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Original Article

Financial toxicity in cancer patients undergoing radiotherapy in a universal health care system – A prospective multicenter study of 1075 patients



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ABSTRACT

Purpose: To establish and confirm prevalence as well as risk factors of financial toxicity in a large national cohort of cancer patients undergoing radiotherapy in a universal health care system.

Methods: We conducted a prospective cross-sectional study offering a patient-reported questionnaire to all eligible cancer patients treated with radiotherapy in 11 centers in Germany during 60 consecutive days. The four-point subjective financial distress question of the EORTC QLQ-C30 was used as a surrogate for financial toxicity. Confirmatory hypothesis testing evaluated the primary study outcomes: overall prevalence of financial toxicity and its association with predefined risk factors. P-values < 0.05 were considered statistically significant.

Results: Of 2341 eligible patients, 1075 (46%) participated. The prevalence of subjective financial distress (=any grade higher than not present) was 41% (438/1075) exceeding the hypothesized range of 26.04–36.31%. Subjective financial distress was felt “A little” by 26% (280/1075), “Quite a bit” by 11% (113/1075) and “Very much” by 4% (45/1075) of the patients. Lower household income, lower global health status/ quality of life, higher direct costs and higher loss of income significantly predicted higher subjective financial distress per ordinal regression and confirmed these risk factors. Higher psychosocial distress and lower patient satisfaction were significantly associated with higher subjective financial distress in an exploratory ordinal regression model.

Conclusion: The overall prevalence of financial toxicity was higher than anticipated, although reported at low or moderate degrees by most affected patients. As we confirmed risk factors associated with financial toxicity, patients at risk should be addressed early for potential support.

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Traditionally, evaluations of costs and finances in oncology are conducted from a societal or payers perspective [1,2]. While these analyses focus on important aspects such as cost-effectiveness of interventions, the subjective perspective of individual patients

has long been overlooked. Yet by analogy with physical or psychological toxicity, financial toxicity is now an increasingly recognized side effect in cancer patients linked to the disease itself or its treatment. Conceptually, financial toxicity is a possible result of subjective financial distress arising from cancer-related objective financial burden [3]. Objective financial burden may be caused by increased direct costs (e.g. higher expenditures) or indirect costs (e.g. loss of income). The presence of financial toxicity has been

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associated with suboptimal outcomes such as lower overall survival, health-related quality of life or patient satisfaction with care [4,5]. Hence, there is a need to recognize, identify and ideally mitigate financial toxicity.

While first data originated from the US, financial toxicity has also been described in publicly funded health care systems more recently [6,7]. There is, however, still insufficient European data on the prevalence and risk factors of financial toxicity, and its implications continue to be elucidated [8]. Furthermore, there is a lack of data on the prevalence and risk factors of financial toxicity in cancer patients undergoing radiotherapy. However, only a small number of current trials investigate the role of financial toxicity in patients undergoing radiotherapy prospectively [9]. This is remarkable as more than 50% of all cancer patients in Europe receive at least one course of radiotherapy and patients treated with radiotherapy may be exposed to financial issues specific to radiotherapy [10,11]. A recent US-American cross-sectional study, for example, surveyed 396 survivors of oropharyngeal cancer of which two thirds were treated with primary radiotherapy [12]. The study reported that 29% of the patients in this cohort experienced financial toxicity. Yet data on the extent of financial toxicity in cancer patients treated with radiotherapy in a universal health care system was lacking so far. Only recently, a small exploratory, cross-sectional pilot study from our group reported a prevalence of 31% of financial toxicity among 100 cancer patients treated with radiotherapy in a universal health care system [13]. Low income as well as high objective financial burden were identified as potential risk factors of perceived financial toxicity [13]. Prospective validation of these preliminary results is still pending but warranted.

