Radiotherapy and Oncology 138 (2019) 59–67

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

# REQUITE: A prospective multicentre cohort study of patients undergoing radiotherapy for breast, lung or prostate cancer

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*Abbreviations:* B, breast cancer patients; BCCT.core, Breast Cancer Conservation Treatment.cosmetic results; BMI, body mass index; BR23, breast module of EORTC QLQ; CTCAE, common terminology criteria for adverse effects; DICOM, Digital Imaging and Communications in Medicine; DVH, dose–volume histogram; EBRT, External beam radiotherapy; EORTC, European Organisation for Research and Treatment of Cancer; GI, gastrointestinal; GPAQ, Global Physical Activity Questionnaire; GTV, gross tumour volume; GU, genito-urinary; HDR, high dose rate brachytherapy; IMRT, intensity modulated radiotherapy; L, lung cancer patients; LDR, low dose rate brachytherapy; LiH, Lithium Heparin; MD, medical doctor; MFI, Multidimensional Fatigue Inventory; QoL, quality-of-life; P, prostate cancer patients; PSA, prostate specific antigen; RILA, radiation-induced lymphocyte assay; RR, relative risk; RT, radiotherapy; SNP, single nucleotide polymorphism; TURP, transurethral resection of the prostate; VMAT, Volumetric Arc Therapy.

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https://doi.org/10.1016/j.radonc.2019.04.034
0167-8140/

ARTICLE INFO

*Article history:*
Received 29 November 2018
Received in revised form 25 April 2019
Accepted 29 April 2019

*Keywords:*
Late radiotherapy side effects
Biomarkers
Prediction models
Breast cancer
Prostate cancer
Lung cancer

ABSTRACT

*Purpose:* REQUITE aimed to establish a resource for multi-national validation of models and biomarkers that predict risk of late toxicity following radiotherapy. The purpose of this article is to provide summary descriptive data.
*Methods:* An international, prospective cohort study recruited cancer patients in 26 hospitals in eight countries between April 2014 and March 2017. Target recruitment was 5300 patients. Eligible patients had breast, prostate or lung cancer and planned potentially curable radiotherapy. Radiotherapy was prescribed according to local regimens, but centres used standardised data collection forms. Pre-treatment blood samples were collected. Patients were followed for a minimum of 12 (lung) or 24 (breast/prostate) months and summary descriptive statistics were generated.
*Results:* The study recruited 2069 breast (99% of target), 1808 prostate (86%) and 561 lung (51%) cancer patients. The centralised, accessible database includes: physician- (47,025 forms) and patient- (54,901) reported outcomes; 11,563 breast photos; 17,107 DICOMs and 12,684 DVHs. Imputed genotype data are available for 4223 patients with European ancestry (1948 breast, 1728 prostate, 547 lung). Radiation-induced lymphocyte apoptosis (RILA) assay data are available for 1319 patients. DNA ($n$ = 4409) and PAXgene tubes ($n$ = 3039) are stored in the centralised biobank. Example prevalences of 2-year (1-year for lung) grade $\geq$2 CTCAE toxicities are 13% atrophy (breast), 3% rectal bleeding (prostate) and 27% dyspnoea (lung).
*Conclusion:* The comprehensive centralised database and linked biobank is a valuable resource for the radiotherapy community for validating predictive models and biomarkers.
*Patient summary:* Up to half of cancer patients undergo radiation therapy and irradiation of surrounding healthy tissue is unavoidable. Damage to healthy tissue can affect short- and long-term quality-of-life. Not all patients are equally sensitive to radiation "damage" but it is not possible at the moment to identify those who are. REQUITE was established with the aim of trying to understand more about how we could predict radiation sensitivity. The purpose of this paper is to provide an overview and summary of the data and material available.

In the REQUITE study 4400 breast, prostate and lung cancer patients filled out questionnaires and donated blood. A large amount of data was collected in the same way. With all these data and samples a database and biobank were created that showed it is possible to collect this kind of information in a standardised way across countries.

In the future, our database and linked biobank will be a resource for research and validation of clinical predictors and models of radiation sensitivity. REQUITE will also enable a better understanding of how many people suffer with radiotherapy toxicity.


Up to half of cancer patients undergo radiotherapy [1] and irradiation of surrounding healthy tissue is unavoidable. Patients vary in sensitivity to ionising radiation with 5–10% suffering from severe long-term effects that impact on their health-related quality-of-life [2,3] and limit the potentially curative doses prescribed to the majority.

The ability to predict those patients likely to develop adverse effects could potentially enable individualised treatments, which could decrease morbidity and/or increase survival. Models including clinical/treatment data and biomarkers have been developed to try identifying radiosensitive patients, e.g. [4–6]. However, the developed models and biomarkers have failed to progress to routine clinical use due to the lack of thorough independent validation. The ability to validate findings has been hampered by the lack of cohorts available. Cohorts are often small and heterogeneous [7–10]. Use of different toxicity scoring systems and the lack of standardised data collection reduces the ability to pool data [11], which is essential for collaborative research exemplified by Radiogenomics Consortium studies [12–19].

