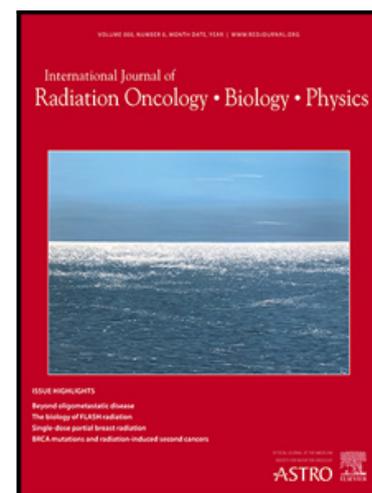# Journal Pre-proof

Online symptom monitoring during pelvic radiotherapy: randomised pilot trial of eRAPID intervention

Patricia Holch PhD , Kate L. Absolom PhD , Ann M. Henry MD , Katrina Walker MSc , Andrea Gibson RN , Eleanor Hudson MSc , Zoe Rogers MSc , Marie Holmes MSc , Rosemary Peacock PhD , Simon Pini PhD , Alexandra Gilbert PhD , Susan Davidson MD , Jacqueline Routledge RN , Anthony Murphy RN , Kevin Franks MD , Claire Hulme PhD , Jenny Hewison PhD , Carolyn Morris BSc , Lucy McParland MSc , Julia Brown MSc , Galina Velikova PhD

Online symptom monitoring during pelvic radiotherapy: randomised pilot trial of eRAPID intervention

Patricia Holch* [1,2], (PhD) Kate L. Absolom (PhD) [2.3] Ann M. Henry (MD) [2,4] Katrina Walker (MSc) [5], Andrea Gibson (RN) [2,4] **Eleanor Hudson (MSc) [5], Zoe Rogers (MSc)[2], Marie Holmes (MSc) [2], Rosemary Peacock (PhD) [2], Simon Pini (PhD) [3], Alexandra Gilbert (PhD), [2,4,5]Susan Davidson (MD)[7]; Jacqueline Routledge(RN) [7], Anthony Murphy (RN)[7], Kevin Franks[4] (MD), Claire Hulme (PhD)[8], Jenny Hewison (PhD) [3] Carolyn Morris (BSc) [2], Lucy McParland (MSc) [6,], Julia Brown (MSc) [5] Galina Velikova (PhD) [2,4] (Joint senior authors)

* **Corresponding author**-Dr Patricia Holch t.holch@leedsbeckett.ac.uk

** **Statistical analysis**- Katrina Walker katrinawalker3@outlook.com

1. Department of Psychology, School of Social Sciences, Leeds Beckett University, Calverley Building, Room CL 815 City Campus, Leeds, LS1 9HE, UK
2. Leeds Institute of Medical Research at St James's, University of Leeds, Bexley Wing, St James's Hospital, Beckett Street, Leeds, LS9 7TF, UK
3. Leeds Institute of Health Sciences, University of Leeds, Leeds, LS2 9JT, UK
4. Leeds Teaching Hospitals NHS Trust, Leeds Cancer Centre, Bexley Wing, St James's Hospital, Beckett Street, Leeds, LS9 7TF, UK
5. Leeds Institute of Clinical Trials Research, University of Leeds, Leeds LS2 9JT
6. PHASTAR, Bollo Lane, London, W4 5LE
7. The Christie NHS Foundation Trust, 550 Wilmslow Rd, Manchester M20 4BX, UK
8. University of Exeter, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU, UK

Abstract

Background Radiotherapy and chemo-radiotherapy for pelvic cancers increase survival but are associated with serious treatment-related symptoms. Electronic-patient self-Reporting of Adverse-events: Patient Information and aDvice (eRAPID) is a secure online system for patients to self-report symptoms, generating immediate advice for hospital contact or self-management. This pilot study aimed to establish feasibility and acceptability of the system.

