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REVIEW

GI Consequences of Cancer Treatment: A Clinical Perspective

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In an era when extensive research is being funded to mitigate the radiation risks of a human traveling to Mars or the potential effects of a nuclear detonation in an urban environment, it is difficult to understand why the medical and research community remains largely uninterested in pelvic radiation disease (PRD), a condition that afflicts half a million patients every year after radiotherapy for pelvic cancer. There has been significant progress in understanding the nature of normal tissue injury, especially as it affects the GI tract. Clear clinical data exist on how best to assess and improve symptoms and there are a number of options for how to modulate the underlying progressive pathophysiology of PRD. Annually, there are more patients who develop PRD than inflammatory bowel disease (IBD). Despite the similarity in PRD and IBD symptoms, the same expertise that promotes assessment, treatment and disease-modifying approaches as standard of care in IBD is almost nonexistent for those suffering from PRD, and as a result the unmet need is enormous. Curing or controlling cancer without addressing quality of life is no longer acceptable when half of all patients diagnosed with cancer live for 10 years after treatment. For those patients afflicted with PRD it can cause significant misery, and this situation is unacceptable; investment in training and research cannot be delayed any longer. **© 2016 by Radiation Research Society**

"You are bringing your hospital into disrepute by speaking about toxicity".
Professor of Clinical Oncology to the author (2015).

THE EPIDEMIOLOGY OF TREATMENT-RELATED TOXICITY

In 2012, over 14 million people were diagnosed with a new cancer worldwide. There have been enormous advances made in treating cancer in the last four decades. As a result, patients currently have a much higher chance of being cured or living for long periods with control of their disease than those diagnosed in the past. For example, only 25% of people diagnosed with cancer in 1971 survived 10 years. The most recent figures available, from 2010, suggest that 50% of all patients diagnosed with cancer can expect to live for 10 years. Clearly, much still remains to be done to develop curative treatments and indeed, dramatic improvements in outcomes in some types of cancer such as brain, lung, esophagus and pancreas remain disappointingly elusive. However, as more people survive for longer periods, quality-of-life issues are becoming increasingly important.

It is inevitable that radical therapies, which aim to cure or control cancer, cause collateral damage in noncancerous tissues. One of the most important organs at risk is the gastrointestinal (GI) tract. Acute GI toxicity often forces reduction in the intensity of anti-cancer treatments, which can potentially compromise the chance of cure and can sometimes be life threatening. Where that toxicity significantly interferes with the delivery of anti-cancer treatment, e.g., bone marrow failure, cancer-induced pain or chemotherapy-induced vomiting, focused research has produced effective therapeutic options. However, for toxicities perceived to be less detrimental to the delivery of cancer treatments (e.g., diarrhea, bloating, flatulence, incontinence, bleeding, food restriction), which nevertheless can have a devastating impact on patients, their families and healthcare resources, little effort has gone into defining how these occur and how they can be prevented or optimally treated. Indeed, while quality of life is sometimes discussed in modern oncology, it has become no one's role to manage quality of life, despite the frequency of symptoms impacting quality of life and the struggles that patients encounter to find expert help (*1*).

The largest single group of cancer patients who are at risk of severe long-term GI toxicity are those treated with radiotherapy for a rectal, gynecological or urological tumor in the pelvis.

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TABLE 1
Summary of Long-Term Effects after Treatment for Rectal Cancer[a]

Symptoms	Surgery alone	Preoperative radiotherapy	Postoperative radiotherapy
Any incontinence	5–38%	51–72%	49–60%
Toilet dependency	6%	30%	53%
Excellent function	32%	14%	Not available

[a] Data shown here were reported by Birgisson *et al*. (*2*).