REQUITE (validating pREdictive models and biomarkers of radiotherapy toxicity to reduce side effects and improve QUalITy of lifE in cancer survivors) was established with the aim of validating models and biomarkers that predict a cancer patient's risk of adverse effects following radiotherapy [20]. In order to address previous limitations in pooling data and validating models and biomarkers, REQUITE carried out an international, multi-centre, prospective observational study. To reflect the real-life situation required for application of predictive models, there was no stipulation of the radiotherapy regimens to be delivered. However, all centres collected the same data housed in a central easily accessible database: demographics, previous and present co-morbidity, treatment and dosimetric information, longitudinal standardised radiotherapy toxicity (health professional and patient reported), and quality-of-life. A centralised biobank was established to store blood samples (extracted DNA, PAXgene tubes). Genome-wide genotyping of single nucleotide polymorphisms (SNPs) was carried out and the data added to the centralised database. A radiation-induced lymphocyte apoptosis (RILA) assay was carried out on a sub-set of patients.

The comprehensive centralised database and linked biobank will be a resource for the prospective evaluation and validation of clinical predictors and models. REQUITE will also enable a better understanding of the scale of radiotherapy toxicity in a multinational setting. As REQUITE is a resource for dissemination and exploitation to the radiotherapy community, the purpose of this paper is to provide a comprehensive overview and summary of the data and material available.

## Study design and methods

### *Study design and recruitment*

A multi-centre, prospective observational cohort study was designed to recruit 5300 patients with breast, lung or prostate cancer undergoing radiotherapy with curative intent. The study aim was validating predictive models and biomarkers of radiotherapy

toxicity. Eligible patients were identified in the multi-disciplinary meetings and out-patient clinics of 26 hospitals (Supplementary Table S1) in eight countries (Belgium, France, Germany, Italy, the Netherlands, Spain, UK, the USA). Adult breast and prostate cancer patients were recruited prior to radiotherapy between 04/2014 and 10/2016 and lung cancer patients until 03/2017 (Supplementary Table S2 with inclusion and exclusion criteria). Conventional and hypofractionated radiotherapy was prescribed according to local standard-of-care regimens. The patients were followed prospectively for a minimum of 12 (lung) or 24 (breast and prostate) months, with longer follow-up encouraged where possible. The primary study endpoints were change in breast appearance (breast cancer patients), rectal bleeding (prostate) at 24 months and dyspnoea/breathlessness at 12 months (lung). Toxicity evaluation beyond these time points was encouraged. Primary and secondary endpoints are summarised in Supplementary Table S3. All patients gave written informed consent. The study was approved by local ethics committees and is registered at www.controlled-trials.com ISRCTN98496463.

*Data and sample collection*

Patients were recruited prior to radiotherapy (baseline) and followed as previously described (Fig. 1). The following standardised data were collected prospectively by case report forms (CRFs): demographics, co-morbidity, treatment (with comprehensive information on radiotherapy regimens and dose to organs at risk), physics, longitudinal standardised radiotherapy toxicity (CTCAE v4.0 healthcare professional and patient reported), quality-of-life, and treatment outcome (including physician reported death). Both acute (at end of radiotherapy or at 3 months) and late toxicity data at 12 and 24 months are available for all three cancer types. Patient reported outcome (PRO) data collected were: quality-of-life including fatigue (EORTC QLQ C30 [21]; BR23 [22]; MFI [23] and physical activity (GPAQ [24])). CTCAE v4.0 based questionnaires developed to collect PRO data were adapted from those published elsewhere for the male pelvis [25] and lung [26]. The patient questionnaires were translated into local languages by two native speakers, merged, back translated by native English speakers, and validated for usability in ten patients per country.

DICOM and DVH files were collected for central storage using a standardised operating procedure (SOP). For the breast cancer patients, breast photos were taken using a SOP before radiotherapy and at the 24-month time point, and scored using BCCT.core software [27] according to a SOP, with 5% of photographs re-scored for quality assurance. A SOP was also produced for collecting blood samples. All patients donated at least two blood samples prior to