Therefore, we conducted a large multicenter, confirmatory, cross-sectional study in cancer patients undergoing radiotherapy. Primary objectives were to confirm the prevalence of and risk factors for financial toxicity as reported in the pilot study [13]. A secondary objective was to explore additional potential risk factors. This will inform and empower future research to mitigate financial toxicity in cancer patients treated with radiotherapy in universal health care systems.

Materials and methods

Study design

We conducted a preregistered, prospective, confirmatory, multicenter, cross-sectional study offering a questionnaire to all eligible patients during a predefined period of 60 consecutive days from June 2022 (German Clinical Trial Registry No. DRKS00028784, ARO 2022-07) (see Supplementary Document 1 for protocol) [14]. Eligible cancer patients were at the end of a radiotherapy course (\pm 2 days), able to understand the questionnaire, >18 years old, had not participated before in this study, and gave informed consent. The survey was anonymous to maximize data protection. Therefore, all data originates from the questionnaires. We predefined a participation rate of at least 30% to reduce the risk of participation bias. The study was conducted within the framework of the young DEGRO [German Society of Radiation Oncology] working party by 10 academic and one non-academic radiation oncology departments in Germany. Ethics committee approval was acquired for each participating center. The STROBE guideline and CONSORT-PRO extension guideline were respected for reporting the study [15,16].

Questionnaire and variables

We used a previously described questionnaire with minor adaptations [13] (Supplementary Document 2). It was pilot tested in March 2022 on five voluntary, potentially eligible patients. In brief, the paper-based and patient-reported questionnaire covered socio-

demographic, disease-related, occupational and financial data in addition to health-related quality of life per question 29 and 30 of the EORTC QLQ-C30 questionnaire [17]. Objective financial burden was assessed in terms of direct costs and indirect costs related to radiotherapy. Direct costs were assessed by additional expenditures and indirect costs by loss of income. Subjective financial distress was assessed per question 28 of the EORTC QLQ-C30 questionnaire as surrogate for financial toxicity. Importantly, subjective financial distress does not necessarily lead to financial toxicity (i.e., worse outcomes due to financial burden) in every case. Yet subjective financial distress is closest to financial toxicity in the conceptual framework proposed by Witt et al. and has been used previously as surrogate [3,7,18]. Respondents to question 28 are instructed to report “Not at all”, “A little”, “Quite a bit”, or “Very much” subjective financial distress. Minor adaptations introduced questions on the duration of radiotherapy, psychosocial distress per distress thermometer, and a single question (10-point Likert-scaled) on overall patient satisfaction with radiotherapy care by analogy with question 61 of the UK National Cancer Patient Experience Survey [19,20]. The variable patient satisfaction was dichotomized (No < 8 \geq Yes) due to a right sided distribution towards higher satisfaction as previously reported [20]. A detailed analysis of the extent and distribution of psychosocial distress and patient satisfaction will be reported separately.

Sample size calculation and statistical analysis

To confirm or reject the overall prevalence of financial toxicity of 31% as reported in the pilot study, we calculated a minimum sample size of $n = 329$ patients assuming a precision of the estimate of 5% [13]. The prevalence of financial toxicity was assumed for values within the 95% binomial exact confidence interval of 26.04–36.31%. Of note, the outcome and sample size calculation for the prevalence of financial toxicity was based on any grade higher than “Not at all” by analogy with the pilot study. This was done in order to allow for a more robust sample size calculation and hypothesis testing instead of separate calculations for each degree of the response categories. To confirm or reject risk factors of financial toxicity based on the predefined regression model used in the pilot study, we calculated a minimum sample size of $n = 504$ patients [13]. This calculation was based on a logistic regression model using G*Power v3.1.9.6 and is described in detail in the protocol (Supplementary Document 1) [21,22]. All patients recruited during the predefined period of enrollment were considered in the analyses to enhance the representativeness of the sample and power of the analyses.

