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Early and late CTCAE and patient-reported outcomes following prostate radiotherapy in the REQUITE cohort

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ABSTRACT

Background: Prospectively collected long-term adverse event data with pre-radiotherapy assessment and regular follow-up reflecting 'real world settings' are still limited. Here, we present the available data on early and long-term outcomes up to eight years after radiotherapy in men with prostate cancer who participated in the international REQUITE cohort study, stratified by treatment modalities and patient characteristics.
Methods: Longitudinal data on pre-radiotherapy, acute and late symptoms up to eight years after radiotherapy were available from 1760 non-metastatic prostate cancer patients recruited in seven European countries and the USA. External beam radiotherapy (EBRT) and/or brachytherapy were given with curative intent between 2014 and 2016 according to local regimens. Gastrointestinal (GI) and genitourinary (GU) symptoms including sexual dysfunction were prospectively assessed by healthcare professionals according to CTCAE v4.0. Patient-reported outcomes were collected.
Results: The highest incidence of clinician-reported grade $\geq$ 2 long-term GI and GU symptoms were for proctitis (12.1%) and haematuria (12.9%) among the EBRT-only treated patients, and proctitis (6.4%) and urinary incontinence (32.4%) among the post-prostatectomy/EBRT patients. Incidence of grade 3 adverse events was below 1.5%, with the only exception of late urinary incontinence in post-prostatectomy patients (10.2%).
Conclusion: The frequency and distribution of GI and GU symptoms in a real-world multicentre cohort of patients following prostate radiotherapy were comparable to those reported in large interventional trials. Our finding highlights the value of standardised data farming approaches like the REQUITE project. Most patients consented to provide their data for future cancer research which is available on request.

1. Introduction

Treatment options for men with localised and locally advanced prostate cancer include prostatectomy, radiotherapy (external beam or brachytherapy, with or without hormone therapy) and active surveillance. Choice is determined by shared decision-making between patient and clinician. The ProtecT trial showed no significant differences in prostate cancer-specific mortality between these three different treatment and monitoring options [1].

Treatment-related long-term gastrointestinal (GI) and genitourinary (GU) symptoms vary by treatment modality and may impair the quality of life of patients [2–4]. When considering radiotherapy, even with recent improvements in radiation delivery, critical organs at risk such as bladder or rectum receive parts of the radiation dose [5]. Doses to organs at risk may vary between different radiotherapy techniques and fractionation schemes.

Outside interventional trials, prospectively collected follow-up data with pre-radiotherapy assessment and regular follow-up evaluation in a standardised way that reflect 'real world settings' are still limited. Data from both observational studies and clinical trials can be heterogeneous and difficult to compare, not least due to differences in the endpoint definitions [6].

The international REQUITE cohort study aimed to build a data and bio repository with standardised prospective data collection for the radiation oncology community for validating predictive models and biomarkers [7]. Here, we present the available data on early and long-term outcomes up to eight years after radiotherapy in men with prostate cancer who participated in the study. The data from this study are available upon request (www.requite.eu) and may be utilised for research purposes. Further details on the lung and breast cancer cohorts within the REQUITE study are published as part of a dedicated article series in this issue.

2. Methods

2.1. Study design

Adult men with confirmed non-metastatic prostate cancer were recruited prior to radiotherapy between 2014 and 2016 at 17 radiation oncology departments in Belgium, France, Germany, Italy, the Netherlands, Spain, United Kingdom, and the United States into the REQUITE cohort study (http://www.requite.eu). Inclusion criteria included treatment with external beam radiotherapy (EBRT) and/or brachytherapy with curative intent according to local standard of care. Both exclusive radiotherapy and post-prostatectomy patients were eligible, with or without hormonal therapy. There was no upper age limit. Exclusion criteria were a metastatic disease, other malignancies in the five years prior to radiotherapy, prior irradiation at the same site, planned use of protons, High Intensity Focal Ultrasound or inability to give informed consent. Blood samples were taken at baseline for genotyping and other biomarker analyses. Patients were prospectively followed annually for at least two years using standardised data collection [7]. For selected REQUITE centres, further data were collected as part of the RADprecise (ERAPerMed JTC2018–244; DRKS00020290) and REQUITEplus (BfS #3619S42261) follow-up extensions, allowing for annual data collection up to eight years after radiotherapy completion. The REQUITE, REQUITEplus, and RADprecise projects (ISRCTN98496463) were approved by local ethical committees, and all patients gave written informed consent.

2.2. Data collection and radiotherapy information

Comprehensive data, including demographics, comorbidities, treatment, symptom information, vital status, and oncologic outcomes were available for 1760 men using standardised case report forms (CRF) and stored in a centralised electronic database. GI and GU symptoms, kidney function, sexual dysfunction (SD) and radiation-induced dermatitis were assessed using Common Terminology Criteria for Adverse Events (CTCAE v4.0). Patient-reported pelvic symptoms, as well as patient-reported outcomes including fatigue and other quality of life-related measures, were collected using standardised validated instruments, including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the Multidimensional Fatigue Inventory (MFI), and the Global physical activity questionnaire (GPAQ). Healthcare professional-reported symptoms and patient-reported outcomes were assessed at baseline before the start of radiotherapy, at the end of radiotherapy and annually up to eight years thereafter.