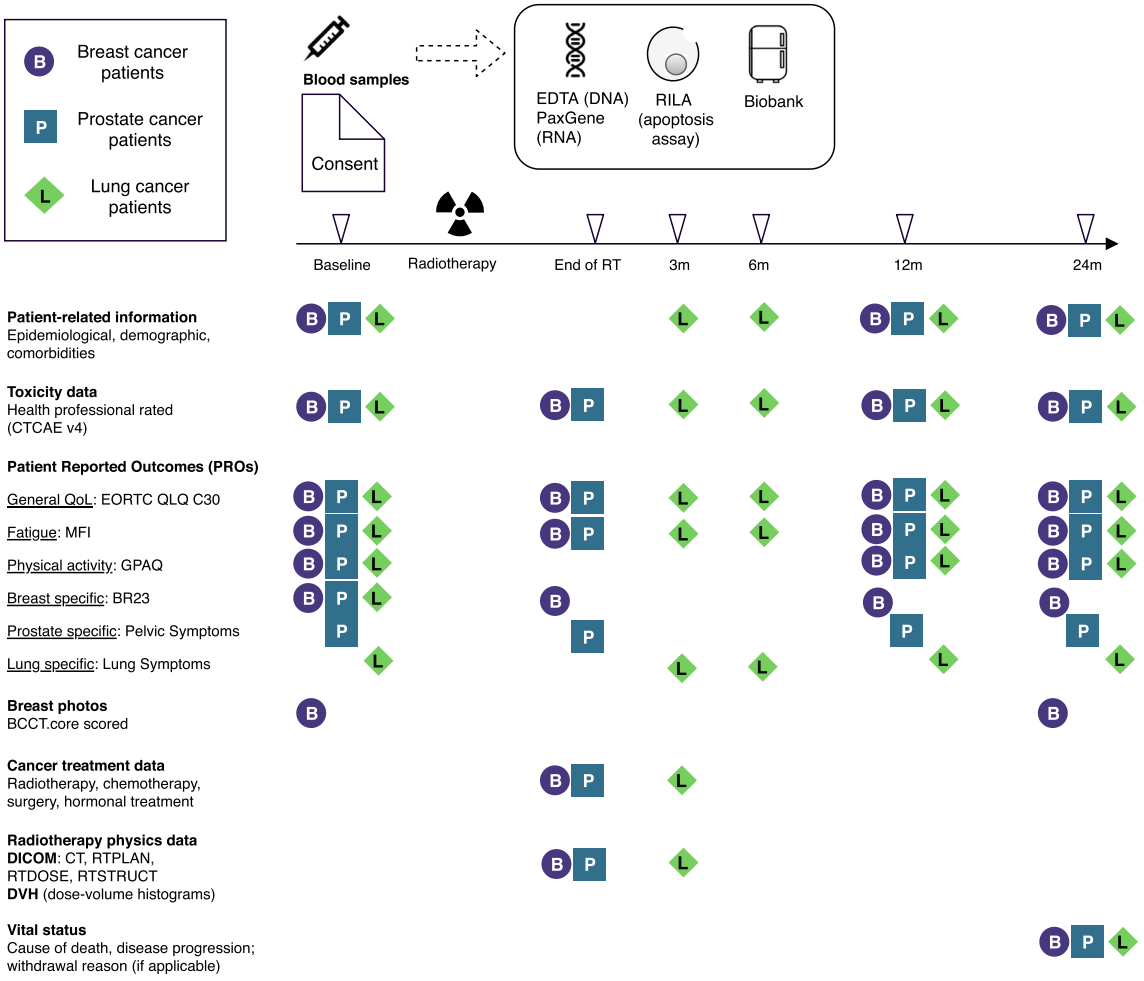


**Fig. 1.** Study Schema. Breast (B), prostate (P) and lung (L) cancer patients were recruited prior to radiotherapy and blood samples taken pre-radiotherapy (baseline). Toxicity was assessed prospectively by healthcare professionals (CTCAE v4.0, common terminology criteria for adverse effects) and patients (patient reported outcomes, PRO) at the end of radiotherapy (B, P), 3 and 6 months (L), 12 months and 24 months. Data collected included comprehensive cancer treatment data including radiotherapy physics data (DICOMs: Digital Imaging and Communications in Medicine, DVHs: dose–volume histograms), comorbid and other patient-related information. Quality-of-life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30 and the breast specific module BR23 (breast cancer patients only), the Multidimensional Fatigue Inventory (MFI) and the Global Physical Activity Questionnaire (GPAQ). For breast cancer patients, photos of the breasts were taken at baseline and 24 months. BCCT.core: (Breast Cancer Conservation Treatment.cosmetic results).

the start of radiotherapy: an EDTA sample for SNP genotyping plus a PAXgene (RNA) and/or a Lithium Heparin (LiH) sample. Blood samples were dispatched according to a SOP under temperature-controlled conditions to the CIGMR Biobank in Manchester, UK, where extracted DNA from blood and PAXgene samples for future RNA analysis are stored. A subset of patients from France, Germany and the UK gave LiH blood samples for prospective radiation-induced lymphocyte apoptosis (RILA) assays using an established method [7] and standardization across laboratories [28]. Genotyping data were generated using the Illumina Infinium OncoArray-500K beadchip. Following standard quality control procedures [29], genotype data were imputed using the 1000 Genomes Project (version 3) as a reference panel. The REQUITE CRFs, questionnaires and SOPs are available on request via www.requite.eu.

### *Data management and quality control*

Each patient was assigned a unique study identifier, which links sample, health and genetic data. The ID includes a check digit to minimise errors. Data were uploaded by each recruitment site to a secure, online centralised database system (OpenClinica (https://openclinica.com), LimeSurvey (https://limesurvey.org) and a bespoke 'Manager' application based on Drupal 7 (https://drupal.org)) with personal logins. Quality assurance and control procedures involved site initiation visits prior to the start of the study, monitoring visits during the study, transcribing error checks, source data verification and plausibility checks including a query system. Blood and DNA samples were 2D labelled. The study is overseen by a Steering Committee that includes a Patient Advisory Board.

### *Analytical considerations and statistical analysis*

It was initially estimated that 2-year toxicity data would be available for 75% of enroled patients, i.e. 1575 of the original target of 2100 breast or prostate cancer patients. Based on effect sizes observed for genetic associations with radiation toxicity (e.g. [17]), a power calculation for the genetic assay showed that 1575 breast or prostate cancer patients has 80% power to detect a relative risk (RR) of >1.56 for grade $\geq$2 toxicity ($\alpha = 5 \times 10^{-5}$ for 1000 SNPs, allele frequency = 0.25, toxicity rate = 20%). For 825 patients with lung cancer the detectable RR would be 1.78. A Kruskal–Wallis test was used for comparisons between the three cancer types using SAS 9.4. Graphs were generated using R 3.5.1, ggplot 3.0.0 or SAS 9.4.