We used descriptive statistics to illustrate the cohort. For univariate analyses, we employed Spearman’s correlation for continuous or ordinal data and the Chi-square test of independence for categorical data. Missing data were excluded in a pairwise manner. A two-sided independent t-test was used to compare differences in mean values in normally distributed data. We used ordinal regression models for multivariate analyses. The ordinal regression model of the pilot study used a cauchit link function to meet the assumption of proportional odds at a lower sample size. The larger sample size in this confirmatory study allowed the use of a logit link function. P-values < 0.05 were considered statistically significant. The software JASP v0.16.3 (JASP Team [2022], Amsterdam, the Netherlands) and IBM SPSS Statistics v29.0 (IBM Corp. [2020], Armonk, NY, USA) were used for analyses.

Results

Of 2341 eligible patients, 1075 returned the questionnaire (Fig. 1). This resulted in a participation rate of 46% (1075/2341).

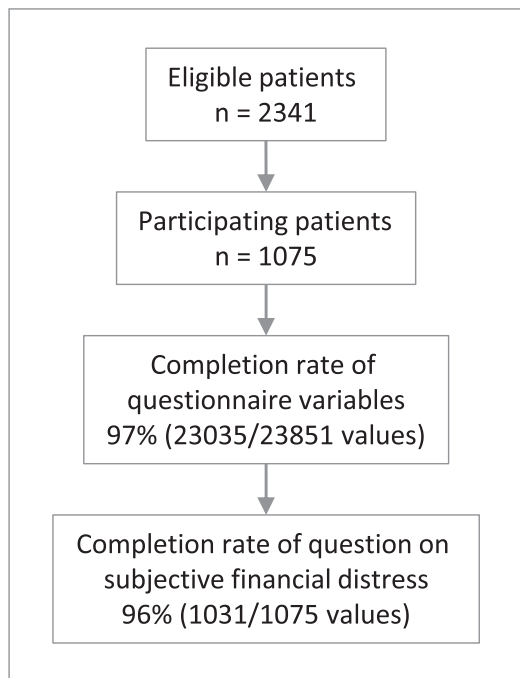


Fig. 1. Study flow diagram.

The completion rate of the questionnaire variables was 97% (23035/23851 values) overall and 96% (1031/1075) concerning the question on subjective financial distress. Forty-nine percent

(529/1075) were female and the median age was 66 years (Table 1). Most patients had breast cancer (26%; 279/1075) followed by prostate (18%; 198/1075) and lung cancer (10%; 103/1075). The median duration of radiotherapy was 21 days.

Objective financial burden in the context of radiotherapy as direct costs was reported by 63% (679/1075), denied by 32% (344/1075) and left unanswered by 5% (52/1075) of the patients (Fig. 2A). Copayments (e.g. for drugs or hospital stays), transportation, and non-refundable supportive care products were reasons for direct costs as reported by 509, 370, and 321 patients, respectively. Indirect costs in terms of loss of income were reported by 27% (290/1075), denied by 69% (746/1075), and left unanswered by 4% (39/1075) of the patients (Fig. 2B). The overall prevalence of subjective financial distress per EORTC QLQ-C30 question 28 was 41% (438/1075) (Fig. 2C), exceeding the predefined range of financial toxicity reported by the pilot study must be rejected due to a higher prevalence in the present study [13]. The degree of subjective financial distress was reported as “A little” by 26% (280/1075), “Quite a bit” by 11% (113/1075) and “Very much” by 4% (45/1075) of the patients. To explore a potential risk of participation bias, the overall rate of subjective financial distress was 42% (108/259) compared to 39% (87/225) in those centers in the lowest versus highest quartile concerning the participation rate (median 50%, interquartile range 40%-59%), respectively. An independent t-test showed that this difference was not statistically significant ($t(4) = 0.5, p = 0.6$).

Next, to confirm risk factors associated with subjective financial distress, we used the multivariate ordinal regression model as developed in the pilot study. Using a logit link function, the assumption of proportional odds was met, as assessed by a full

Table 1

Patient characteristics (n = 1075). Absolute numbers are given in brackets. Numbers may not add up to 100% due to rounding error or missing values. Abbreviations: IQR interquartile range, QoL quality of life, SD standard deviation.