The REQUITE data resource also includes DICOM-RT for the full radiotherapy course, genotyping data generated using the Illumina Infinium OncoArray500K beadchip and imputed using the 1000 Genomes Project (version 3) as a reference panel, biobank material (DNA and PAXGene samples) [8]. For a subset of patients, whole blood RNA and data on radiation-induced lymphocyte apoptosis (RILA) assays

using an established method and standardisation across laboratories are available [9]. mRNA and microRNA sequencing data are available for around 120 prostate cancer patients in the discovery and 300 in the validation cohort. RILA data is available for around 500 men with prostate cancer.

2.3. Statistical methods

Data availability, including healthcare professional-rated adverse events as well as patient-reported outcomes, was summarised in bar plots (absolute frequencies) and categorised by data collection forms using standardised questionnaires and follow-up time point. Information on vital status frequencies were summarised and presented in tabular form.

Prevalences of all symptoms were calculated at baseline prior to radiotherapy, at the end of radiotherapy (or first follow-up visit for brachytherapy patients), and yearly up to eight years after radiotherapy initiation, separately for EBRT with no brachytherapy and treatment including brachytherapy.

Results were stratified by presence vs. absence of prostatectomy (EBRT only vs. EBRT + Prostatectomy) and by brachytherapy as exclusive treatment vs. brachytherapy as a boost (Brachytherapy only vs. Brachytherapy + EBRT) and reported as absolute and relative frequencies in tables and graphically depicted in bar plots.

In addition, data were grouped and presented by irradiation of lymph nodes (yes vs. no), use of neoadjuvant/adjuvant hormone therapy (yes vs. no), fractionation (<2.2 Gray (Gy) vs. ≥2.2 Gy) and by median age (≤70 years vs. >70 years).

Incidences of early symptoms were calculated by taking the baseline situation into account as explained below for the late adverse event endpoint definition.

Actuarial incidences up to eight years after radiotherapy (late symptoms, excluding assessments at the end of RT) were calculated using the Kaplan-Meier method separately for grade ≥ 1, grade ≥ 2 and grade ≥ 3 symptoms. The endpoint definitions took the baseline scoring of symptoms into account. Therefore, an event is defined as a deterioration compared to baseline. Actuarial incidences of up to eight years are reported in tables. All statistical analyses were carried out using the statistical software R version 4.1.1 (R core team 2022, Vienna, Austria).

3. Results

3.1. Cohort description and data availability

Table 1 shows demographic, disease- and treatment-specific characteristics of 1760 prostate cancer patients enrolled before the start of radiotherapy, further stratified by follow-up participation two years (primary endpoint assessment; $N = 1527$) and ≥ 5 years ($N = 747$) later. The median age at enrolment was 70 years. As some recruiting centres (e.g. USA and certain subsites) did not participate in long-term follow-up and due to impact of the COVID pandemic on research follow-up, there was a shift in the case mix of the population over the course of the study (Table 1). The D'Amico high-risk group was the most prevalent at enrolment (50%) and two-year follow-up (49%), while at five years its prevalence was similar to the intermediate-risk class (44% vs 45%, respectively). The proportion of patients who underwent prior prostatectomy increased from 27% before radiotherapy to 33% beyond 5 years of follow-up, while the fraction of patients who received neoadjuvant/adjuvant hormone therapy remained largely stable at around two-thirds. The proportions of patients who received short-term ADT with a duration of less than including six months and of patients who received long-term ADT with a duration of more than six months remained largely stable throughout the follow-up period, at just over 50% and 15% respectively. Fewer patients treated with hypofractionation remained in the cohort after five years (4.3% vs. 10%). Around a third of men received pelvic radiotherapy.

Table 1
Characteristics.

Characteristic	Pre-RT, N = 1,760[1]	2 Years, N = 1,527[1]	≥5 Years, N = 747[1]
Age at Enrolment			
Median (IQR)	70 (65, 74)	70 (65, 74)	69 (64, 74)
Range	42–88	42–88	49–88
Country			
Belgium	326 (19%)	300 (20%)	142 (19%)
France	251 (14%)	233 (15%)	207 (28%)
Germany	77 (4.4%)	59 (3.9%)	15 (2.0%)
Italy	195 (11%)	147 (9.6%)	96 (13%)
Netherlands	74 (4.2%)	71 (4.6%)	33 (4.4%)
Spain	284 (16%)	270 (18%)	202 (27%)
UK	509 (29%)	413 (27%)	52 (7.0%)
USA	44 (2.5%)	34 (2.2%)	0 (0%)
D'Amico Risk Classification[2]			
Low risk	122 (9.6%)	106 (9.6%)	54 (11%)
Intermediate risk	521 (41%)	451 (41%)	226 (45%)
High risk	631 (50%)	542 (49%)	221 (44%)
Prostatectomy	483 (27%)	425 (28%)	243 (33%)
Hormone Therapy	1221 (69%)	1058 (69%)	528 (71%)
Duration of Hormone Therapy			
None	539 (31%)	469 (31%)	219 (29%)
Short-term (≤6 months)	963 (55%)	828 (54%)	390 (52%)
Long-term (>6 months)	258 (15%)	230 (15%)	138 (18%)
Radiotherapy			
EBRT regimens without brachytherapy	1578 (90%)	1365 (89%)	708 (95%)
EBRT regimens with brachytherapy	103 (5.9%)	93 (6.1%)	28 (3.7%)
Brachytherapy only	79 (4.5%)	69 (4.5%)	11 (1.5%)
Fractionation			
<2.2 Gy per fraction	1218 (73%)	1037 (71%)	602 (82%)
2.2–2.9 Gy per fraction	290 (17%)	263 (18%)	102 (14%)
3.0–3.4 Gy per fraction[3]	172 (10%)	157 (11%)	32 (4.3%)
EBRT Technique			
3D conformal	288 (17%)	274 (19%)	202 (27%)
IMRT	232 (14%)	209 (14%)	109 (15%)
VMAT	1161 (69%)	975 (67%)	425 (58%)
Pelvic Radiotherapy	524 (31%)	445 (30%)	247 (33%)