## Results

### *Cohort characteristics*

Within the time-period available, 4438 patients were enroled: 2069 breast (99% of the original target), 1808 prostate (86%) and 561 lung (51%) cancer patients. Comprehensive cancer treatment data were available for 2057 breast, 1760 prostate and 530 lung cancer patients. The baseline characteristics and treatment information are summarised for each cancer type in Tables 1–3. Patients were aged between 23 and 91 years. The breast cancer patients were younger (median 58 years) at enrolment than the prostate (70 years) and lung (69 years) cancer patients. Most patients (>94%) identified as being of European ancestry (data not shown). As expected, there were significantly more lung cancer patients who were current smokers at the time of diagnosis (43%) compared with breast (18%) and prostate (14%) patients ($p < 0.001$). Patients with lung (17%) and prostate (13%) cancer were also more likely than breast patients (6%) to have diabetes ($p = 0.049$).

The age distribution did not vary substantially by country, but per-centre analyses highlight some heterogeneity in patients and treatments across centres/countries that might pose a challenge when attempting to validate predictive models and biomarkers. For example, cancer patients tended to have a higher BMI in Spain and the UK than in the other countries (Supplementary Fig. S1a), and the proportion of *in situ* breast tumours ranged from <10% (Italy, Spain, UK) to 25% in the US centre. About one third of the breast cancer patients received adjuvant or neoadjuvant chemotherapy, with rates varying from ~20% (France, UK, US) to >40% (Italy, Spain). Half of the breast cancer patients were treated with intensity-modulated radiotherapy (IMRT), with a lower proportion in France and no IMRT in Italy and the US. Breast cancer patients who received IMRT ranged from <20% (France, Italy, Spain, US) to >80% (Belgium, UK). Most patients received an additional boost (68%), with lower proportions in the US (40%) and UK (10%). Hypofractionation rates were highest in Belgium and UK.

For the prostate cancer patients, 27% had a prostatectomy prior to radiotherapy (Table 2). As patients with and without previous prostatectomy differ, their characteristics are reported separately. Post-prostatectomy patients were younger, reported fewer comorbidities (e.g. hypertension: $p < 0.001$), had a higher risk class and received lower radiotherapy doses than those who underwent radical radiotherapy. The proportion of patients having a prostatectomy prior to radiotherapy varied from 7% in the UK to 55% in Belgium (Supplementary Fig. S1b). In terms of their treatment, most prostate cancer patients received 74–81 Gy with 1.8–2.0 Gy per fraction (68% of the radically irradiated patients) or 66–72 Gy with 1.8–2.0 Gy per fraction (66% of the post-prostatectomy patients). About one third of the radically treated patients and 10% of the post-prostatectomy patients received hypofractionation regimens. Most patients received Rapid arc/VMAT radiotherapy, except in Spain where 3D-conformal radiotherapy and brachytherapy were used (Supplementary Fig. S1c). In the US centre, about half of patients underwent brachytherapy. The proportion receiving hormone treatment varied from 13% (Germany) to about 80% (Belgium, UK). About 26% of the patients received hypofractionation with highest rates in Belgium, the Netherlands and UK (Supplementary Fig. S1d).

For the lung cancer patients (Table 3), 9% had surgery prior to radiotherapy with the highest proportion in Spain (19%, Supplementary Fig. S1e). About half of the patients received chemotherapy, mostly applied concurrently. Radiotherapy techniques varied widely across countries with the highest IMRT rates in Belgium and the US (Supplementary Fig. S1f). Most French patients were treated with stereotactic radiotherapy. Tomotherapy was only used at the Italian site. Moderate hypofractionation rates were highest in Belgium, Italy, the Netherlands and UK (Supplementary Fig. S1g).

### *Baseline levels of toxicity and quality-of-life scores*

The pre-radiotherapy baseline level of adverse effects for both healthcare professional rated CTCAE v4.0 scoring as well as patient reported outcomes are presented in Supplementary Figs. S2a–2d by cancer type. They highlight that across all cancers and toxicities healthcare professional graded scores are lower than patients' grades, in particular for breast pain, certain genitourinary prostate symptoms and lung toxicities. Healthcare professional rated baseline toxicity data were available for >99.8% of the patients with radiotherapy data: 2056 breast, 1758 prostate and 529 lung. PROs were filled in by 2000 breast (97.2%), 1681 prostate (95.5%) and 462 lung (87.2%) cancer patients. In general, adverse effects grade $\geq$2 evaluated by a physician were low at baseline (particularly for gastrointestinal related toxicities in prostate cancer patients) and