Total number of patients		100% (1075)
Sex	Female: male	49%: 51% (529: 545)
Age		Median: 66; IQR: 57-74
Marital status	Living alone	27% (294)
	Living with partner	72% (773)
Education	< 10 years of school	31% (330)
	10 years of school	35% (379)
	> 10 years of school	32% (342)
Health insurance	Public health insurance	80% (859)
	Of these, exempt from copayments	17% (147)
	Private health insurance	19% (205)
Employment status	Employed	28% (304)
	Self-employed	5% (59)
	Unemployed	8% (86)
	Retired	56% (597)
Net household income	< 1.300 €	19% (205)
	1.301 – 1.700 €	16% (170)
	1.701 – 2.600 €	21% (228)
	2.601 – 3.600 €	15% (163)
	3.601 – 5.000 €	12% (134)
	> 5.000 €	5% (58)
Tumor entity	Breast cancer	26% (279)
	Prostate cancer	18% (198)
	Lung cancer	10% (103)
	Brain tumor (primary or secondary)	7% (79)
	Head and neck cancer	7% (75)
	Gynecological cancer	4% (39)
	Rectal cancer	3% (37)
	Other	22% (242)
Duration of radiotherapy	In days (including weekends)	Median: 21; IQR: 15–30
Concomitant chemotherapy	Yes	26% (280)
	No	73% (784)
Hospitalized during radiotherapy	Yes (in part or throughout)	21% (227)
	No	77% (830)
Global health status/ QoL	per EORTC QLQ-C30	Mean: 55; SD: 22

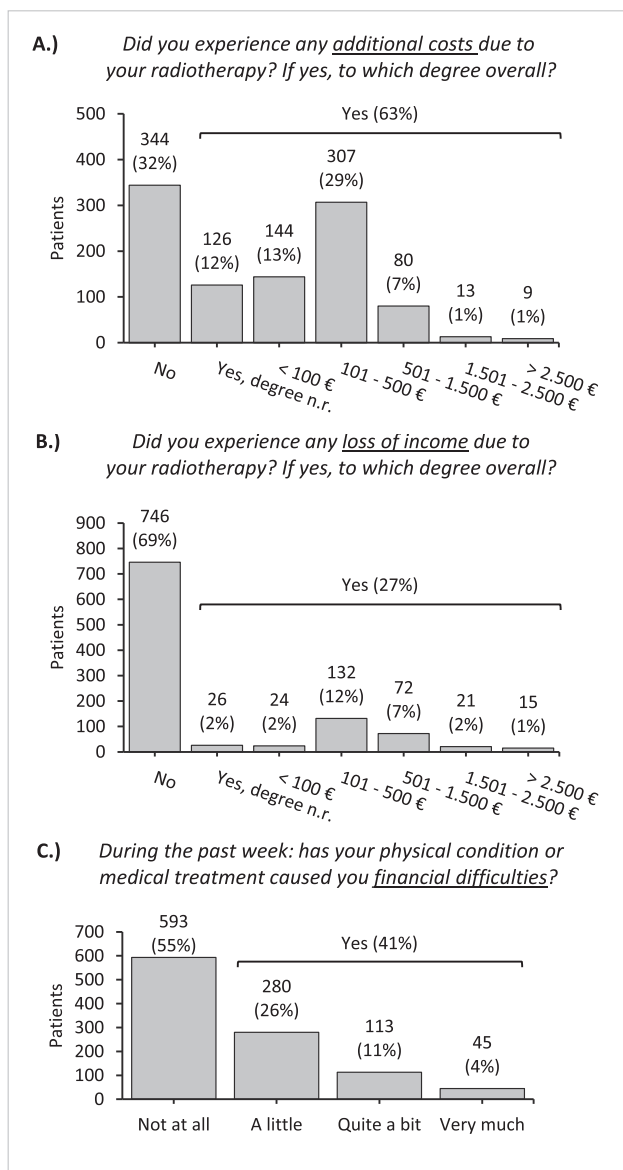


Fig. 2. Prevalence and degree of objective financial burden is shown as direct costs (A) and indirect costs as loss of income (B) in the context of radiotherapy. The prevalence and degree of subjective financial distress (C) is shown as per EORTC QLQ-C30 question 28. Percentages may not add up due to rounding error and missing values. Abbreviation: n.r. not reported.