EBRT: External beam radiotherapy; Gy: Gray.
[1] n (%); [2] For patients not undergoing prostatectomy.; [3] Patients received hypofractionation and no stereotactic body radiotherapy.

At baseline, CTCAE, patient-reported pelvic symptoms and EORTC QLQ-C30 data were available for more than 94–99% of patients included in the initial 1760 patient cohort, while MFI or GPAQ data were not collected at certain study sites, e.g. not in Belgium. Therefore, baseline MFI/GPAQ data was available for 58% of patients (Fig. 1; Supplementary Table S1). CTCAE data at follow-up time points were available for 92% of the patients at year 1 and 84% at two years. Beyond two years, data were only available for a maximum of 35% of patients at any specific follow-up point due to aforementioned reasons. Vital status and progression data was additionally collected, although data collection beyond two years was not systematically accomplished by all study centres (Supplementary Table S2).

3.2. Symptom prevalence and patient-reported outcomes

Urinary frequency, urinary urgency, and SD symptoms, including erectile dysfunction and ejaculation disorder, were among the most prevalent CTCAE-reported adverse events in the patient cohort, with most grade ≥ 1 at the end of radiotherapy. Patients who underwent prostatectomy more often presented with grade ≥ 2 urinary incontinence (91/415 at two years; Fig. 2a) compared to men who received brachytherapy (4/147), whereas grade 2 urinary retention was more prevalent in the brachytherapy group from the end of radiotherapy (58/182) up to two years later (22/147; Fig. 3a). Fig. 3b shows the absolute frequencies of GI and SD symptoms stratified by brachytherapy. Grade 4 Creatinine raise or Acute Kidney Injury was reported for one patient two

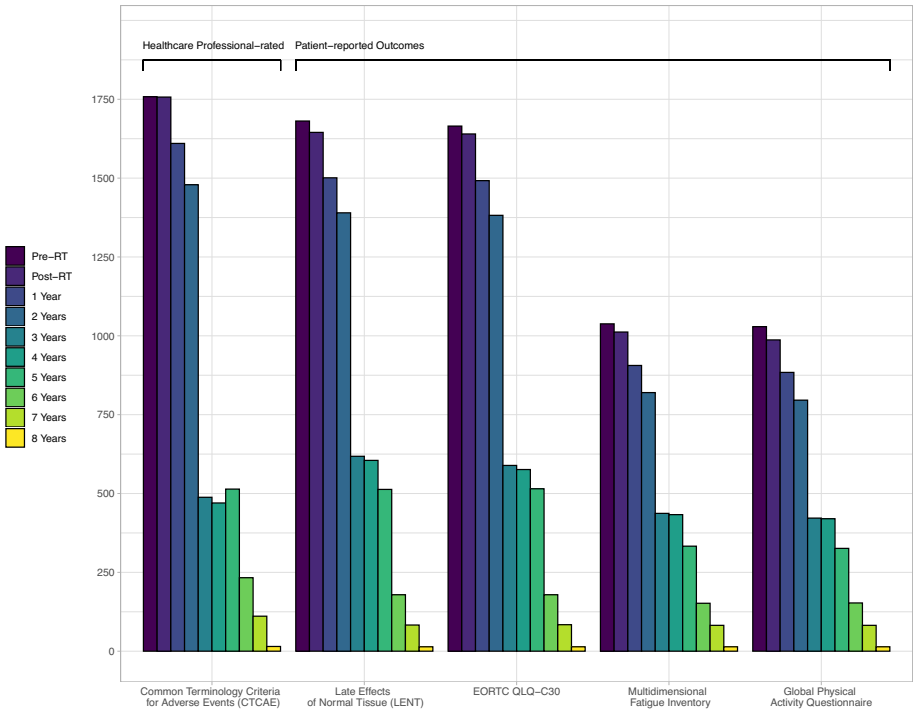


Fig. 1. CRFs by timepoint

years after post-prostatectomy EBRT. Although grade 3 symptoms were rare in the cohort, most were observed for erectile dysfunction before radiotherapy in patients receiving post-prostatectomy EBRT (39/483), followed by EBRT only (23/1093; Fig. 2b).