**Table 1**
Baseline characteristics of the REQUITE breast cancer patients.

| Characteristics | | Breast cancer patients ($N$ = 2057) |
|---|---|---|
| Age at enrolment | Median (range), years | 58 years (23–90) |
| BMI | Mean (standard deviation), kg/m$^2$ | 26.5 kg/m$^2$ (±5.6) |
| Smoking status at diagnosis | Current | 365 (18%) |
| | Former | 514 (25%) |
| | Never | 1156 (56%) |
| Selected comorbidities | Diabetes, antidiabetics | 127 (6%) |
| | Heart disease | 143 (7%) |
| | Delayed healing >3 weeks post-surgery | 52 (3%) |
| | Post-operative haematoma | 260 (13%) |
| | Post-operative oedema | 145 (7%) |
| | Post-operative infection | 91 (4%) |
| Family history of breast cancer | First degree relatives | 410 (20%) |
| Tumour size (pre-radiotherapy) | *in situ* | 252 (12%) |
| | T1-T2 | 1728 (84%) |
| | T3, T4 | 16 (<1%) |
| Nodal status (pre-radiotherapy) | Negative | 1488 (72%) |
| | Positive | 394 (19%) |
| Tumour histology | Infiltrating ductal | 1318 (64%) |
| | Other (including lobular, in situ, mixed) | 739 (36%) |
| Oestrogen receptor positive | | 1667 (81%) |
| HER2 positive | | 1581 (10%) |
| Additional cancer treatment | Chemotherapy | 638 (31%) |
| | Tamoxifen, aromatase inhibitors | 1574 (77%) |
| | Anti-HER2, targeted therapy | 170 (8%) |
| Radiotherapy | IMRT | 1018 (49%) |
| Patients without boost* | | 662 (32%) |
| | 50–56 Gy/≤ 2.0 Gy*2 | 203 (31%) |
| | 39.9–45 Gy/2.5–3.2 Gy | 452 (68%) |
| | 28.5–32.5 Gy/5.7–6.5 Gy | 7 (1%) |
| Patients with simultaneous boost** | | 257 (12%) |
| | 50–52 Gy/≤ 2.0 Gy + 6–15.6 Gy/0.2–0.5 Gy (partly plus 2 Gy)*3 | 179 (70%) |
| | 40.05 Gy/2.67 Gy + 6.75–10.95 Gy/0.45–0.73 Gy | 35 (14%) |
| | 28.5 Gy/5.7 Gy + 4–6 Gy/0.8–1.2 Gy | 43 (17%) |
| Patients with sequential boost** | | 1138 (55%) |
| | 50 Gy/≤2.0 Gy + 9–20 Gy/2–3 Gy*4 | 641 (56%) |
| | 39.6–49.5 Gy/2.25–3.6 Gy + 10–16 Gy/2.0–3.99)*5 | 380 (33%) |
| Brachytherapy boost** | | 117 (10%) |
| | 50.0 Gy/2.0 Gy + 8.5–10 Gy/8.5–10 Gy | 40 (34%) |
| | 39.9–42.56/2.66 Gy + 8.5–10 Gy/5–10 Gy | 77 (66%) |

BMI: Body mass index. IMRT: Intensity modulated radiation therapy.
*RT regimens: Total whole breast irradiation dose (WBI)/fraction dose.
**RT regimens: Total whole breast irradiation (WBI)/fraction dose + total boost dose/fraction dose.
*2Including 6 patients with WBI dose <50 Gy.
*3Including 24 patients with 4 Gy or 10 Gy from sequential boost in 2 Gy fractions; 1 patient with WBI dose <50 Gy.
*4Including 24 patients with WBI dose <50 Gy; 3 patients with boost dose <9 Gy or boost fraction dose >3 Gy.
*5Including 4 patients with boost dose <10 Gy; 2 patients with boost dose 18.6 Gy.
BMI: Body mass index. IMRT: intensity-modulated radiotherapy. WBI: Whole breast irradiation dose. Numbers might not add up due to missing data.

usually <10%. Notable exceptions were the high frequencies of sexual dysfunctions among prostate cancer patients (e.g. 27% erectile dysfunction) and dyspnoea in lung cancer patients (23%).

A total of 2000 breast (97.2%), 1665 prostate (94.6%) and 457 lung cancer patients (86.2%) filled in the EORTC QLQ C30 quality-of-life baseline questionnaire (Supplementary Table S4, transformed into a scale of 0–100). Supplementary Table S5 shows the differences in baseline toxicities and quality-of-life data by country.

### *Summary of data available*

Supplementary Table S6 provides an overview of the REQUITE resource and summarises the comprehensive data and samples available at the end of the funding period (October 2018). More than 45,000 physician and over 50,000 patient forms (including quality-of-life, fatigue and physical activity) were collected. Breast photos at baseline and 24-month of over 1500 breast cancer patients were scored to assess changes in breast appearance. More than 17,000 DVHs and 12,000 DICOMs for organs at risk were uploaded. Imputed genotype data are available for >4200 REQUITE patients with European ancestry (55.2 billion genotypes). About 1300 patients also have data on the radiation-induced lymphocyte assay. A PAXgene tube was collected from >3000 patients for future RNA analysis.

As of October 2018, follow-up CTCAE v4.0 toxicity data are available for about 1700 breast (82% of recruited patients) and 1430 prostate (79%) at 24 months and for 330 lung cancer patients (59%) at 12 months. For breast, common toxicity rates with grade ≥2 at 2 years were ~5–13%, for prostate below 5% for GI toxicities, ~3–8% for GU toxicities and ~20–31% for sexual problems. Common lung toxicity rates at one year were ~4–7% and dyspnoea rates at 27%.

## Discussion

REQUITE is one of the largest radiotherapy patient cohorts with standardised longitudinal data and sample collection from multiple hospitals and countries. To overcome issues of heterogeneity encountered in previous cohorts, considerable efforts were made to ensure standardisation of data collection, which include quality assurance and quality control measures. It is hoped that other studies will use the CRFs and multi-lingual CTCAE v4.0 PRO questionnaires to further improve data collection and our ability to validate models and biomarkers of radiosensitivity [20]. Although established as a resource to validate predictive models, we anticipate its use also in discovery science, e.g., in contributing data to radiogenomics studies identifying common genetic variants associated with risk of radiotherapy toxicities [13].