likelihood ratio test comparing the fit of the proportional odds model to a model with varying location parameters ($\chi^2(12) = 10.4, p = 0.579$). The final model statistically significantly predicted the dependent variable over and above the intercept-only model ($\chi^2(6) = 248.129, p < 0.001$). Lower household income

Table 2

Confirmatory ordinal regression analysis of subjective financial distress per question 28 of the EORTC QLQ-C30 as dependent variable and risk factors as independent variables in a prescribed model. Italic numbers indicate statistically significant *p*-values < 0.05. Abbreviations: CI confidence interval.

Dependent variable: subjective financial distress						
Independent variables	regression coefficient B	Wald- χ^2	Odds ratio	<i>p</i>	Upper 95% CI	Lower 95% CI
Age	-0.011	1.988	0.989	0.159	1.004	0.974
(Self-)employed (Yes)	0.172	0.681	1.188	0.409	1.788	0.789
Net household income	-0.421	55.214	0.656	< 0.001	0.733	0.587
Global health status/ quality of life	-0.284	24.811	0.753	< 0.001	0.842	0.673
Degree of direct costs	0.434	35.741	1.544	< 0.001	1.780	1.339
Degree of loss of income	0.523	63.050	1.688	< 0.001	1.920	1.483

(OR 0.656 [95% CI, 0.733–0.587]; $p < 0.001$), lower global health status/ quality of life (OR 0.753 [95% CI, 0.842–0.673]; $p < 0.001$), higher direct costs (OR 1.544 [95% CI, 1.780–1.339]; $p < 0.001$) and higher loss of income (OR 1.688 [95% CI, 1.920–1.483]; $p < 0.001$) statistically significantly predicted worse subjective financial distress (Table 2). Therefore, all risk factors of subjective financial distress described in the pilot study were confirmed with the addition of lower global health status/ quality of life.

Predefined secondary analyses aimed to evaluate associations of additional factors not covered in the pilot study and subjective financial distress. The duration of radiotherapy in days was not associated with subjective financial distress per Spearman's correlation ($n = 989$; Spearman's rho 0.007 [95% CI, -0.055–0.069]; $p = 0.8$). In contrast, higher psychosocial distress was statistically significantly associated with higher subjective financial distress ($n = 1017$; Spearman's rho 0.227 [95% CI, 0.168–0.285]; $p < 0.001$). Moreover, patient satisfaction with radiotherapy care was statistically significantly associated with subjective financial distress per Chi-square test for independence ($n = 1011$; $\chi^2(3) = 49.236$; $p < 0.001$). Unsatisfied patients reported higher subjective financial distress than satisfied patients as evidenced by the respective contingency table (Supplementary Table 1). To explore the impact of psychosocial distress and patient satisfaction on subjective financial distress in a multivariate analysis, we added both factors to the ordinal regression model described above. Again using a logit link function, the assumption of proportional odds was met as shown by a full likelihood ratio test comparing the fit of the proportional odds model to a model with varying location parameters ($\chi^2(16) = 25.505, p = 0.061$). The final model statistically significantly predicted the dependent variable over and above the intercept-only model ($\chi^2(8) = 259.715, p < 0.001$). Higher psychosocial distress (OR 1.142 [95% CI, 1.229–1.062]; $p < 0.001$) and being unsatisfied with care (OR 1.874 [95% CI, 2.861–1.227]; $p = 0.004$) remained statistically significantly associated with higher subjective financial distress (Table 3). Yet the global health status/ quality of life no longer yielded a statistically significant impact in this exploratory model (OR 0.883 [95% CI, 1.012–0.771]; $p = 0.075$).