For those diagnosed with rectal cancer, one-year survival has increased from 50% in the early 1970s to >80% today as a result of large randomized trials, which have demonstrated how pretreatment staging, improved surgical techniques and neoadjuvant and adjuvant chemoradiotherapy should be combined to transform outcomes. However, in these trials it has been carefully documented that after receiving these improved treatments, half of all survivors are affected by chronic fecal incontinence, toilet dependency and anterior resection syndrome (Table 1) (*2*). In contrast to the effort expended in defining how best to treat cancer optimally, barely a single study has been reported that addresses the management of severe side effects of successful cancer therapy.

The available data for patients treated with chemoradiation for gynecological cancer are similar, significantly improved survival but no reduction in long-term, serious toxicity (*3, 4*). Many clinicians deny that significant toxicity is frequent and point to trials suggesting that most patients suffer ''only'' grade 1–2 toxicity (*5*). However, for many years, there has been steady criticism of how toxicity is recorded. Most toxicity scores require the clinician to judge the severity of their patients' symptoms. However, patient-focused studies, which use patient-reported outcome measures, increasingly suggest that most cancer treatment-related toxicity scoring systems are not fit for this purpose; not only do they ignore toxicities that are critically important for their impact on quality of life (*6*) to patients (e.g., fecal incontinence), but they give great weight to toxicities that clinicians consider important (e.g., degree of rectal bleeding, which unless it is severe, often does not have great impact on daily life). Indeed, in patient-focused symptom reporting, it is clear that after pelvic radiotherapy, 90% of patients report a permanent change in bowel habit, in 50% of all patients this bowel dysfunction affects quality of life and, depending on the primary tumor site treated and the type of treatment, up to 20–40% of patients rate this change in quality of life as moderate or severe (*7*). Approximately one million people are treated worldwide with pelvic radiotherapy annually, so the number of affected people exceeds the number of patients diagnosed with the inflammatory bowel diseases (IBD) Crohn's disease and ulcerative colitis. Every hospital in the Western world has a gastroenterologist who specializes in treating IBD and there are sophisticated research programs and enormous pharmaceutical endeavors predicated to improving outcomes for this patient group. Patients with IBD deserve this attention, but why is it that patients with GI radiation-induced toxicity who have the same symptoms as those with IBD do not receive the same attention?

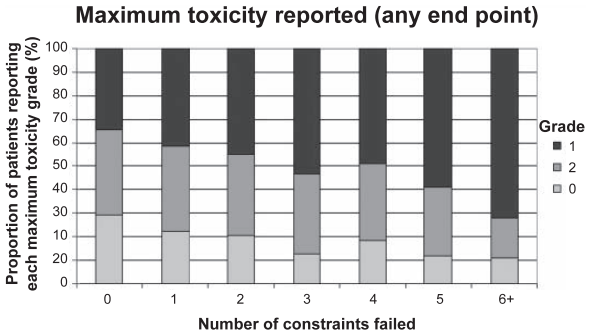


FIG. 1. Data reported by Gulliford *et al*. (*8*) showing the frequency of grade 0–2 toxicity during prostate irradiation depending on the number of constraints breached.

Some clinicians assert that modern treatment techniques will abolish toxicity, however, data from a study in urological patients suggests that this is incorrect. Gulliford *et al*. have shown in a large cohort of prostate cancer patients treated with conformal radiotherapy, that if six or more constraints were breached, then two-thirds of patients developed grade 2 toxicity. If no constraints were breached, one-third still developed grade 2 toxicity (Fig. 1). In other words, toxicity cannot be abolished by the perfect delivery of radiotherapy (*8*). This also suggests that toxicity is not entirely due to radiotherapy. Radiotherapy may initiate a response in normal tissues, but patient-related factors (*9*) and the consequential effect (*10*) also act to drive the process. It is argued that toxicity is so reduced once intensity modulated radiotherapy (IMRT) becomes the treatment standard that the findings of Gulliford *et al*. from a previous era become irrelevant, however, it is clear that IMRT does not abolish toxicity completely and secondly, the long-term effects of IMRT are as yet not clearly defined.

