

# Long-term complications of pelvic radiotherapy

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## Abstract

Complications following pelvic radiation are frequently under-reported and inadequately addressed. This overview examines the nature and the intensity of complications encountered by cancer survivors; it focuses specifically on gastrointestinal and vaginal complications, and the problems surrounding the methods of recording and assessing toxicities.

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## Introduction

Pelvic malignancies are a common occurrence, with cervix carcinoma being one of the most common cancers in women in sub-Saharan Africa. The majority of patients present with locally advanced disease. This precludes surgical treatment and leaves pelvic radiotherapy as the mainstay of curative therapy. Adjuvant radiation is also frequently used following surgery for both cervical and endometrial carcinoma.

The benefits of treatment outweigh toxicity in most cases. However, the late toxicity of treatment can have a significant impact on cancer patient survivors. Not only can quality of life be affected but additionally ability to work and care for family can be compromised, which is of great importance in the developing world where many women are the primary bread-winners and care-givers.

The challenge in the management of late toxicities is, firstly, to recognise the complications, manage them as far as one is able and to support the patient. This overview will discuss the types of toxicities, frequency and recording methods. The details of all toxicity are beyond the scope of this article and the focus will be on gastrointestinal and vaginal toxicity, these being the most common problems.

## Types of late complications

Complications are numerous and varied following pelvic radiotherapy (see Table I). Patients may suffer from a single or a number of complications. The theoretical cause of late radiation damage relates to obliterative endarteritis and resultant ischaemia and fibrosis formation.<sup>1</sup> Neovascularisation leads to the problems of rectal bleeding, haemorrhagic cystitis and vaginal contact bleeding. These processes are occasionally

amenable to specific interventions but, on the whole, toxicities are 'managed', not reversed.

Table I: Types of complications

Site	Symptom/sign
Gastrointestinal	Rectal bleeding Diarrhoea Mucous discharge Faecal incontinence Tenesmus Rectal pain Flatulence Cramps Fistulae Strictures
Urological	Cystitis Haemorrhage Frequency Incontinence Fistulae Urethral strictures
Genital	Perineal oedema Telangiectasia
Hormonal	Vaginal shortening/narrowing Sexual dysfunction Infertility Menopause
Bone	Avascular necrosis Insufficiency fractures
Lymphatic	Lymphoedema

Gastrointestinal complications are the most readily identifiable in the literature and are most frequently studied and reported. However, it appears that vaginal complications, paradoxically,

are the most frequently reported in prospective studies, yet very seldom addressed in retrospective reports in the literature. This may very well be due to reluctance by both patient and doctor to discuss problems of sexual dysfunction.

### Incidence of complications

The true incidence of late effects of radiation in cervix and endometrial carcinoma is surprisingly very poorly reported in the large international radiation studies. However, these studies are probably the best source of data, as the patients are rigorously followed-up and evaluated.

This issue was addressed in the most recent meta-analysis regarding chemoradiation in cervix carcinoma.<sup>2</sup> The paucity of data led the authors to conclude that they were unable to assess whether late toxicity is related to choice of treatment. In addition it was felt that the data was not representative of the real incidence of complications.

Of the pivotal studies published in 1999 evaluating chemoradiation in cervix carcinoma, the late toxicity data were noticeably poor. In the Morris study the late grade 4 toxicities were 8% in the study arm and 10% in the radiotherapy alone arm.<sup>3</sup> The majority of toxicities were large bowel or rectum. Though one cannot draw reliable conclusions from this data, one may reasonably deduce that there is no additional toxicity if chemotherapy is added to pelvic radiation in cervix carcinoma.

A national UK audit comprising 1 075 patients published by Vale et al evaluated patients with cervix carcinoma who received radical radiotherapy, radical chemoradiation or surgery followed by postoperative radiotherapy.<sup>4</sup> The overall grade 3-4 toxicities were 8%, 10% and 5%, respectively. The majority of toxicities related to radiation were vaginal. The major factor related to increased toxicity was that of increased age, though medical comorbidities were not noted.

In the adjuvant radiotherapy setting in endometrial carcinoma, a new landmark study, PORTEC-2, laid out the benefits of reducing pelvic external beam radiation dose by treating with vaginal brachytherapy alone.<sup>5</sup> Overall, the late gastrointestinal toxicity grade 3 was very limited in both the brachytherapy alone and the external beam group. Grade 1 toxicity was significantly more in the external beam arm, but this reduced over time. In the subsequent quality of life study of the patients recruited in the PORTEC study, patients receiving vaginal brachytherapy reported an improved quality of life compared to the external beam group.<sup>6</sup>

The more relevant issue in establishing the incidence of late complications may be investigated via patient-reported symptoms and not doctor-reported toxicities. Many studies show a significant discrepancy between these. A Norwegian study showed doctor-reported grade 3-4 toxicity for bowel and vaginal toxicity to be 15% and 23%, respectively,<sup>7</sup> and patient-reported severe symptoms were 45% and 58%, respectively.