**Table 2**
Baseline characteristics of the REQUITE prostate cancer patients.

| Characteristics | Radical radiotherapy (*N* = 1277) | Post-prostatectomy patients (*N* = 483)[#] |
|---|---|---|
| Age at enrolment (median, range) | 71 years (42–88) | 66 years (46–85) |
| BMI (mean, standard deviation) | 27.7 kg/m$^2$ (±4.5) | 27.3 kg/m$^2$ (±3.6) |
| Smoking status at diagnosis | | |
| Current | 165 (13%) | 84 (17%) |
| Former | 600 (47%) | 221 (46%) |
| Never | 508 (40%) | 175 (36%) |
| Selected comorbidities + pre-radiotherapy surgery | | |
| Diabetes, antidiabetics | 185 (14%) | 51 (11%) |
| Hypertension, hypertensive medication | 750 (59%) | 237 (49%) |
| Use of statins, cholesterol lowering drugs | 486 (38%) | 163 (34%) |
| History of heart disease | 289 (23%) | 83 (17%) |
| Previous abdominal surgery | 675 (53%) | 175 (36%) |
| TURP | 104 (8%) | 10 (2%) |
| Family history of prostate cancer (1st degree) | 220 (17%) | 100 (21%) |
| Tumour size (pre-radiotherapy)[*] | | |
| T1 | 377 (30%) | – |
| T2 | 554 (43%) | 202 (42%) |
| T3, T4 | 220 (16%) | 247 (51%) |
| Nodal status (pre-radiotherapy)[*] | | |
| Negative | 1093 (86%) | 215 (45%) |
| Positive | 59 (5%) | 75 (16%) |
| Gleason's score | | |
| Gleason < 7 | 244 (19%) | 70 (14%) |
| Gleason 7 | 709 (56%) | 296 (61%) |
| Gleason 8–10 | 320 (25%) | 119 (24%) |
| Pre-diagnostic biopsy PSA (median, range) | 9.6 ng/ml (0.35–300) | 8.0 ng/ml (0.1–270) |
| ≤10 ng/ml | 681 (53%) | 283 (59%) |
| 10–20 ng/ml | 337 (26%) | 94 (19%) |
| >20 ng/ml | 246 (19%) | 53 (11%) |
| Risk class (National Comprehensive Cancer Network version1.2018) | | |
| Low (T1-T2a + Gleason ≤ 6 + PSA < 10 ng/ml) | 110 (9%) | (<1%) |
| Intermediate (favourable plus unfavourable) (T2b-T2c OR Gleason = 7 OR PSA 10–20) | 618 (48%) | 180 (37%) |
| High plus very high (T3-T4 OR Gleason 8–10 OR PSA > 20 ng/ml) | 543 (44%) | 287 (59%) |
| Hormonal treatment | | |
| None | 291 (23%) | 248 (51%) |
| Yes | 986 (77%) | 235 (49%) |
| Radiotherapy | | |
| *EBRT* | | |
| 3D conformal radiotherapy | 187 (16%) | 101 (21%) |
| IMRT | 145 (12%) | 87 (18%) |
| VMAT | 866 (72%) | 295 (61%) |
| Pelvic radiotherapy | 363 (28%) | 161 (33%) |
| Total EBRT dose (Gy), without brachytherapy | 54.4–81.0 Gy | 51.2–77.0 Gy |
| EBRT regimens without brachytherapy (*N* = 1578, 90%) | | |
| 1.6 Gy fraction dose; 59.2 Gy total dose | 2 (<1%) | – |
| 1.8–2.0 Gy fraction dose; 66–72 Gy total dose | 10 (<1%) | 317 (66%) |
| 1.8–2.0 Gy fraction dose; 74–81 Gy total dose | 745 (68%) | 116 (24%) |
| 2.1–2.5 Gy fraction dose; 63–77 Gy total dose | 106 (10%) | 20 (4%) |
| >2.5–3.4 Gy fraction dose; 51.2–69.25 Gy total dose | 231 (21%) | 30 (6%) |
| EBRT regimens with brachytherapy (*N* = 103, 6%) | | |
| 1.8–2.0 Gy fraction dose; 45–50.4 Gy[§] | 24 (23%) | – |
| 2.45–2.54 Gy fraction dose; 36.8–38.1 Gy | 79 (77%) | – |
| *Brachytherapy* | 182 (14%) | – |
| Brachytherapy alone | 79 (43%) | – |
| HDR | 8 (10%) | – |
| LDR | 71 (90%) | – |
| HDR dose (Iridium; median, range) | 19 Gy (19–25) | – |
| LDR dose (mostly iodine; median, range) | 145 Gy (124–160) | – |
| Brachytherapy + EBRT | 103 (57%) | – |
| HDR | 84 (82%) | – |
| LDR | 19 (18%) | – |
| HDR dose (Iridium, Cobalt-60; median, range) | 15 Gy (13–21) | – |
| LDR dose (mostly palladium; median, range) | 100 Gy (85–108) | – |

BMI: Body mass index. EBRT: External beam radiation therapy. HDR: High dose rate. IMRT: Intensity-modulated radiation therapy. LDR: Low dose rate. PSA: Prostate specific antigen. TURP: transurethral resection of the prostate. VMAT: Volumetric Arc Therapy.
[#]salvage (prostatectomy ≥12 months prior to RT) 56% and adjuvant (prostatectomy <12 months prior to RT) 44%. [*]Clinical T/N stages for radical radiotherapy patients and pathological T/N stages for post-prostatectomy patients. [§]Including 1 patient with incomplete dosage. Data might not add up to 100% due to missing data.

