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Late morbidity of pelvic radiotherapy

Prospective analysis of patient-reported late toxicity following pelvic radiotherapy for gynaecological cancer

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ABSTRACT

Background and purpose: As late radiotherapy toxicity impacts negatively on the quality-of-life of cancer survivors and is often under reported, a study was set up to prospectively collect patient-reported data in an unselected series of patients with gynaecological malignancy. Aim 1 – To provide 3 year results for the longitudinal study. Aim 2 – To improve the questionnaire used to collect data by identifying redundant items and modifying for use to collect Common Terminology Criteria for Adverse Events (CTCAE) data.
Material and methods: Aim 1 – Patient reported outcome data were collected prospectively by 226 patients before and up to 3 years following radiotherapy for gynaecological cancer using a questionnaire developed to collect LENT subjective data. Aim 2 – A factor analysis was performed to identify which questions gave the most and least information.
Results: Aim 1 – Faecal urgency and incontinence (all grades) peaked at 79% and 24%, respectively at 1 year then settled to 69% and 18% at 3 years, respectively. Urinary urgency (all grades) increased with time and was described in 75% at 3 years. Other symptoms reported at 3 years include diarrhoea in 12%, urinary incontinence in 27% and vaginal dryness in 29%. A third of patients did not feel their sex life had changed following treatment, while a quarter felt that it had. Aim 2 – some questions overlapped and others were non-specific. The questionnaire has subsequently been altered.
Conclusions: The extent of late toxicity is substantial. This detailed information is important for both patients and clinicians in terms of treatment decisions and follow-up care. The LENT questionnaire provides a feasible tool for capture of this information in the clinic.
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Late toxicity following radiotherapy to the pelvis for gynaecological malignancy is crucially important to patients, in particular when these effects limit a patient's activity or ability to work. Clinical trials mostly use physician-reported late toxicity grades 3–4 [1,2], for example fistulae, necrosis, telangiectasia. The impact and extent of less severe symptoms of urinary or bowel frequency, urgency and incontinence and sexual dysfunction is an area of increasing interest and is under recognised [3–5].

Improved recognition of the frequency and severity of these late treatment effects may lead to better quality of care for patients in the years following pelvic radiotherapy. Decisions regarding the balance of benefits versus side effects from pelvic radiotherapy in the adjuvant setting may also be influenced by more detailed knowledge of long term toxicity. There are few prospective series of patient-reported morbidity in the literature [1,2,6,7].

The LENT SOMA (Subjective Objective Management Analysis) system of assessing late toxicity was introduced by a joint working party from the EORTC and RTOG in 1995 [8,9]. It is a very detailed and comprehensive system relating to symptoms assessed subjectively, signs assessed objectively, the management recommended for symptom control and an analytical assessment of any investigations required. The LENT SOMA questionnaires have been devised in order to use the scales across many cancer sites including prostate, gynaecological, breast, head and neck and bladder malignancies [10–16]. As part of validation the LENT SOMA questionnaires have been compared with the Franco-Italian Glossary for reporting toxicity in cervical cancer [13]. LENT items have been incorporated within the National Cancer Institute Common Toxicity Criteria and Adverse Events (NCI CTCAEv3) scoring system, which is now the preferred platform for toxicity assessment in clinical trials [17].

We have reported the early toxicity from prospectively collected data from a patient-completed paper questionnaire using the subjective assessments of the LENT system following pelvic radiotherapy for gynaecological malignancy from our institution

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in 2003 [18]. The 3 year data using this paper questionnaire are now available and are presented here. The first aim of this study was to describe the rates of patient-reported late toxicity elicited. The second aim was to analyse the efficacy of the questionnaire and enable appropriate alteration of some questions. Future data collection should then yield more informative conclusions about the late toxicity experienced by patients following pelvic radiotherapy for gynaecological cancer.

Methods

Patients offered radical or adjuvant pelvic radiotherapy for gynaecological cancer between 1998 and December 2008 were invited to complete a paper questionnaire regarding pelvic symptoms. Ethical approval was obtained from South Manchester Research Ethics Committee. A disease site-specific questionnaire developed from the LENT SOMA scales was used to score the patient data [18]. The time points at which the questionnaires were completed were pre-treatment (external beam radiotherapy, days 0–4), immediate post-treatment (±3 days), then at 1 year (±4 weeks), 2 years (±4 weeks) and 3 years (±3 months) post treatment. A research nurse interviewed all patients pre-treatment in private to explain the questionnaire in detail and to facilitate the use of subsequent postal questionnaires. Reminders were posted to patients to enhance data collection. Patients were withdrawn from the study in the event of tumour recurrence.