PELVIC RADIATION DISEASE: A CONSEQUENCE OF THE SURVIVORSHIP ERA

So why has there been this widespread refusal to address the burden from toxicity that radiotherapy causes? One key reason is that chronic radiation-induced toxicity has only recently been acknowledged as a disease. Most clinicians have felt that the myriad symptoms that patients report after radiotherapy are difficult to understand and to treat and if they are not related to tumor relapse and do not respond to simple interventions, these symptoms are not their business and can be legitimately ignored.

However, these consequences of radiotherapy are now recognized as pelvic radiation disease (PRD) (*11, 12*). As with all diseases, PRD can be transient or chronic, can be understood anatomically (it affects noncancerous tissues exposed to radiotherapy given for a pelvic tumor), has

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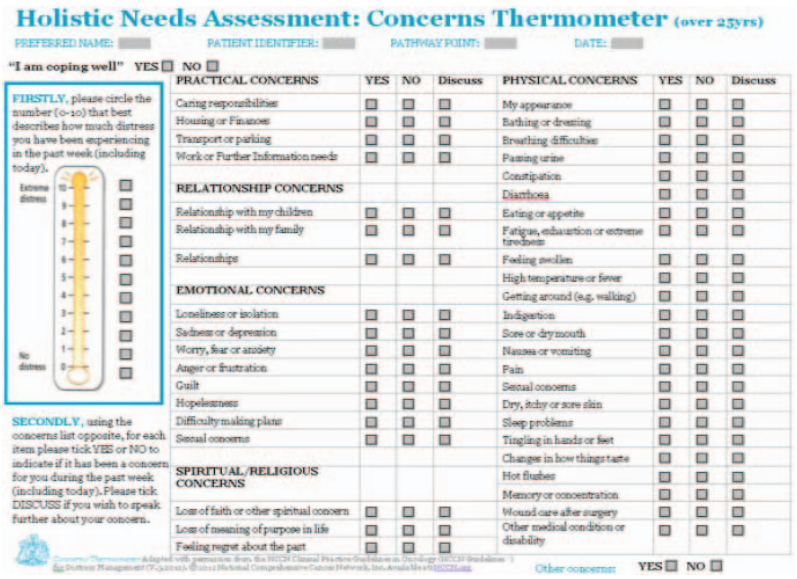


FIG. 2. The holistic needs assessment questionnaire used in our clinic.

defined symptoms (*13*) (which can vary from mild to very severe), has a typical pathophysiology (*14, 15*) and can be easily identified using responses to simple questions (*16*). Therefore, it is incumbent upon clinicians to properly diagnose PRD and offer patients the best possible treatment. Optimal management of a common disease also requires the development of appropriate national services and identification of research priorities.

With the recognition of PRD as a disease based on the above criteria, four principles for managing PRD have quickly emerged.

Principle 1: A Holistic, Multidisciplinary, Systematic Approach is Needed

Radiation treatment for a pelvic tumor does not confine its potential toxicities to a single organ system. In our clinic where GI consequences of cancer treatment are addressed, our standard medical assessment is augmented by a modified Gastrointestinal Symptom Rating Scale that patients complete at each clinic visit, along with a Bristol Stool Chart (*17*) to indicate what types of stool they are experiencing. This helps us focus the consultation on all of the patient's GI issues. However, in addition, we offer all our new patients a holistic needs assessment questionnaire (Fig. 2). In our experience, there is an enormous appreciation of this approach by patients. In addition to their GI problems, 80% of these patients report moderate or severe bother from fatigue, 45% from urinary problems, 36% from nutritional issues, 35% from sexual issues, 11% from emotional concerns and 2% from dermatological issues. So while our focus is with GI and nutritional issues, these other areas cannot be ignored and require thoughtful management strategies.