We successfully showed that it is possible to collect standardised clinical data prospectively from multiple hospitals across countries, given adequate funding to perform the labour intensive work. The actual accrual of 84% of target (4438 versus 5300) was reduced due to some centres being slow to open and the constraints due to funding limited the possibility of extending the recruitment period. There was a high return rate for questionnaires, e.g. 76% for 24 months PRO data and 81% healthcare professional reported toxicity in prostate cancer patients. In comparison single centre studies in prostate cancer patients carried out up to two years following radiotherapy reported overall questionnaire completion rates of 50% [30], 85% in ProtecT [31], and 69% in CHHiP [32]. The REQUITE study also aimed at a low level of missing data, e.g. only 2% of the 1665 prostate cancer patients with EORTC C30 forms had ≥10% missing quality-of-life items at baseline. In a review of randomised control trials on the extent of missing quality-of-life data, 36% of the studies had >10% missing items and for 21% the level of missing data was unclear [33].

The REQUITE baseline toxicity rates and quality-of-life scores were comparable with other studies. For example, 27% of the prostate cancer patients recruited reported grade ≥2 erectile dysfunction at baseline compared with 32% in the radiotherapy group of

**Table 3**
Baseline characteristics of the REQUITE lung cancer patients.

| Characteristics | | Lung cancer patients ($N$ = 530) |
|---|---|---|
| Sex | Female | 158 (30%) |
| | Male | 370 (70%) |
| Age at enrolment | Median (range), years | 69 years (39–91) |
| BMI | Mean (standard deviation), kg/m$^2$ | F: 25.8 (±6.2) |
| | | M: 26.6 (±4.8) |
| Smoking status at diagnosis | Current | F: 65 (41%) M: 148 (40%) |
| | Former | F: 78 (49%) M: 212 (57%) |
| | Never | F: 15 (9%) M: 8 (2%) |
| Selected comorbidities | COPD | F: 65 (41%) M: 150 (41%) |
| | Tuberculosis of the lung | F: 3 (2%) M: 10 (3%) |
| | Diabetes, antidiabetics | F: 19 (12%) M: 69 (19%) |
| | Hypertension, hypertensive medication | F: 78 (49%) M: 222 (60%) |
| | Heart disease | F: 32 (20%) M: 129 (35%) |
| Family history of lung cancer | First degree relatives | 94 (18%) |
| Tumour histology | Squamous | 176 (33%) |
| | Adenocarcinoma | 194 (37%) |
| | Small cell | 20 (4%) |
| | Other, undifferentiated | 51 (10%) |
| | Radiological diagnosis, unknown | 89 (17%) |
| Clinical tumour size stage (pre-radiotherapy) | 0 | 11 (2%) |
| | 1a, 1b | 180 (34%) |
| | 2a, 2b | 139 (26%) |
| | 3 or 4 | 193 (36%) |
| Clinical nodal stage (pre-radiotherapy) | Negative | 235 (44%) |
| | Positive | 289 (55%) |
| Tumour stage at diagnosis | I-II | 232 (44%) |
| | IIIa, IIIb | 287 (54%) |
| Additional cancer treatment | Chemotherapy | 271 (51%) |
| | – Sequential chemotherapy | 62 (23%) |
| | – Concurrent chemotherapy | 203 (75%) |
| | – Consolidation chemotherapy | 6 (2%) |
| | Surgery | 48 (9%) |
| Radiotherapy technique | 3D conformal radiotherapy | 161 (30%) |
| | ARC therapy (VMAT, RapidARC) | 70 (13%) |
| | IMRT | 140 (26%) |
| | Tomotherapy | 12 (2%) |
| | Stereotactic body radiotherapy | 147 (28%) |
| Radiotherapy regimens | | |
| Conventional fractionation/moderate hypofractionation | | 383 (72%) |
| | 1.5 Gy fraction dose, 30–42 fractions | 48 (13%) |
| | 1.8–1.99 Gy fraction dose, 25–39 fractions | 31 (8%) |
| | 2.0 Gy fraction dose, 21–40 fractions | 179 (47%) |
| | >2.0–3.0 Gy fraction dose, 20–33 fractions[#1] | 109 (28%) |
| | 4.0–5.0 Gy fraction dose, 12–24 fractions[#2] | 16 (4%) |
| SABR | | 147 (28%) |
| | 3 fractions à 18–20 Gy, total of 45–60 Gy | 30 (20%) |
| | 4 fractions à 8.75–15 Gy, total of 35–60 Gy | 64 (44%) |
| | 5 fractions à 10–15.27 Gy, total of 50–76.39 Gy | 30 (20%) |
| | 8 fractions à 7.5–9.18 Gy, total of 60–73.44 Gy | 23 (16%) |

BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. F: Female. IMRT: Intensity-modulated radiation therapy. M: Male. SABR: Stereotactic ablative radiotherapy. VMAT: Volumetric Arc Therapy.
[#1]Including 5 patients with incomplete dosage. [#2]Including 1 patient with incomplete dosage.
Numbers may not add up to 100% due to missing data.

the ProtecT randomised trial [34]. In lung cancer patients the rate of physician reported grade ≥2 dyspnoea at baseline in REQUITE was 23% compared with 15% reported elsewhere [35]. A systematic review of toxicity reporting in clinical trials identified that only 43% reported baseline data [36], highlighting the lack of reporting standards for adverse events and the need to improve the collection of baseline data. A study with 367 cancer patients [37] reported an EORTC C30 general health status/quality-of-life score of 67 at start of radiotherapy which is comparable with the REQUITE scores ranging from 61 to 74 at baseline.

We found that healthcare professional grading of adverse effects was lower than patient reported scores across three cancer types (Supplementary Figs. 2a–2d). These findings in a multinational setting confirm a previous report [36]. Although the collection of PRO data has become established in clinical trials, challenges remain to increase understanding of clinical relevance, and to increase use in routine clinical practice [38]. Definition of treatment-induced clinically meaningful changes requires standardisation and is currently subjective [39]. The REQUITE resource will be useful for future studies developing standards that are applicable across countries.