In stratified analyses, more grade $\geq$ 2 sexual dysfunction symptoms were observed in men who received irradiation of lymph nodes (128/289 vs. 171/627 for ejaculation disorder at two years), less than 2.2 Gy per fraction (182/756 vs. 9/335 for orgasmic dysfunction at the end of RT) and/or hormone therapy (289/742 vs. 54/174 for erectile dysfunction at two years) (Supplementary Figures A-C). Stratification by median age of 70 years showed only minor differences (Appendix D). Patient-reported outcomes showed more frequent use of medications related to diarrhoea, constipation and bladder symptoms, especially at the end of radiotherapy in men who received EBRT only (Appendix E).

3.3. Incidence of acute symptoms and actuarial incidences of late symptoms

The incidences of acute and late symptoms are reported in Supplementary Tables S3-S5. When accounting for baseline symptoms, men treated with EBRT alone generally had higher rates of acute grade $\geq$ 2 proctitis and of acute grade $\geq$ 2 GU symptoms than post-prostatectomy EBRT patients. The highest incidence rates for acute grade $\geq$ 2 symptoms were among the brachytherapy patients (urinary retention 27.8% in patients receiving exclusive low-dose rate brachytherapy and 30.1% in high-dose rate brachytherapy as a boost).

For late symptoms up to two years, the incidence of rectal bleeding was higher in men treated with EBRT only compared to patients with post-prostatectomy EBRT (5.4% vs. 2.4%). The incidences of haematuria and urinary incontinence up to two years were higher in patients with post-prostatectomy EBRT (2.1% and 16.1%, respectively) compared to EBRT-only patients (1.0% and 3.3%, respectively), while the incidence of haematuria up to eight years was higher in the EBRT-only cohort (12.9%) compared to the post-prostatectomy EBRT group (5.3%). The incidence of urinary incontinence up to eight years remained higher in the post-prostatectomy EBRT cohort (32.4%) compared to the EBRT-only group (9.1%). Overall, urinary incontinence and haematuria were the only GI/GU symptoms with grade $\geq$ 3 incidences >1% both during the initial two-year follow-up and also up to eight years, with incidences of 10.2% and 1.4% up to eight years, respectively, among post-prostatectomy EBRT men (vs. 0.6% and 0.8% among men with EBRT alone). The SD endpoints were excluded from the incidence analysis due to the high volume of missing data at two years and beyond that were most likely not missing at random.

4. Discussion

This paper reports data availability and early- and long-term outcomes in an international observational cohort of 1760 non-metastatic prostate cancer patients treated with local radiotherapy regimens and followed up prospectively for at least two years and up to eight years. The centralised REQUITE study database can be used to analyse patterns of outcomes and identify relationships between patient-related factors. REQUITE used the 'data farming' conceptualisation (compared to the 'data mining' concept), with an investment in human resources and data collection and curation [10]. The REQUITE database resulted from a community effort and multi-disciplinary collaboration to reach a complete picture of early- and long-term outcomes after radiotherapy. Key elements include collecting baseline data before radiotherapy, including comprehensive standardised information on comorbidities, oncological treatment, patient-reported outcomes, and standardised follow-up time points up to two years. This prospective approach reduces the under-reporting of mild/low-grade symptoms, information fragmentation, and gaps during the early-mid phase of follow-up.

REQUITE's primary endpoint was adverse event incidence at two years, where data were available for almost the whole prostate cancer cohort. We collected the data beyond the two years within the two separate follow-up projects RADprecise and REQUITEplus. Despite efforts, the data beyond two years are limited for multiple reasons: (i) not all centres participated in the extended follow-up, e.g., subsites did not participate due to funding reasons, and no data were available from the US centres after four years; (ii) The COVID-19 pandemic substantially affected in-person attendance at follow-up visits in the 2020–2022 period, so some patients completed the patient-reported questionnaires