Patients with cervical, endometrial or vaginal cancer were treated radically, with external beam radiotherapy to the pelvis followed by intra-cavitary therapy, or adjuvantly following radical or total hysterectomy. Concurrent chemotherapy for cervical cancer was given latterly when appropriate, as this was introduced at our centre from 2000.

The questionnaire included 38 items from the LENT subjective scale. This is described in Routledge et al. [18]. The questionnaire can be accessed at http://www.christie.nhs.uk/pro/depts/clinonc/lent_soma/docs/CxPQV9.pdf.

Statistical analysis

All statistical calculations were carried out using the statistical package, SPSS v14.0 (http://www.spss.com). Complete-case analysis was used in order to determine the frequencies/incidence of different items at all time points. No imputation methods were employed. Compliance was calculated by the total number of completed questionnaires returned divided by the total number administered or sent. The reliability of toxicity data at each time point (i.e. within questionnaire) was assessed by determining the Cronbach's α coefficient. This is a measure of how well each item correlates with all other items under consideration, e.g., in the entire questionnaire or a given subscale. A coefficient of $\geqslant 0.6$ was taken to indicate good reliability.

(1) Item and subsection scores (Aim 1)
The item scores for a given question in the questionnaire were classified into three levels namely, no score (item score = 0), low (item scores = 1, 2), and high (item scores = 3, 4). The frequencies for these three groups were plotted on the left ordinate axis with respect to time on the abscissa. Maximum and mean item scores were calculated across the entire set of patients and obtained for each question at each time point. Average toxicity scores for each patient for individual subsections (rectum/bowel, bladder/urethra, vagina, and sexual function) were obtained at each time point. If more than half of a patient's answers for a subsection were missing then the average value for that patient and particular scale was taken as missing. The average and maximum scores for each item were plotted on the right ordinate axis on the graphs.

(2) Factor analysis (Aim 2)
Factor analysis was carried out in order to identify both the less informative and the most important questions, i.e. those that are likely to account for most of the inter-patient variability in subjective toxicity. This involved measurements of correlation identified between questions using principal component analysis (PCA) [19–21]. A PCA was carried out with respect to a Pearson correlation matrix for scores obtained within each time point for the questionnaire data. The extent of correlation was expressed in a factor loading and indicates the importance of each variable to each factor. The structure of correlations between different questions were analysed by consideration of factors after Varimax rotation with Kaiser Normalisation. The cut off point for a factor loading to be considered important was taken to be 0.5, a level used elsewhere [22]. Questions with small factor loadings (<0.2) were taken to be unimportant and were omitted. Those items that correlated very strongly with each other indicated that they were measuring very similar aspects of treatment toxicity. The number of these items might therefore be reduced safely. However, these items might be quite important clinically when they occur and care is needed in deciding whether to remove such items from the questionnaire.

Results

Two hundred and twenty-six patients were recruited prospectively. The patient characteristics are given in Table 1. The numbers of questionnaires completed were 224, 185, 83, 66 and 57 before and immediately, 1 year, 2 years and 3 years following treatment, respectively. Overall, 126 patients withdrew from the study: 60 patients stopped completing the questionnaires at various points throughout the study (patient choice, lost to follow-up, too unwell); 3 patients did not complete the course of radiotherapy; 3 developed a second primary cancer; 44 patients were excluded

Table 1
Patient characteristics.

Number of patients recruited	226	
Age at the end of radiotherapy treatment (years)		
Mean	54.7	
Median	56.5	
Range	24–86	
Cancer site	Number of patients	Percent (%)
Cervix	165	73.0
Uterine	52	23.0
Vagina	1	0.5
Unknown	8	3.5
Stage of disease		
I	74	33.0
II	88	39.0
III	37	16.0
IV	16	7.0
Unknown	11	5.0
Treatment received		
Radiotherapy alone	56	25.0
Radiotherapy and surgery	94	41.0
Radiotherapy and chemotherapy	45	20.0
Radiotherapy, chemotherapy and surgery	31	14.0