Principle 2: Symptoms do not Reliably Predict Their Cause

Conventional oncological toxicity scoring tools, the Radiation Therapy Oncology Group (RTOG) score, Late Effects Normal Tissue-Subjective, Objective, Management (LENT-SOM) scales and Common Terminology Criteria for Adverse Events (CTCAE) are not only insensitive measures of the patient experience and frequently significantly underestimate the amount of toxicity suffered, but also cannot explain clinical outcomes (*18, 21*). In addition, we have shown that ''typical'' symptoms widely thought to be representative of specific toxicity, such as radiation proctopathy, are surprisingly unreliable. For example, 1 in 3 new GI symptoms arising after pelvic tumor irradiation, which are not due to the radiotherapy at all (*20, 22, 23*). Indeed, it is not widely appreciated that in PRD, as in other GI diseases, pathological change in the GI tract correlates poorly with symptoms (*24, 27*).

The principle of Occam's razor, which guides so much of medical practice, is profoundly unhelpful for determining the cause of GI symptoms arising during or after pelvic irradiation. In this setting, Hickam's dictum is much more appropriate. For example, at least 13 different causes for diarrhea have been defined and the majority of patients in our clinic with diarrhea have more than one cause. In addition, it is clinically impossible to differentiate among causes that are simple to treat, such as bile acid malabsorption (18% of patients in our clinic), from complex consequences of treatment, such as a radiotherapy-induced enteric stricture (up to 10% of patients). Table 2 gives an example of two consecutive patients seen in our specialist clinic and referred for treatment of ''typical radiation-induced toxicity'', which exemplifies how symptoms can mislead clinicians.

This failure by most clinicians to appreciate the lack of sensitivity of any given GI symptom to predict the

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TABLE 2
Two Consecutive Patients Seen in Our Specialist Clinic

Patient 1	Patient 2
76 years old:	64 years old:
Normal bowel function before radiation therapy	Normal bowel function before radiation therapy
Prostate cancer, 1 year after conformal radiation therapy	Prostate cancer, 1 year after IMRT
Normal PSA	Normal PSA
Symptoms reported:	Symptoms reported:
Bowels open 4× per day	Bowels open 3–6× per day
Urgency	Urgency
Often loose stool	Often loose stool
Fecal incontinence weekly	2× Fecal incontinence/month
Tenesmus	Tenesmus
Perianal soreness	Perianal soreness
Diagnoses made after investigation:	Diagnoses made after investigation:
No radiation-induced toxicity	No radiation-induced toxicity
Symptoms due to excess dietary fiber	Giardia infection
	Sigmoid 2 cm polyp

Note. Patients were referred with a letter stating they had typical radiation symptomatology, exemplifying how symptoms are not a reliable measure of radiation-induced toxicity.

underlying cause is extremely important. Not only does it have implications for the patient's experience as they progress through and after cancer treatments, it also indicates that there has been a systematic failure over the last few decades to assess the toxicity of new anti-cancer treatments accurately. Measuring the frequency of new-onset symptoms with any new treatment is not adequate, since it does not measure the seriousness of the problem or give good guidance on how best to mitigate that problem.

Principle 3: The Physiological Model of GI Symptomatology

Cancer treatments may initiate pathological changes in the GI tract, but crucially pathological change *per se* does not usually cause symptoms. Symptoms only arise if pathological change induces change in normal physiological functioning. It is the change in physiology that induces symptoms (Fig. 3) (*28*). The types of physiological change are described in Table 3. Understanding that changes in GI physiology, not the underlying pathology, are the direct cause for GI symptoms is an important conceptual advance to help manage patients with difficult symptoms in complex diseases. This approach allows the clinician to help people who otherwise are believed to be untreatable.