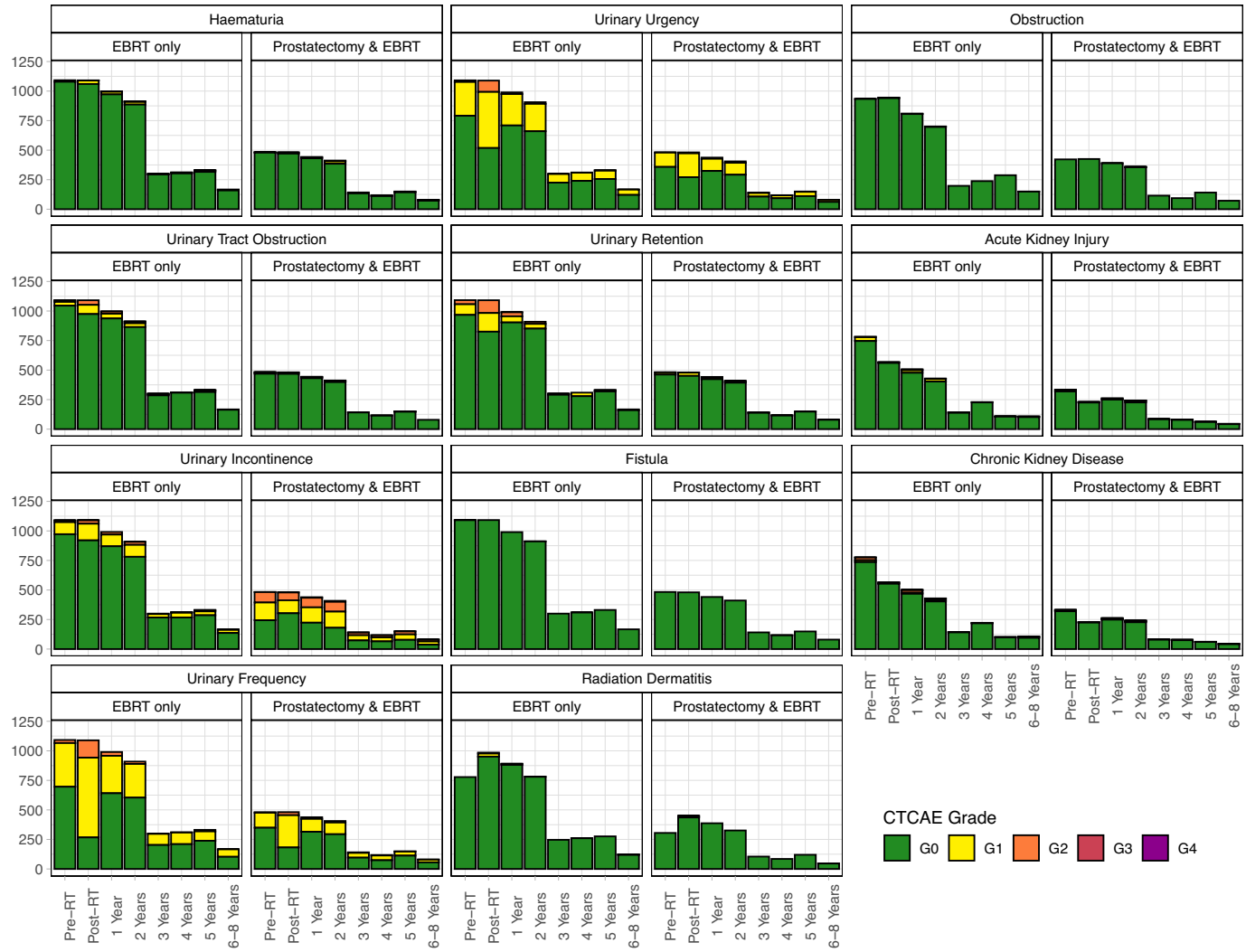


Fig. 2. (a) Absolute frequencies of EBRT GU + UK. (b) Absolute frequencies of EBRT GI + SD.

remotely but are lacking CTCAE scoring or did not participate at all, (iii) some centres limited the follow-up routinely to five years and some others had gaps between two years and five years or delays due to the pandemic and administrative reasons. Most participants in the extended follow-up had only 1–2 further visits between three and eight years. This may have resulted in underreporting of mild/low-grade transient symptoms but should be less detrimental to the scoring of moderate/severe side effects. Few (42%) patients had a follow-up (CTCAE or patient-reported) beyond five years, and very few (0.9%) patients at eight years, which makes adverse events rated beyond five years affected by significant uncertainties.

Information on vital status, biochemical/clinical relapse, and progression is available for participants within two years. Data is more limited beyond this point, which makes the investigation of tumour endpoints and survival challenging given the relatively high long-term survival of prostate cancer.

As not all centres and patients participated in the long-term follow-up, there is a non-random shift in the population case mix. We see an increased proportion of post-prostatectomy patients and a decreased proportion of hypofractionation and high-risk patients in the longer-term data.

Up to two years, data on symptoms were available for most men, with low amounts of missing data for intestinal and urinary symptoms. However, one quarter of patients had missing information on sexual dysfunction, which is a common problem also in other studies. For example, the response rate for sexual symptoms in the ProtecT trial was 72% at baseline, 85% at one year and 83% at two years [11]. The CHHiP trial reported higher response rates for sexual assessment but still 10% missing compared to bowel and bladder scoring [2]. Possible reasons may include reluctance among men with prostate cancer and/or healthcare professionals to address sexual function [12–14]. The missing sexual dysfunction data are unlikely to be at random, i.e. patients with sexual problems may be more hesitant to answer sensitive questions. Factors influencing sexual dysfunction, such as medication for erectile dysfunction, must be accounted for when analysing these endpoints, mainly because the use of hormonal therapy depends on the hospital and risk group (data not shown).

As the kidneys are typically not directly targeted during prostate radiotherapy, there are few studies that explicitly assessed kidney dysfunction, mainly conducted among transplant patients or patients on haemodialysis [15,16]. Although rare, kidney dysfunction was the REQUITE cohort's only grade 4 symptom, which aligns with another study [15]. The absence of clinical signs might have guided the high number of missing data for this adverse event. The available data may well reflect the prevalence of severe symptoms, while mild symptoms may be underrepresented for these endpoints.