Methods In a prospective two-centre randomised parallel-group pilot study. Patients undergoing radical pelvic radiotherapy for prostate cancer (prostateRT) or chemo-radiotherapy for lower gastrointestinal and gynaecological cancers (chemoRT) were randomised to usual care (UC) or eRAPID (weekly online symptom reporting for 12, 18 & 24 weeks). Primary outcomes were recruitment/attrition, study completion and patient adherence. Secondary outcomes were impact on hospital services and performance of patient outcome measures. Missing data, floor/ceiling effects, and mean change scores were examined for FACT-G, EORTC-QLQ-C30, self-efficacy, EQ5D-5L.

Results From 228 patients approached, 167 (73.2%) were consented and randomised (83-eRAPID,84-UC;87-prostateRT;80-chemoRT). 150/167 completed 24 study weeks. Only 16 patients (9.6%) withdrew (10-eRAPID; 6-UC). In the eRAPID arm, completion rates were higher in patients treated with prostateRT compared to chemoRT: week 1 93% vs 69%; week 2 93% vs 68%; week 12 69% vs 55%). Overall over 50% of online reports triggered self-management advice for milder AEs. Unscheduled hospital contact was low, with no difference between

eRAPID and UC. Return rates for outcome measures were excellent in prostateRT (97%-91%; 6-24 weeks) but lower in chemoRT (95%-55%; 6-24 weeks). Missing data was low (1%-4.1%), ceiling effects were evident in EQ5D-5L, self-efficacy-scale and FACT-PWB. At 6-weeks the chemoRT-eRAPID group showed less deterioration in FACT-G, EORTC QLQ-C30 and EQ5D-VAS than UC, after baseline adjustment.

Conclusions eRAPID was successfully added to UC at two cancer centres in different patient populations. Acceptability and feasibility was confirmed with excellent adherence by prostate patients, but lower by those undergoing chemoRT for gynaecological cancers.

Introduction

Radiotherapy and chemoradiotherapy are key components of curative treatment for pelvic malignancies [1, 2]. However, during and after radiotherapy (RT), patients may experience significant short and longer-term treatment-related bowel, urinary and sexual side-effects [3, 4] . Traditionally measured in clinical trials using the Common Terminology Criteria for Adverse Events (AEs) [5] , there is evidence that patients can robustly self-report on symptomatic toxicity using standardised questionnaires (known as Patient Reported Outcome Measures (PROMs)[6]. When integrated into routine practice, PROMS can improve the timing and accuracy of symptom-reporting, communication and decision-making [7-9]. Online PROMS reporting with symptom alerts delivered to the clinical team, may also facilitate earlier intervention preventing more serious complications and result in improved survival [10]; with this approach having the potential to transform patient care by improving the monitoring and management symptoms [11]. However, currently the research into use of

PROMS for routine symptom-monitoring has mainly focussed on patients treated with systemic therapies, with a paucity of data in patients treated with radiotherapy [12-14]. Notable exceptions are studies describing electronic reporting of late effect post pelvic RT (bowel toxicity) [15] and post RT toxicity in lung cancer patients [16].

The eRAPID system (electronic patient self-Reporting of Adverse-events: Patient Information and aDvice) was developed by xxxxxxxxxxxxxxxxxxxxxxxx. The system utilises a severity dependent algorithm to advise patients to self-manage symptoms or contact the hospital when symptoms are severe, supporting patient self-management in reducing symptom severity and improving quality of life [17]. The system enables real-time transfer and display of the patient responses for clinical use within the electronic records; generating clinical alerts for severe symptoms [18]. As part of the programme eRAPID RT was successfully integrated into the Electronic Patient Record systems (EPR) of two XXX trusts in the XX [17]. A definitive single-centre randomised trial of eRAPID with patient undergoing systemic oncological treatments showed improved physical well-being during treatment and increased patient self-efficacy [19,20].

In this pilot study the eRAPID system was adapted to support patient care during and immediately after pelvic radiotherapy [21]. The aims of this study are to determine the feasibility and acceptability of the eRAPID system in this patient population.