Quality of life studies examining pelvic radiation are frequently published and all appear to show that radiation therapy has an adverse effect on the day-to-day life of cancer survivors.<sup>8,9,10,11</sup> This leads us to the conclusion that, despite the best attempts at clinician-recorded toxicity scores, we are vastly underestimating the impact of toxicity on the lives of our patients.

### Reporting of late toxicities

The above clearly points to a failure in the accurate reporting of late effects. In some studies, this may be due to poor documentation and, in meta-analyses, there is a lack of comparability due to the wide variety of toxicity scores in use. In general, toxicities are graded 0-5, with grade 0 being no symptoms and grade 5 being death. The most commonly used are the RTOG,<sup>8</sup> CTC v2<sup>9</sup> and LENT-SOMA.<sup>10</sup> Of these, the RTOG is the simplest but least detailed, and the LENT-SOMA is the most extensive but entirely unsuited for day-to-day use in the busy clinic setting. Many studies use their own toxicity scores, as investigators have found the above to be inadequate. In addition, in the developing world, patient-based questionnaires are not appropriate, due to language and literacy constraints. In summation, the recording of late toxicity is very unsatisfactory.

There has been a move towards cooperation and cohesion and the production of a common record and one that is simple to use. Dische et al proposed that grading of morbidity can be more simply attributed to the effect of that symptom on the patient's day-to-day life.<sup>11</sup> Criteria taken into account are medication and efficacy, changes in lifestyle, inpatient care, and surgery. However, even this more pragmatic approach is time consuming in a pressurised clinic setting.

This author uses an abridged version of the RTOG late toxicity score including the most common side effects involving the upper gastrointestinal, lower gastrointestinal, bladder, skin and vaginal sites. This quick and easy-to-use scoring system helps to identify and treat those who are suffering from side effects, including those that, as clinicians, we may overlook. It is an aid to record keeping and documentation of the impact of treatment. Until such time as there may be a common toxicity scoring system, it is imperative that clinicians proactively adapt some form of scoring system.

### Management of individual toxicities

#### *Gastrointestinal toxicity*

Rectal bleeding is the most readily reported symptom reported by patients when one examines the literature. In addition, change in bowel habit, a mucous discharge and rectal pain may occur. Where resources allow, patients should be offered the opportunity to be referred to gastroenterology colleagues for a detailed review if they develop any related symptoms. In all patients, a sigmoidoscopy or colonoscopy should be performed and suspicious areas may be biopsied if there is concern that a second pathology may be present, such

as malignancy. The treatment of rectal bleeding has been approached in a varied manner, as seen in Table II.

**Table II: Interventions for the treatment of gastrointestinal toxicity**

Intervention
5-aminosalicylates
Corticosteroids
Sucralfate
Metronidazole
Formalin enemas
Laser
Heater probe
Hyperbaric oxygen
Surgical resection

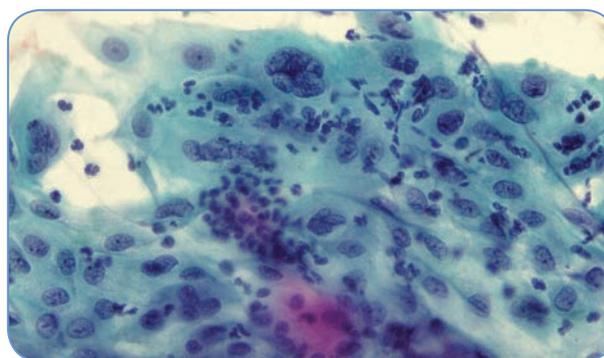
A systematic review by Denton et al was undertaken to identify the effective components of this long “shopping list” of interventions.<sup>12</sup> It was found that trials were very limited, often small, single institution interventional studies, and very few compared the interventions to a placebo. However, it was found that metronidazole at a dose of 400 mg three times a day for a year was superior to mesalazine and betamethasone enemas alone (study population n = 60). Furthermore, rectal sucralfate was superior to oral sulphasalazine and rectal steroids for four weeks (study population n = 37). There were no reported studies on the use of formalin, but individual reports suggest some success. There is no clear guidance on when to institute rectal formalin and, in this author’s institution, it is attempted if sucralfate enemas fail.