Despite differences in patient characteristics, the frequencies of late symptoms were comparable to randomised controlled trials. For

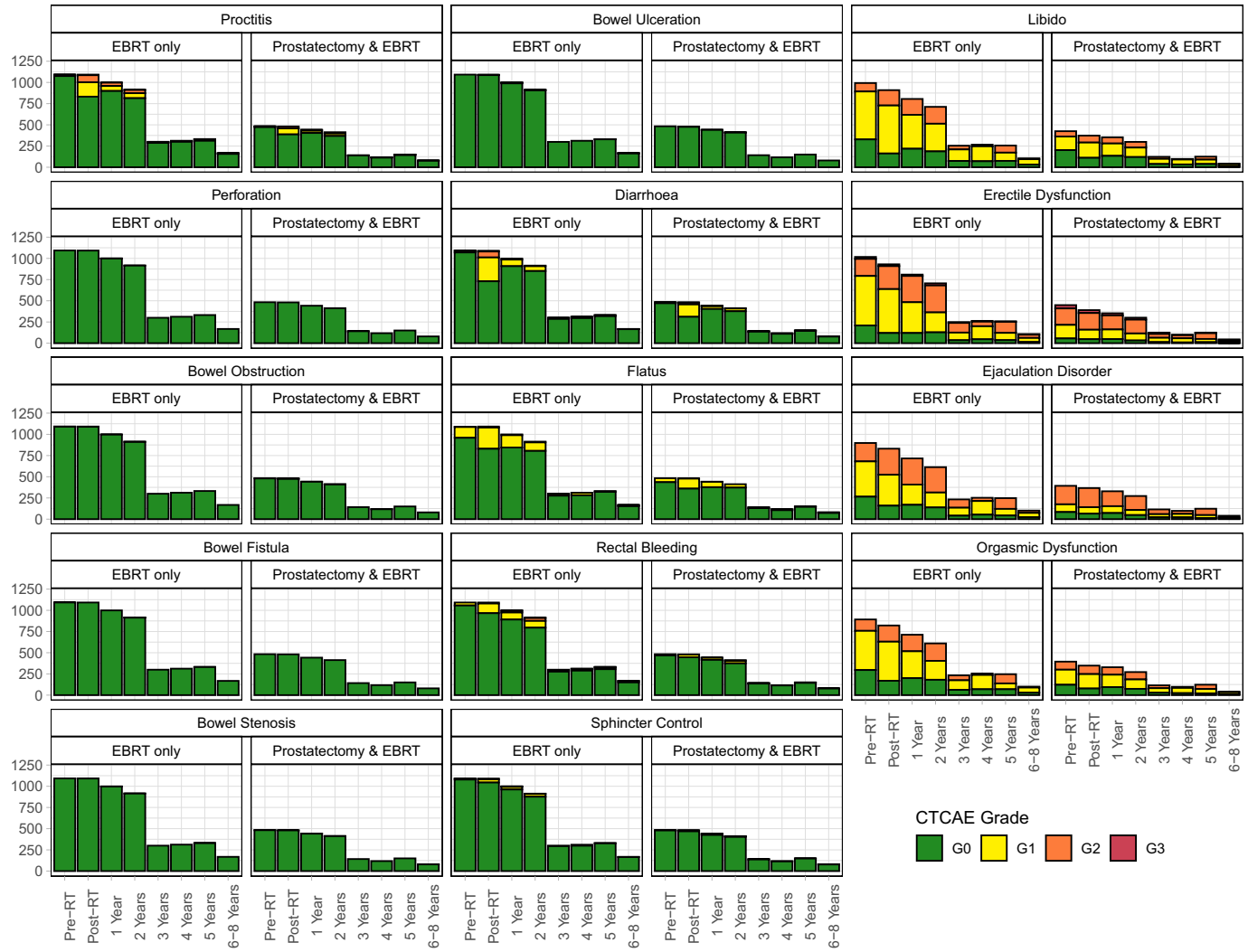


Fig. 2. (*continued*).

example, in the GETUG AFU17 trial for patients with prostatectomy + EBRT, the incidences were 32.1% for any GI grade $\geq$ 1 symptoms and 51.2% for any GU grade $\geq$ 1 symptoms, compared to 32.8% and 54.2% at two years after radiotherapy in the comparable REQUITE group (data in Table S5) [17]. In the HYPRO trial among patients with exclusive EBRT, it was reported that any GI and any GU grade $\geq$ 2 incidences after three years were 17.7% and 39.0% in the standard fractionation group and 21.9% and 41.3% in the hypofractionation group, respectively, while it was 11.2% and 10.9% in the REQUITE exclusive EBRT group after two years and 12.9% and 13.5% at eight years [4]. The late grade $\geq$ 2 incidences reported by the CHHiP trial also among EBRT-only men were lower than 10% both in the standard fractionation and in the hypofractionation group when using RTOG/EORTC scoring and increased to 16% and 17.6% for grade $\geq$ 2 GI symptoms and to 28.8% and 30.9% for grade $\geq$ 2 GU symptoms when considering LENT/SOMA scale [2]. A recent meta-analysis of randomised trials, including CHHiP, on conventionally fractionated or moderately hypofractionated prostate radiotherapy involving more than 6500 patients showed that acute adverse events were associated with late adverse events and a reduced quality of life, highlighting the importance of large prospective cohort studies such as REQUITE, which provide a vital resource for investigating the prediction of and biological mechanisms underlying radiotherapy sensitivity [18].