Methods

Study design and participants

This pilot study is a prospective randomised two-arm parallel group trial over 24 weeks with repeated outcome measures conducted across two centres (xxxxxxxxxxxxxxxxxxxxxx) and the xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx).

We tested the eRAPID intervention in two distinct treatment groups: (1) radical external beam radiotherapy (EBRT) for prostate cancer (prostateRT); (2) chemoradiotherapy (chemoRT) for lower gastrointestinal (anal, rectal – neoadjuvant) and gynaecological cancers (cervical, vaginal, vulval, endometrial; adjuvant EBRT alone).

Trial procedures are described in the published protocol [21]. In brief, eligible patients had a diagnosis of (1) prostate cancer requiring radical radiotherapy (+/– brachytherapy boost and +/- hormone therapy) or (2) anal, rectal, cervical (+/- brachytherapy), vaginal or vulval cancer requiring chemoRT or adjuvant EBRT for endometrial cancer; were 18 years ; had access to home internet or mobile devices and able to read and understand English. Patients were excluded if participating in other clinical trials with extensive PROMs completion or exhibiting cognitive dysfunction. Consenting patients were randomised 1:1 to Usual Care (UC) or eRAPID intervention (supplementing UC), randomised by centre (xxxxx or xxxxxx) and stratified by treatment (prostateRT and chemoRT). Clinicians who took part (senior oncologists, trainees, senior nurses, radiographers) saw patients in both study arms. Randomisation was performed centrally by the XXXXXXXXXXXXXXXX via a 24-hour automated system.

Approval was gained from xxxxxxxxxxxxxxxxxxxxxx (REC reference xxxxxxx; ClinicalTrials.gov xxxxxxxx).

Procedures

Usual care

Prior to starting treatment patients are assessed by a clinician and given verbal and written information on expected treatment-related symptoms, their management and when and how to contact the hospital., including a 24/7 telephone hotline facilitating emergency oncology admissions. During radiotherapy, patients attend for treatment Monday-Friday and are seen weekly by a clinician. On completion, prostate patients are seen in clinic 6-8 weeks later and then discharged. Anal/vulval/ and cervix patients are reviewed at 6 weeks and 3 months, rectal patients are referred to surgery after a 6 week scan. Radiotherapy schedules varied slightly between the two centres (detail on radiotherapy schedules are provided in the supplementary file 6 S Table 3).

Intervention

eRAPID is a complex intervention with a number of interactive components and was codesigned with patients and clinical teams [21]. To enable replication and transparency we have adhered to the Template for Intervention Description and Replication (TIDIER) standards [22]. Patients were asked to report online symptoms weekly (or additionally when experiencing symptoms) during and post-treatment for 12-weeks (to capture acute symptoms) and then once at 18 and again at 24-weeks to capture later side-effects (see supplementary file 1 (S Figure 1). The baseline online symptom report was completed within 24-hours of study entry. Reminders

were sent via email or text message, and self-reports were immediately available within the electronic patient records (EPR) The xxxxxxxxxx EPR (PPM-Patient Pathway Manager) is used in xxxx trusts across the xxxxxxx region. Alerts for severe symptoms were sent to a shared clinical team email, monitored by senior nurses and oncologists, (see supplementary file 2 S Figure 2 for overview). Immediate automated advice was provided to patients for self-management of mild symptoms or a prompt to contact the hospital for serious symptoms (see supplementary file 3 S Figure 3). More detailed information on symptom management was available via hyperlinks to the eRAPID website.

The eRAPID self-report items were developed by adapting and developing existing validated questionnaires for each cancer site (gynaecological, lower gastrointestinal and prostate). The majority of symptom items were taken from the male and female pelvic questionnaires (MPQ and FPQ) [23] which were based on the LENT SOMA Scales with additions from EPIC (Expanded Prostate Cancer Index) [24], EORTC QLQ-C30 [25] and QLQ-PR25 (prostate module) [26]. Additional questions were added form the eRAPID systemic therapy item pool based on a version of the PRO-CTCAE format by translating the CTCAE into patient language [20]. For each tumour group there was a set of 25 core symptomatic toxicity items covering bowel, urinary, fatigue and physical side effects taking approximately 20-25 minutes to complete. Participants could also select chemotherapy relevant items (n=9), stoma (n=7), sexual issues (n=10) from an additional drop-down menu (n=11) including social and psychological issues, hot flushes etc (51 items in total).