We have previously defined 22 separate symptoms that patients develop after pelvic radiotherapy (*13*). In further cohort studies (*23, 29, 30*) and a randomized controlled trial (*31*), we showed that by asking patients to systematically define their symptoms, investigating them for each symptom using an algorithm and then treating all the identified abnormalities, patients improve. Our results have been corroborated by others (*32*) and suggest that specialist nurses can be trained to manage this patient group using our structured algorithmic approach. This is important since current gastroenterology services are unable to cope with the number of affected patients. Further published studies confirm the validity of this approach not only in patients treated with pelvic radiotherapy, but also after GI surgery and during chemotherapy and in patients receiving biological therapies (*16, 33, 34*). An example of the consequences of this approach for a typical patient seen in our multidisciplinary clinic is given in Table 4.

Principle 4: Modifying the Radiation-Induced Ischemia/Fibrosis Pathophysiology by Manipulating the Consequential Effect

In IBD, there are four main priorities, early diagnosis, optimal assessment, best available symptom management and modification of the inflammatory process, to bring the disease under control. The management of PRD should follow the same model.

Early diagnosis of PRD is easily achieved; it occurs only after therapeutic irradiation. Patients can be educated in advance about the symptoms that may indicate the development of PRD, and those at higher risk of PRD (Table 5) can be more closely monitored at their follow-up appointments. In comparison, IBD occurs sporadically and those afflicted may

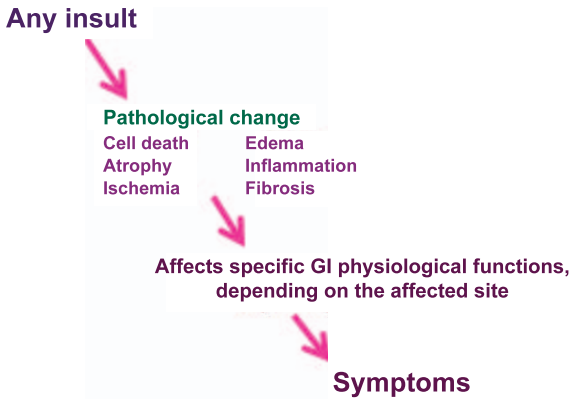


FIG. 3. The physiological model of GI symptomatology.

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TABLE 3
Frequency of Reported Physiological Changes after Radiotherapy

	Acute toxicity during radiotherapy	Chronic toxicity
Lactose intolerance	50%	5–7%
Malabsorption of other disaccharides	?	?
Bile acid malabsorption	50%	1–73%
Small bowel bacterial overgrowth	25%	8–45%
Rapid transit	100%	?
Viral infection	?	?
C. difficile infection	?	?
Side effects of non-chemotherapy medication	10%	5%
Pancreatic insufficiency	?	2%
Primary inflammatory bowel disease	?	4–5%

have no prior knowledge of the condition. Optimal assessment and best symptom management of the GI and urinary symptoms of PRD are defined by algorithms, which have been endorsed in the UK by the appropriate professional entities (*13, 35*). The final priority of modifying the underlying pathobiology and thus the progression of PRD is feasible.

There is an acute phase during radiotherapy characterized by an inflammatory response and a chronic phase defined by cytokine activation leading to progressive ischemia and fibrosis. While the target cell hypothesis of radiation-induced injury has previously suggested that modification of this process was futile, it has become more clearly understood as

TABLE 4
An Example of How Complex Symptoms can be Investigated and Managed to Give Significant Benefit by Following Published Algorithms (*13*)

