedback ($n=19$) and percutaneous tibial nerve stimulation (PTNS, $n=6$). Among those undergoing biofeedback, 13 patients (68%) responded, 5 (26%) reported no response and 1 had an unknown response. Among those undergoing PTNS, five (83.3%) responded and one (16.7%) had no response.

Other therapeutics

Overall 131 patients (48.7%) received at least one other therapy, 40 patients (14.9%) received two therapies, 8 (3.0%) received three therapies and 5 (1.9%) received four therapies. This included 94 patients (35%) receiving dietary advice (63 (23%) by dietetic review, 16 (6%) receiving low FODMAP dietary advice and 15 (6%) receiving other dietary advice), 57 (22%) receiving probiotics, 54 (20%) receiving laxatives (most commonly: movicol ($n=20$) and fybogel ($n=20$)) and 33 (12%) patients receiving antimotility drugs.

Follow-up

At the time of analysis 164 patients were discharged, 21 lost to follow-up and 84 still in follow-up. Among discharged patients, the median time to discharge was 7 months (IQR 3–16.5), after a median of two appointments (1–3.5). Among patients still in follow-up, the median follow-up time was 22 months (IQR 16–44.75) after a median of four appointment.^{2–6} Among patients lost to follow-up, one was later rereferred with a new problem and two rereferred for the same problem. Among discharged patients, nine patients required rereferral and six for a new problem.

Considering oncological diagnoses, those with cervical/vaginal/vulval cancers were followed-up for a longer median time (40 months (95% CI: 15.8–64.2), $n=58$) than those with prostate (14 months (7.3–16.7), $n=141$), ovarian/endometrial (12 months (7.8–16.2), $n=61$) or colorectal cancers (1 month (0–3.9), $n=4$, (overall comparison $p<0.01$)).

Considering GI diagnoses, discharged patients with SIBO had more outpatient appointments (6, IQR 2–13, $n=15$) than patients without SIBO (2, IQR 1–3, $n=170$, $n=0.15$). The median time to discharge was longer (27 months, (95% CI: 4.3–49.7) vs 7 months,

(5.1–8.9), $p<0.01$). Including all patients, this difference persisted (6 appointments (IQR 2.8–13, $n=22$) vs 3 appointments (1–4, $n=247$), $p<0.01$), with longer median follow-up (33 months (95% CI: 15.7–50.3), $n=22$ vs 12 months (8.1–15.9), $n=247$) although this did not reach significance ($p=0.07$).

DISCUSSION

PRD represents an urgent, unmet need given its clinical relevance^{8–13} and increasing frequency,^{9 10 28} yet remains under-recognised and under-resourced. The Royal Marsden has published extensively in this area^{17 19–22 29}; however, most UK hospitals managing PRD do so within busy general gastroenterology services, without dedicated resources. Indeed, both oncologists⁸ and gastroenterologists³⁰ believe that services nationally are suboptimal. The PRD service at UCLH, although sizeable, is representative of many of these centres. We, therefore, believe this represents important 'real-world' data as regards clinical descriptors and outcomes.

We speculate variation in referral practice locally, given that no referrals were received from nearly half of oncologists treating pelvic cancers at UCLH. Some patients were potentially referred to other clinics including surgery, which was not captured, and most likely accounts for our low rates of patients treated for colorectal cancers. These observations align with the anecdotal experience of inconsistent referral patterns at other centres. Potential reasons include a lack of formal referral pathways and awareness among referrers of the potential for chronic GI toxicity.

Our results confirmed the range of, often non-specific, symptoms reported by patients with PRD whose primary cancers have often been treated by multiple modalities. Without specialised training and in the context of pressured GI clinics, these symptoms may be attributed to irritable bowel syndrome when initial investigations (eg, blood tests) are normal. Rectal bleeding was the most common symptom reported perhaps because 'hard symptoms' are more often asked about and reported (in the absence of symptom questionnaires being used). We have since introduced a 'PRD help sheet' for referrers, listing questions proposed by the Macmillan charity to improve detection of more vague symptoms, and suggesting investigations to be undertaken alongside referral. There was a median of 40 months between symptom onset and GI referral. We did not address whether this was due to delayed patient reporting or onward referral by general practitioners/oncology teams; this remains an important question.

We diagnosed relatively low proportions of SIBO. Anecdotally local practice has evolved such that BTs are requested less frequently owing to concerns over the low sensitivity of glucose hydrogen BT (the only test available in our Trust), and clinicians are more inclined to treat empirically. Interestingly, a 55%

response (similar to that in published studies^{31 32}) was observed among both patients after positive BTs and when treated empirically. Rifaximin, widely used to treat SIBO internationally but unlicensed for this indication in the UK, is unavailable at our Trust meaning that conventional antibiotics were generally used. The lower response rates observed among patients with negative BTs suggests that clinical decision making regarding empirical therapy was appropriate, acknowledging the low numbers treated. We did not distinguish between SIBO subtypes, nor response to specific antibiotics.

Overall slightly more patients were assessed for BAM by empirical prescription of BSS than by undertaking SeHCAT scan. This most likely reflects the low cost, easy accessibility and tolerance of treatment. Anecdotally formal testing by the SeHCAT scan was reserved for complex cases where BSS might not be tolerated. We report a relatively low response rate (67%) to BSS after positive SeHCAT scans. This may reflect that although secondary syndromes such as BAM and SIBO can occur in patients with PRD, multiple mechanisms may contribute to symptoms. We report a 50% response in patients with negative SeHCAT scans, partly attributable to 'borderline' retention rates of 15%–20%, which in some will be relevant. It was difficult to determine dosages and duration of treatment or the use of strategies such as low-fat diets.

PEI was uncommon in our cohort (4.5%). Elastase tests were requested in a small proportion of patients (17.8%), but high (75%) response rates were observed. It is unclear whether elastase results between 200 µg/g and 500 µg/g were treated nor whether 'false-positive' results were untreated.

Radiation proctopathy was the most frequent diagnosis. APC has been the favoured first-line treatment locally, as in other UK centres. Reasons include universal access and familiarity. However, reported complication rates as high as 63%³³ mean alternatives such as sucralate enemas and formalin application have been adopted. Therefore, although we observed no major complications, APC is no longer used as the first-line therapy for proctopathy. All three referrals for HBOT were made prior to publication of the HOT2 trial.³⁴

GI physiology tests may be underused (15.6% of patients), despite high response rates to biofeedback and PTNS. Nuanced questioning regarding bowel habits may improve the identification of suitable patients for therapeutics. Dietetic services were also underused. The potential role of dietetics in managing PRD is recognised³⁵ and providing specialist dietetic support concurrently in clinics may improve care.

Presenting symptoms poorly predict secondary syndromes in patients with PRD.²⁹ Our approach is to request multiple investigations upfront, rather than sequentially. Results are reviewed and treatment started on the second appointment. Where necessary

third appointments provide treatment review and management plans for durable symptom relief. Patients are usually subsequently discharged communicating advice for self-management to patients and referrers. Although data from other centres suggest that a minority of patients may represent some years later,²³ at least in the period of this study, our strategy seems to maintain low rereferral rates.

This study carries limitations. Incomplete data points and the consequent risk of bias are inherent in retrospective studies. Temporal variation was not captured, which is important given evolving clinical decision making. Finally, a single-centre report cannot recognise the variation between Trusts.

In conclusion, descriptive studies of patients with PRD from UK centres are needed, as well as an understanding of variations in service provision and consistent deviations from published guidelines. This will aid service planning nationally and locally, and inform future strategies for education, training and awareness of PRD.

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