Patient-friendly and clinically accurate advice was developed and adapted for each cancer site [21]. In consultation with health-care professionals and patients using

consensus and discussion based methods, key treatment-related symptoms were selected and severity levels agreed for the patient advice and alerts scoring algorithms [27] (see supplementary file 4 S Table 1 for an example)). The eRAPID patient website was designed (separate versions for each participating centre) collating the existing patient information at each centre, available local supportive services and reputable national web resources (xxxxxxxxxxxx).

Patients received one-to-one eRAPID user training from a researcher and were given an eRAPID 'postcard' with a unique username and password, and a user-manual including contact numbers for technical problems. Clinicians were trained by researchers at team meetings, one-to-one sessions or via an inactive eRAPID eLearning programme.. Staff were advised to discuss the symptoms reports in patient consultations without specific recommendations for actions.

Outcome measures and analysis

The primary outcome was feasibility measured by recruitment/attrition rates, study completion and eRAPID patients' adherence to symptom reporting.

Study completion was defined in two ways:

1) Number/proportion of patients who remained on the study at 24 weeks (i.e. did not actively withdraw or die);

2) Number/proportion of expected patients who returned the paper outcome measures at 24 weeks (i.e. not including those who withdrew or died).

Patient adherence to online reporting was examined by:

1) Proportions of expected patients completing the online reports per protocol once a week (adjusting for withdrawals/deaths);

2) The total number of reports per participant over 24 weeks, including extra completions.

The secondary outcomes were: impact on hospital services; selection of appropriate patient outcome measure for a future randomised controlled trial and refining the intervention by exploring patient and staff views.

Impact on hospital services. Data was collected on: the number of hospital contacts (admissions, clinic visits, phone calls) from the electronic patient records and the number of clinician alerts generated from eRAPID severe symptom reports. The data was summarised descriptively.

Missing items, floor and ceiling effects. Missing data items were examined as the proportion of returned questionnaires with significant number of missing items, (as per questionnaires scoring guidance) thus making the calculation of scores not possible.

Score distributions were examined to detect ceiling and floor effects on outcome questionnaires (defined as > 15% of patients reporting highest or lowest scores), by study arm (eRAPID, UC), treatment group, centre and time of data collection. A pooled analysis of all returned questionnaires across all timepoints was also performed.

Data Trends were examined to aid selection of a primary patient outcome measure in a future trial. The mean score changes from patient outcome measures at baseline to 6, 12 and 24 weeks for eRAPID and UC arms were calculated. A post-hoc exploratory analysis of covariance (ANCOVA) was performed on the raw scores of completed outcome data for both treatment groups to adjust for a single covariate (baseline scores) [28]. We present mean differences with 95% CI's (both adjusted

and unadjusted) without p-values, suggested by CONSORT statement for pilot studies [29].

Analyses were performed separately for the two patient treatment groups (prostateRT and chemoRT). Analyses were carried out using SAS version 9.4 and SPSS Version 26 on the Intention to Treat (ITT) population (unless stated otherwise).

Sample size

A sample of 30 participants per study arm per treatment group (prostateRT and chemoRT) was set according to Lancaster's (2004) recommendations for plot studies [30]. Allowing for 30% overall attrition, the recruitment target was n=84 per study arm(total n=168). Analyses were performed separately within the two patient cohorts (prostateRT and chemoRT).