A post hoc secondary analysis showed that patients with public health insurance had higher subjective financial distress compared to patients with private health insurance per chi-square test for independence ($n = 1020, \chi^2(3) = 19.2, p < 0.001$). Public versus private health insurance, however, was not significantly associated with subjective financial distress when added to the ordinal regression model (Supplementary Table 2).

Discussion

In this confirmatory study of financial toxicity in patients undergoing radiotherapy, the prevalence of financial toxicity was higher than expected, although reported at low or moderate degrees by most patients. Low income, low global health status/ quality of life, and high objective financial burden were confirmed

Table 3

Exploratory ordinal regression analysis of subjective financial distress per question 28 of the EORTC QLQ-C30 as dependent variable and potential risk factors as independent variables. Italic numbers indicate statistically significant *p*-values < 0.05. Abbreviations: CI confidence interval, RT radiotherapy.

Dependent variable: subjective financial distress						
Independent variables	regression coefficient B	Wald- χ^2	Odds ratio	<i>p</i>	Upper 95% CI	Lower 95% CI
Age	-0.007	0.780	0.993	0.377	1.009	0.978
(Self-)employed (Yes)	0.248	1.359	1.281	0.244	1.943	0.845
Net household income	-0.395	47.868	0.674	< 0.001	0.753	0.602
Global health status/ quality of Life	-0.124	3.177	0.883	0.075	1.012	0.771
Degree of direct costs	0.404	29.939	1.498	< 0.001	1.731	1.296
Degree of loss of income	0.506	57.279	1.659	< 0.001	1.892	1.455
Psychosocial distress	0.133	12.633	1.142	< 0.001	1.229	1.062
Patient satisfied with RT care (No)	0.628	8.458	1.874	0.004	2.861	1.227

as risk factors. Moreover, financial toxicity was associated with higher psychosocial distress and lower patient satisfaction.

The prevalence of financial toxicity in cancer patients is challenging to compare across studies as cohorts and measures vary greatly [3]. The prevalence of financial toxicity was higher than expected in this cross-sectional multicenter study as compared to the previous pilot study. Of note, the degrees of subjective financial distress as surrogate for financial toxicity were reported as “A little”, “Quite a bit” and “Very much” by 26%, 11%, and 4% of the patients in the present study compared to 21%, 6%, and 4% in the pilot study, respectively. This indicates that the overall higher prevalence was driven by the categories “A little” and “Quite a bit” of subjective financial distress as surrogate for financial toxicity [13]. Reasons for the overall higher rate of financial toxicity remain speculative, but increased general costs during a period of high inflation rates could have had a negative impact [23]. This notion might be supported by the fact that the prevalence of financial toxicity was 42% (35/83) in the confirmatory study compared to 33% (26/78) in the pilot study concerning the center which participated in both studies (University Hospital Schleswig-Holstein Kiel, data not shown). On the other hand, however, it is also possible that previous studies simply underestimated the prevalence of financial toxicity. Buettner and colleagues, for example, recently reported a prevalence of financial toxicity of 45% in a large German cohort of sarcoma patients as measured by question 28 of the EORTC QLQ-C30 [18]. A US-American study surveyed adolescent and young adult oncology patients, a subgroup which appears to be specifically affected by financial toxicity, using the Comprehensive Score for financial Toxicity questionnaire (COST) and reported a prevalence of 46% [24]. Younger age, however, was not a significant risk factor for financial toxicity in our cohort.