Medical treatments are, on the whole effective, however in the minority of cases where this approach fails laser therapy, hyperbaric oxygen and surgery may need to be considered. Hyperbaric oxygen has been increasingly the focus of international studies. Clarke et al reported a randomisation of 120 patients with refractory radiation proctitis.<sup>13</sup> The results showed a significant improvement in healing in the treatment arm (responders per clinical assessment 88.9% vs 62.5%; p = 0.0009). Resource constraints may preclude the use of hyperbaric oxygen, though there are centres linked to academic institutions in South Africa. In the Western Cape, these services are offered at a reduced rate for state patients.

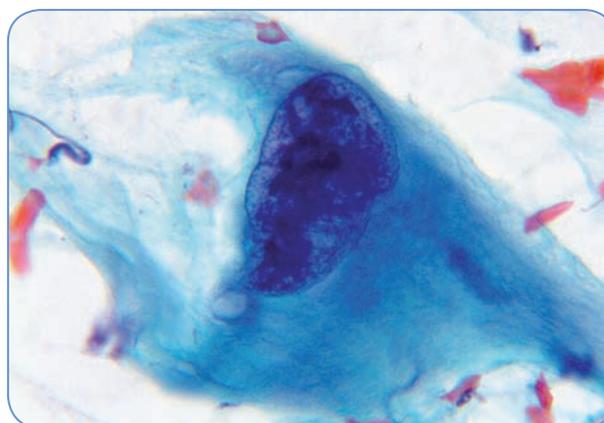
Surgical intervention with bowel resection or colostomy formation is necessary when fistula formation or bowel obstruction occurs, or medical therapy fails. Details of surgical management are beyond the scope of this review, but it is important to note that cooperation between radiotherapists and surgical colleagues is essential in order to provide best patient care.

**Vaginal toxicity/sexual dysfunction**

Vaginal toxicity may include shortening, narrowing due to fibrotic bands, teleangiectasia and vaginal bleeding, dryness secondary to local changes and menopausal effects, and associated dyspareunia.



**Figure 1:** Radiation effect in a vault smear. Large cells with abundant cytoplasm are arranged in a monolayered sheet. Some of the cells are multinucleated. Many neutrophils are present in the cytoplasm of the large cells. Papanicolaou stain (original magnification 400x).



**Figure 2:** Radiation effect in a vault smear. The nucleus of the cell is markedly enlarged and has a bizarre appearance but the nuclear-to-cytoplasmic ratio is preserved. Cytoplasmic vacuolisation can be seen (07:00). Papanicolaou stain (original magnification 1000x).

For patients that have been, and remain, sexually active after pelvic radiation, this is a significant toxicity with a major impact on quality of life and social interaction. Vistad et al, as detailed above, found that 58% of patients investigated in a self-report study complained of significant vaginal discomfort.<sup>7</sup> Essentially, 6 out of every 10 patients that enter the clinic are experiencing a toxicity that is largely ignored. In addition to the physical changes, there are additional psychosexual issues, with fear of inducing a relapse, fear of pain, and sexual aversion post-therapy.<sup>14</sup> Contributing to this is the failure of the clinician to adequately address these issues, both prior to and after therapy. Both clinician and patient may be hesitant to enter into a discussion due to embarrassment, lack of rapport, opposite sex, and lack of knowledge. Once again language, cultural barriers and pressure on clinic time are additional obstacles in the developing world setting.

Thought must be given to how these issues can be addressed. Firstly, as clinicians we must remove the taboo around

discussions of physical and psychosexual problems, so that patients feel they can bring these issues to clinic. Secondly, we must consider practical solutions in order to ease the patient's discomfort as detailed in Table III. It must be noted that the continuation of normal sexual activity is the best form of prevention of vaginal stenosis. Furthermore, if at all possible, attempts should be made to engage the patient's partner in discussion and education.

**Table III: Interventions for the treatment of vaginal toxicity**

Intervention
Topical oestrogen
Hormone replacement therapy
Lubricants
Vaginal dilators

### Conclusions

In conclusion, it is clear that pelvic radiation impacts the quality of our patients' lives. It appears that we are underestimating the true incidence and severity of these complications, due to imperfect scoring systems and poor communication with patients. In the developing world, we are further restricted by language and cultural barriers, poor follow-up attendance and the unknown impact of HIV infection on late complications. As far as time allows in busy clinical practice, we must enquire specifically about symptoms of toxicity, and take responsibility to address not only the physical problems, but also the psychological impact that pelvic radiation has had on our cancer survivors.

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