Patient outcome measures

Validated measures of Quality of Life (QOL) (EORTC QLQ-C30, FACT-G) and health utility (EQ5D-5L, EQ5D-VAS) [25, 31-32] were collected on paper at baseline (before randomisation), at 6, 12 and 24 weeks; measures for patient self-efficacy and engagement (Self-Efficacy Scale for Managing Chronic Disease questionnaire; Patient Activation Measure (PAM) [33, 34] were collected at baseline and 12 weeks; and satisfaction with the eRAPID technology at 24-weeks (eRAPID only). See Table 1 for details on patient outcome measures and the published protocol [21]. All measures were administered intact (including all subscales). Please see table 1 for more detail

*** Insert Table 1 Patient Outcome Measures***

Results

Primary outcome

Recruitment

Between Dec 1st 2016 and May 14th 2018 (17.5 months) 253 patients were identified (Figure 1 CONSORT diagram) and 25 patients did not meet eligibility criteria. Of 228 fully eligible patients 61 declined participation (26.8%) (Reasons: no internet access, personal circumstances and not having treatment), 167 patients consented, and were randomised. Recruitment rate was 73.2% (167/228).

Baseline characteristics

Baseline patient demographic, clinical characteristics, and patient outcomes scores are presented in Table 2. Patients undergoing chemoRT were younger (40 years) than those on prostateRT, had a lower education level (33.8% with university/professional degree vs 47.1% respectively) and fewer co-morbidities (51.3% no-comorbidity vs 37.9%).

*** Insert Table 2 Baseline and demographic information ***

Within the prostateRT group, patients' characteristics were well balanced between eRAPID and UC, with a small trend in the baseline patient outcome measures scores being better in UC arm. Within the chemoRT group there were imbalances with a higher proportion of eRAPID patients had basic school education (42.5%) than those in UC (22.5%) and importantly, eRAPID patients reported higher (better) baseline scores than UC on almost all outcome measures completed before randomisation (except EQ5D-5L).

Table 1: Outcome measures- scoring, interpretation and time scale

Outcomes	Instrument/Method	Item information/data collection	Score range	High score	Time points
Patient Self-efficacy					
Self-Management	Self-Efficacy Scale for Managing Chronic Disease questionnaire [31]	6-items with 10-point question response scale from 1-10 (not at all confident – totally confident).	0-10	Better outcome	Baseline and 12-weeks
Patient engagement in their own healthcare	Patient Activation Measure [32]	13-items 5-point response scale 1-disagree strongly to 5-strongly agree.	0-100	Better outcome	Baseline, and 12-weeks.
Health-related quality of life					
	FACT-G questionnaire (physical, social, emotional and functional wellbeing scales) [29]	27-items 5-point response scale from 0-not at all to 4-very much)	0-108	Better outcome	Baseline, 6, 12, 18 & 24 weeks
	EORTC QLQ-C30 (symptom and functional scales) [25]	30-items 4-points response scale from 1-not at all to 4- very much) Summary score used, calculated using 2 items on Overall QOL/Health-, score 1 (worse QOL) to 7 (best QOL)	0-100	Better outcome	Baseline, 6, 12, 18 & 24-weeks
Health Utility measure	EQ-5D-5L [30]	5-items 5-point response scale from no problems to extreme problems.	Utility score 1 to–0.285	Better outcome	Baseline, 6, 12, 18 & 24-weeks
	EQ-5D VAS	Vertical 100-point response scale 0-worst health you can imagine to 100-best health you can imagine	0-100	Better outcome	Baseline, 6, 12, 18 & 24-weeks
Delivery of eRAPID Intervention/Fidelity					
	Patient adherence to online reporting.	Downloaded from the online software (QTool).	0-100%		During the 24-week study period
	Type, frequency, severity of self-reported symptoms.	Downloaded from the online software (QTool).	0-100%		During the 24-week study period
	Frequency of activated clinical algorithms and alerts.	Downloaded from the online software (QTool).	0-100%		During the 24-week study period

Table 2: Participants baseline demographic, clinical characteristics and outcome measures scores