4.1. Use of data

The presented analyses illustrate standardised healthcare professional- and patient-reported pre-radiotherapy, acute and long-term adverse events in a prospective international cohort of 1760 prostate cancer patients. Furthermore, they provide an important resource for researchers interested in conducting further analyses based on the REQUITE cohort, in which longitudinal adverse events, as well as data on biomarkers, quality of life, fatigue, and physical activity, are available. We collected CTCAE scores and multiple patient-reported outcomes, allowing more robust analyses of subjective, less observable symptoms, such as proctitis and urinary urgency, which are better captured by patient-reported outcomes [18]. Moreover, the international setting of REQUITE enables the examination of cross-cultural dimensions concerning the healthcare professionals' documented side effects and patient-reported measures. The heterogeneity of the population in terms of doses, fractionation, radiotherapy techniques and comorbidities should be accounted for when studying absolute rates of radio-induced symptoms, yet it remains a resource for the investigation of risk associated with patient- and treatment-specific features.

Due to the heterogeneity of the population in terms of doses, fractionation, radiotherapy technique, hormone treatment and comorbidities, we included subgroup analyses for the prevalence of symptoms. This would facilitate the appraisal of the REQUITE resource for possible numbers of analyses on specific clinical/treatment scenarios (e.g., use of

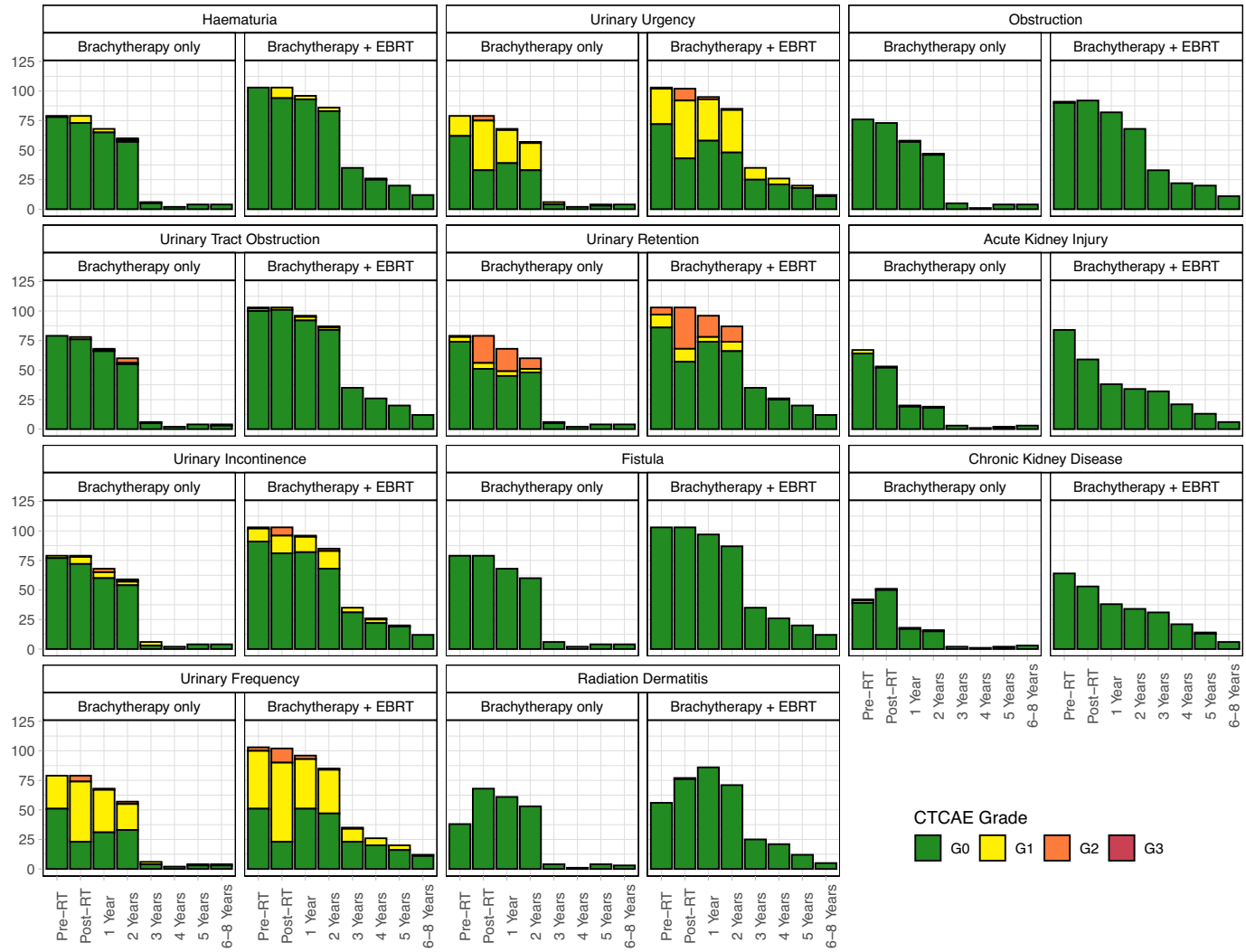


Fig. 3. (a) Absolute frequencies of Brachytherapy GU + UK. (b) Absolute frequencies of Brachytherapy GI + SD.

whole pelvis radiotherapy, hypofractionation, elderly population). For future statistical analyses, the baseline situation, follow-up time and differences in treatment (e.g. lower doses for post-prostatectomy patients) need to be considered.