Randomised controlled trials comparing the efficacy of different treatments provide a route for collecting multi-centre data, but are limited by restricted inclusion and exclusion criteria. Our study cohort reflects "real world" clinical radiotherapy practice across countries and will form the basis for further projects to improve prediction before treatment of those with a higher risk of long-term adverse effects after radiotherapy. The database can also be used to study various clinical questions regarding the determinants of long-term adverse effects and the longitudinal effect on quality-of-life. REQUITE will also enable a better understanding of the scale of radiotherapy toxicity in a multi-national setting and can be used to compare similarities and differences between countries. Country-specific analyses are possible. For example, fewer US lung cancer patients smoked at time of diagnosis compared to the other countries; male patients from one Spanish recruitment centre came from rural areas with lower education levels compared to other recruitment centres; and breast cancer patients in Germany were more reluctant to answer questions on sexual activity than in other countries (Supplementary Fig. S3).

The strengths of the REQUITE study are the scale of data collected, use of standardised CRFs, the centralised database and bio-

bank, the quality control methods used to maximise data quality, and the availability of genotyping data. The majority of cancer patients consented to share their data and samples with other researchers outside the REQUITE project. A data and sample access committee has been established to maximise dissemination of the resource and a cost-recovery model implemented to ensure sustainability contact. External researchers can contact requite@manchester.ac.uk for further information on how to apply for access to the data (fees apply). The www.requite.eu website provides an overview of the project and a summary of the patient characteristics. Limitations of the study include poor recruitment of lung cancer patients, follow-up currently limited to 2 years (with extension planned) and the small number of cancer types studied.

As several toxicities such as breast fibrosis may emerge many years after completion of radiotherapy, follow-up beyond two years is desirable. A longer follow-up would also allow assessment of fluctuations in symptoms over time. Funding for an extension of the follow-up to five years in some centres was secured through an ERA PERMED grant.

In summary, we successfully established an international cohort of more than 4400 cancer patients with radiotherapy and longitudinal data for future epidemiological studies. The comprehensive centralised database and linked biobank is a valuable resource for the radiotherapy community for validating predictive models and biomarkers.

## Acknowledgements

REQUITE received funding from the European Union's Seventh Framework Programme for research, technological development, and demonstration under grant agreement no. 601826. We sincerely thank all patients that participated in the REQUITE study and all REQUITE staff involved at the following sites: Belgium: Ghent University Hospital; KU Leuven. France: ICM Montpellier, CHU Nîmes (Department of Radiation Oncology, CHU Nîmes, Nîmes, France). Germany: Praxis für Strahlentherapie an der Stadtklinik Baden-Baden; Klinikum Darmstadt GmbH; Zentrum für Strahlentherapie Freiburg; Städtisches Klinikum Karlsruhe; St. Vincentius-Kliniken gAG Karlsruhe; Klinikum der Stadt Ludwigshafen GmbH; Universitätsklinikum Mannheim: Anke Keller and Christiane Zimmermann; Strahlentherapie Speyer. The researchers at DKFZ also thank Dr Sabine Behrens and Kerstin Pieper. Italy: Fondazione IRCCS Istituto Nazionale dei Tumori, Milano; Candiolo Cancer Institute – FPO, IRCCS. The Netherlands: Sylvie Canisius at Maastro Clinics, Maastricht. Spain: Santiago: Complexo Hospitalario Universitario de Santiago. Ana Vega is supported by Spanish Instituto de Salud Carlos III (ISCIII) funding, an initiative of the Spanish Ministry of Economy and Innovation partially supported by European Regional Development FEDER Funds (INT15/00070, INT16/00154, INT17/00133; PI16/00046; PI13/02030; PI10/00164), and through the Autonomous Government of Galicia (Consolidation and structuring program: IN607B); Barcelona: The authors acknowledge the Cellex Foundation for providing research facilities and equipment. S. Gutiérrez-Enríquez is supported by the Miguel Servet Program from ISCIII (CPII16/00034). UK: University Hospitals of Leicester NHS Trust, Dr Tim Rattay was funded by a National Institute of Health Research (NIHR) Doctoral Research Fellowship (DRF-2014-07-079); Manchester: Jacki Routledge at Christie NHS Foundation Trust, Manchester. Catharine West, Ananya Choudhury and Rebecca Elliott are supported by NIHR Manchester Biomedical Research Centre and Catharine West is supported by Cancer Research UK (C1094/A18504, C147/A25254); University Hospitals Birmingham NHS Foundation Trust; Derby Hospitals NHS Foundation Trust; Nottingham University Hospitals NHS Trust; Salford Royal NHS Trust. USA: Mount Sinai Hospital, New York; Memorial Sloan Kettering Cancer Center, New York.

## Conflict of interest

D. Azria is involved in the creation of the start-up NovaGray in 2015. D. De Ruysscher: none related to the current manuscript. Outside the current manuscript: advisory board of Astra Zeneca, Bristol-Myers-Squibb, Roche/Genentech, Merck/Pfizer, Celgene, Noxxon, Mologen and has received investigator initiated grants from Bristol-Myers-Squibb, Boehringer Ingelheim and AstraZeneca. E. Sperk: none related to the current manuscript. Outside the current manuscript: General speakers bureau Zeiss Meditec, travel support Zeiss Meditec.

The other authors have no conflict of interest to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.034.

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