	Pelvic Chemoradiotherapy			Prostate Radiotherapy		
	eRAPID n=40	Usual Care n=40	Total n=80	eRAPID n=43	Usual Care N=44	Total n=87
Demographic characteristics						
Age summaries (years)						
Mean (s.d.)	51.1 (15.9)	53.0 14.3)	52.1 (15.1)	70.5 (7.1)	70.8 (6.9)	70.7 (7.0)
Median (range)	52.0 (22.0, 80.0)	55.0 (26.0, 78.0)	54.0 (22.0, 80.0)	70.0 (51.0, 84.0)	70.5 (55.0, 82.0)	70.0 (51.0, 84.0)
Gender (N,%)						
Male	9 (22.5%)	7 (17.5%)	16 (20.0%)	43 (100.0%)	44 (100.0%)	87 (100.0%)
Female	31 (77.5%)	33 (82.5%)	64 (80.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Education						
Basic school education	17 (42.5%)	9 (22.5%)	26 (32.5%)	14 (32.6%)	10 (22.7%)	24 (27.6%)
Beyond basic school education	8 (20.0%)	15 (37.5%)	23 (28.8%)	6 (14.0%)	13 (29.5%)	19 (21.8%)
University or professional degree/qualification	13 (32.5%)	14 (35.0%)	27 (33.8%)	22 (51.2%)	19 (43.2%)	41 (47.1%)
Missing	2 (5.0%)	2 (5.0%)	4 (5.0%)	1 (2.3%)	2 (4.5%)	3 (3.4%)
Clinical characteristics						
Hospital						
Leeds Cancer Centre	21 (52.5%)	21 (52.5%)	42 (52.5%)	22 (51.2%)	23 (52.3%)	45 (51.7%)
Christie Hospital Manchester	19 (47.5%)	19 (47.5%)	38 (47.5%)	21 (48.8%)	21 (47.7%)	42 (48.3%)
Diagnosis site						
Lower GI	17 (42.5%)	16 (40.0%)	33 (41.3%)			
Gynaecology	23 (57.5%)	24 (60.0%)	47 (58.8%)			
Comorbidity categories						
No comorbidities	22 (55.0%)	19 (47.5%)	41 (51.3%)	13 (30.2%)	20 (45.5%)	33 (37.9%)
1 comorbidity	10 (25.0%)	11 (27.5%)	21 (26.3%)	16 (37.2%)	13 (29.5%)	29 (33.3%)
2 comorbidities	7 (17.5%)	5 (12.5%)	12 (15.0%)	10 (23.3%)	3 (6.8%)	13 (14.9%)
3+ comorbidities	1 (2.5%)	5 (12.5%)	6 (7.5%)	3 (7.0%)	7 (15.9%)	10 (11.5%)
Missing				1 (2.3%)	1 (2.3%)	2 (2.3%)
QOL baseline scores						
Mean (s.d)						
FACT-G Overall	83.9 (14.3)	77.8 (20.6)		88.5 (13.8)	91.6 (12.1)	
FACT-G PWB	23.0 (4.9)	20.5 (7.5)		24.3 (3.3)	25.6 (3.1)	
EORTC QLQ C-30 Summary score	81.2 (14.9)	75.3 (20.0)		86.3 (8.7)	88.0 (11.2)	
EORTC QLQ C-30 Global/QOL	69.8 (20.9)	65.8 (24.5)		76.4 (15.2)	81.7 (15.9)	
EQ5D Utility	0.8 (0.2)	0.8 (0.2)		0.9 (0.1)	0.9 (0.2)	
EQ5D VAS	74.7 (18.4)	67.0 (24.0)		76.3 (17.0)	80.4 (17.7)	
SES	7.3 (1.6)	6.6 (2.4)		8.0 (1.8)	8.4 (1.5)	

Functional Assessment of Cancer Therapy (FACT-G) Physical Wellbeing (PWB), European Organisation for Research and Treatment of Cancer, Quality of Life (EORTC QLQ C-30) EuroQol (EQ5D), Self-Efficacy Scale (SES).