Despite limited availability of follow-up data beyond the two-year period, driven by the COVID-19 pandemic and a gap in international funding between the end of REQUITE in 2018 and the start of the follow-up projects RADprecise and REQUITEplus in 2019, comprehensive data collection in an observational setting was achieved. Adequate data collection and curation demand substantial investments in human resources.

5. Conclusion

The data reported in this paper illustrate the value of standardised data farming approaches like the REQUITE project. The incidences of GI and GU symptoms in our observational cohort were comparable to large clinical interventional trials. Most patients consented to use of their data in future cancer research. Data is available on request (www.requite.eu). This will help achieve the main goal of REQUITE in establishing reliable prediction models and biomarkers for individual radiation sensitivity and protecting patients at risk of developing significant RT-related symptoms.

Additional REQUITE and/or RADprecise/REQUITEplus Consortium Collaborators are listed in conclusion section

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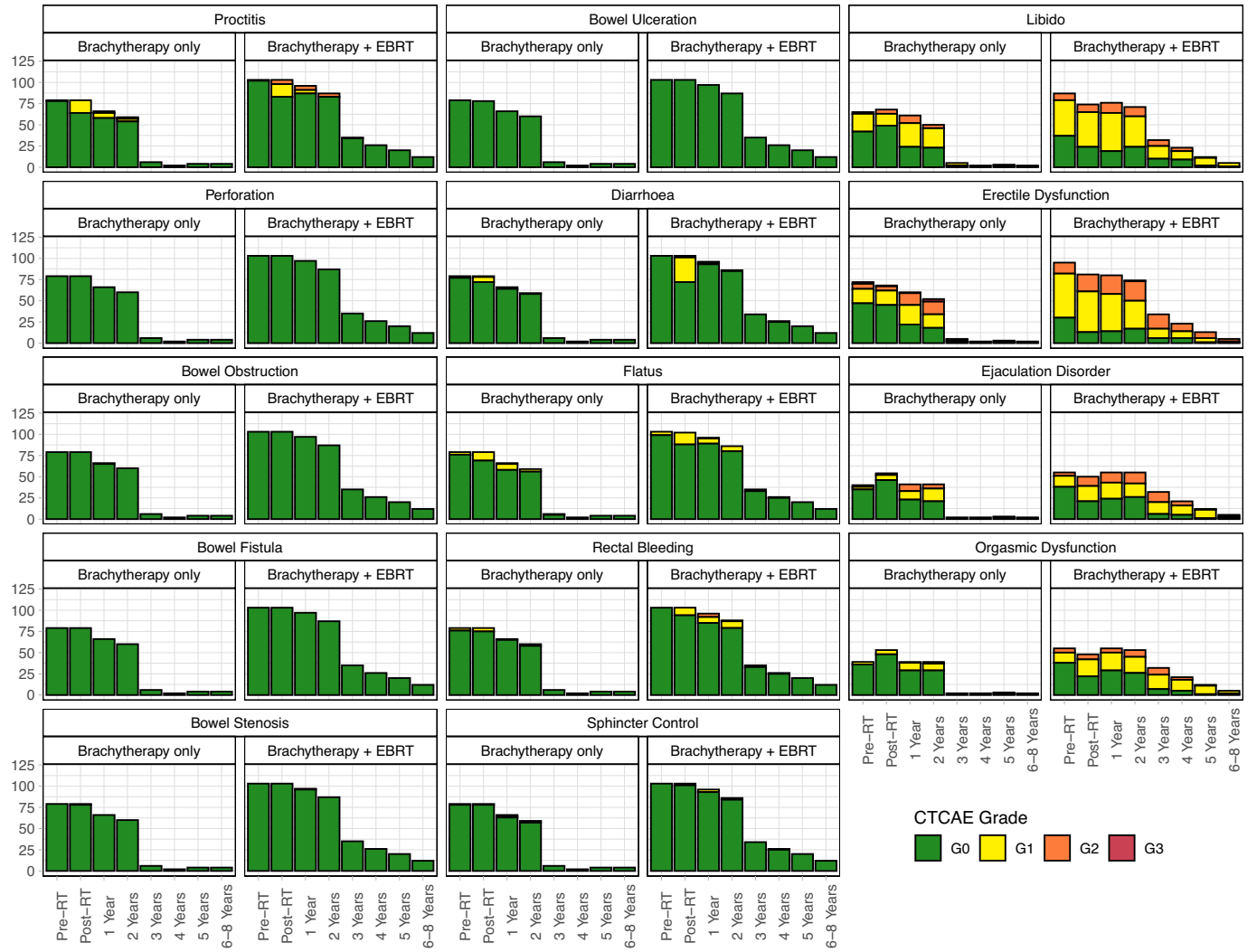


Fig. 3. (*continued*).

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Declaration of competing interest

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