68-Year-old woman
Past history:
Cervical cancer, radiotherapy, 1986
Renal impairment secondary to the radiotherapy requiring bilateral ureteric stents, 1990
Left nephrectomy and re-implantation of right ureter, 2008.
She was referred for evaluation in 2014 and reported the following symptoms and history:
Bowels open 5–10/day since completion of her radiotherapy;
Marked urgency of defecation with episodes of fecal incontinence several times a week for the last 25 years;
She also reported tenesmus, severe offensive flatulence with loud borborygmi;
Her stool was generally loose (type 6 or 7 on the Bristol stool chart) and several times a week, frankly steatorrheic;
Recently, she had become frightened to eat and as a result had lost 25% of her body weight;
She had seen 2 previous gastroenterologists and over the years had had many blood tests, stool sent for culture, 3 colonoscopies, a CT virtual colonoscopy and had been prescribed many antidiarrheals, empircal antibiotics (rifaximin) and a brief trial of colestyramine 4 g od. In addition, she had changed her diet to try to improve her symptoms on many occasions. None of these interventions produced any benefit. A frequently expressed sentiment by her doctors was ''nothing can be done... you will have to live with it... but at least you do not have any cancer.''
She was referred and systematically assessed in our unit in 2013 and completed a holistic needs assessment.
The following diagnoses were made:
Depression requiring psychological support and an antidepressant (citalopram);
Vaginal bleeding requiring gynecological referral and treated after assessment with topical hormone therapy;
Profound deficiency of magnesium, calcium, vitamin B12 and D deficiencies requiring replacement;
Pancreatic exocrine insufficiency requiring full dose pancreatic enzyme supplementation;
Severe bile malabsorption, diagnosed following a 23-selenium homocholic acid taurine scan (7 day retention 0%) requiring treatment with colesevelam (off license) in full dose together with education to follow a low-fat diet (20% fat comprising only 20% of total calorie intake);
Small bowel bacterial overgrowth, on the basis of a positive hydrogen component of a glucose hydrogen methane breath test and a jejunal aspirate, which grew coliforms resistant to rifaximin but sensitive to ciprofloxacin;
Severe biliary gastritis requiring treatment with mucaine.
Outcome:
Once all her therapies were instituted, there was a rapid improvement in her health, her bowel function normalized and she regained her normal weight.
When reviewed 6 months later, she described herself as ''thriving'' and had never felt so well.

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TABLE 5
Risk Factors for the Development of Radiation-Induced GI Toxicity[a]

Diabetes mellitus	IBD	Collagen vascular disease	HIV disease	Low BMI	Obese patients	Smokers	Hypertension
2×	0–46%	Unknown	HR of 1.4 (95% CI 0.7–2.8)	×2–4	Unknown	HR of 2.2 for rectal toxicity HR of 4 for SI toxicity	7 clinical studies (n = 5,549) Protective in 4 studies (n = 3,340)

Note. IBD = inflammatory bowel disease; BMI = body mass index; CI = confidence interval; HR = hazard ratio; SI = small intestinal.
[a] Data shown here were reported by Fuccio *et al*. (*9*).

a dynamic process, which raises the potential for therapeutic manipulation (*14, 15*). A number of approaches have preliminary clinical data and a significant scientific basis making them worthy of further investigation.

Statins are a class of drugs that have been postulated to mitigate radiation-induced toxicity by reducing 3-hydroxy-methylglutaryl coenzyme-A reductase activation of the Rho/ROCK profibrotic and proinflammatory signaling pathway (*36*). In a published retrospective study, it was suggested that statins were beneficial in humans and that there may be added benefit when another class of drugs, angiotensin I-converting enzyme (ACE) inhibitors, are combined with statins (*37*).

It has also been postulated that hyperbaric oxygen therapy improves radiation injury, and while this was demonstrated in one published randomized trial (*38*), those results were not corroborated in the recently completed UK HOT2 trial (*39*).

An intriguing retrospective pilot study was performed using an electronic nose to assess gases emitted from stool samples provided by patients before undergoing radiotherapy. Those patients who developed severe acute toxicity could be differentiated with 100% accuracy from those who had minimal acute toxicity (*40*). It is likely that differences in the gases analyzed from these samples is due to specific changes in the microbiota composition which in turn, somehow predisposes to toxicity. Studies are ongoing to investigate this further, as other evidence also suggests that the composition or functionality of the microbiota is important to the development of radiation-induced toxicity, and manipulation of the microbiota may have a role in attenuating toxicity (*41*). Perhaps probiotics or even fecal transplantation could have an important role here, but as yet there are no studies showing clear benefit (*42*).

Animal data are compelling as to the etiological role of pancreatic and biliary secretions in promoting radiation-induced toxicity. Somatostatin antagonists may influence this process and a new generation of these agents are starting to be investigated.

A number of studies have been performed to investigate the role of pentoxifylline with or without vitamin E in ameliorating radiation-induced toxicity and have demonstrated possible benefit. Recent data suggest that while pentoxifylline and vitamin E are effective, pentoxifylline combined with tocotrienols may be significantly better (*43*). This hypothesis is currently being tested in the ongoing PPALM study.

CONCLUSIONS

Patients need a greater awareness of the side effects of cancer therapies. Symptoms are important and they determine who needs assessment and treatment. In addition, however, symptoms are more common than generally appreciated, their severity is often worse than scoring tools suggest and ''typical symptoms'' arising during or after cancer treatments are poor indicators of the underlying cause (*22*). It is also clear that the same symptom can be mediated by many different physiological changes and many patients have more than one cause for their symptoms. Most importantly, it is now known that symptoms can be improved using systematic algorithms, and therefore it is now mandatory to identify symptomatic patients and refer them to someone trained to manage them. Emerging data suggest that the costs associated with sorting out these symptoms is a small fraction of the costs associated with treating the cancer in the first place (*44*).

While radiotherapy techniques have been greatly improved in the last few years, manipulating the radiation dose alone will not abolish toxicity, since toxicity is not entirely due to the dose delivered. The consequential effect also contributes to that toxicity and is open to intervention.

The building blocks for rapid progress are in place, but as clinicians, we need to commit to developing new models of care for our patients. Some of the urgent research priorities are shown in Table 6. It is a tragedy for millions of patients

TABLE 6
Important Questions that Address Future Research Priorities for Pelvic Radiation Disease

How are patients with chronic GI effects of cancer therapies best detected?
What are the best objective tools to measure the severity of chronic gastrointestinal problems?
What are the best objective biomarkers of damage to noncancerous tissues?
What are the drivers of the consequential effect?
What nonradiation-dose-related measures reduce the acute toxicity of the GI tract
How are chronic side effects best prevented?
What treatments work for late side effects?

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that so far, evidence of that clinical commitment is almost entirely absent.

GLOSSARY OF TERMINOLOGY

- Acute toxicity: Toxicity that occurs during treatment or in the 3 months after completion of radiotherapy.
- Adjuvant: Additional treatment given after completion of definitive treatment as an attempt to reduce the risk of relapse.
- Anterior resection syndrome: Syndrome that occurs after surgery for rectal cancer characterized by a constellation of symptoms including fecal incontinence, urgent, frequent and unpredictable bowel patterns, a constant desire to defecate, the inability to discriminate between stool and flatus and difficulty evacuating the rectum.
- Chronic toxicity: Toxicity that persists more than 3 months after completion of radiotherapy or that arises as a new symptom related to the treatment at any point after that.
- Fecal transplantation: A procedure whereby fecal matter is collected from a donor and given to a patient to optimize the amount of good bacteria they have in their bowel.
- Hyperbaric oxygen: Oxygen therapy delivered for medical reasons at more than therapy atmospheric pressure in a high pressure chamber.
- Ischemia: Inadequate blood supply to tissues.
- Microbiota: Germs that colonize in specific areas of the body (pertaining to this article, the GI tract).
- Neoadjuvant: Treatment administered to shrink a tumor before definitive therapy is given with the goal of curing the cancer.
- Probiotic: Live ''good'' bacteria promoted for the prevention and treatment of a wide variety of conditions.
- Proctopathy: A disease process affecting the rectum.
- Tenesmus: A clinical symptom, where there is a feeling of constantly needing to pass stools, despite an empty rectum.
- Toilet dependency: A condition of being ''tied to the toilet'' to the point of being unable to work or even leave the house.
- Toxicity grade: A measure of the severity of side effects (grade 0 = none, grade 5 = dead).

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