Risk factors we were able to confirm included lower household income, lower global health status/ quality of life, and higher objective financial burden. These factors have been described in other settings and may therefore be regarded as robust, also in the case of patients undergoing radiotherapy in a universal health care system [4,18,25–27]. Concerning additional factors associated with financial toxicity, we hypothesized that a longer duration of radiotherapy might have had a negative impact for example due to increased transportation costs which were a common source of additional costs in our cohort. This was, however, not the case. This negative finding was also reported by a recent cross-sectional study in breast cancer patients treated with radiotherapy in the US [28]. On the other hand, we also hypothesized that higher psychosocial distress and lower patient satisfaction could be associated with higher financial toxicity based on previous studies in other cohorts of cancer patients [5,29]. Both associations were indeed present in our cohort per multivariate regression. Global health status/ quality of life, however, was no longer a significant variable in the regression model expanded by psychosocial distress. This effect could be due to an inverse correlation of psy-

chosocial distress and health-related quality of life although formal collinearity was not detected in the model [30,31]. Lastly, we evaluated the role of the type of health insurance as this may have implications on financial toxicity. Presence of public health insurance was associated in a univariate, but not in a multivariate post hoc analysis with higher financial toxicity. Public and private insurances coexist in the German health care system. In general, only persons with high income may opt out of the compulsory public health insurance and choose a private health insurance instead. Accordingly, the type of health insurance was strongly associated with net household income in our cohort (data not shown). Net household income was a variable in the multivariate model and confirmed as risk factor for financial toxicity. This may be a reason why the type of insurance was not associated with financial toxicity in the multivariate analysis.

Meanwhile, first studies are about to move on and to prospectively investigate interventions to mitigate financial toxicity primarily in the US. This includes, for example, financial navigation which aims to support patients at different levels such as insurance coverage or medication cost savings [32]. Such desirable studies, however, will have to be customized to the national conditions in each health care system and the targeted population. Therefore, a nuanced understanding of the prevalence and risk factors of financial toxicity is paramount, as reported by our study for a large cohort of cancer patients undergoing radiotherapy in a universal health care system.

Limitations of our study are, first, the use of a single-item measure of subjective financial distress as surrogate for financial toxicity. To the best of our knowledge, there was no multi-item questionnaire validated in German at the time of the conception of the study which could have offered more detail. The single-item measure we used, however, has also been used by various other studies which simplifies the comparison across studies [18,26]. Furthermore, our predefined primary analysis was the overall prevalence of subjective financial distress as surrogate for financial toxicity. We acknowledge that varying degrees of this outcome affect patients to a different extent. The overall prevalence may therefore overestimate the associated burden as most affected patients indicated “A little” subjective financial distress. Second, we cannot rule out a possible participation bias resulting in false-high rates of financial toxicity. Reasons for non-participation cannot be tracked back due to the anonymous nature of the survey. The participation rate, however, met the predefined minimum range and did not significantly differ between centers with lower versus higher participation rates. Third, although our study reports a large national cohort, its results should only cautiously be extrapolated to or compared with other countries such as the US given inherent differences in health care systems. Lastly, the median age of the study cohort was relatively high at 66 years with a predominance of retired patients. Although this reflects a representative cross-section of patients undergoing radiotherapy,

a tailored study protocol to evaluate financial toxicity in younger patients could offer further insights into this potentially vulnerable cohort.

In conclusion, the prevalence of financial toxicity in cancer patients undergoing radiotherapy in a universal health care system was higher than anticipated. As we robustly confirmed risk factors associated with financial toxicity, patients at risk may be addressed early for potential support. The results of our study inform future research which should evaluate interventions against financial toxicity and its negative impact on outcomes.

CRedit authorship contribution statement

Alexander Fabian: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Alexander Rühle:** Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing. **Justus Domschikowski:** Investigation, Writing – review & editing. **Maïke Trommer:** Investigation, Writing – review & editing. **Simone Wegen:** Investigation, Writing – review & editing. **Jan-Niklas Becker:** Investigation, Writing – review & editing. **Georg Wurschi:** Investigation, Writing – review & editing. **Simon Boeke:** Investigation, Writing – review & editing. **Mathias Sonnhoff:** Investigation, Writing – review & editing. **Christoph A. Fink:** Investigation, Writing – review & editing. **Lukas Käsmann:** Investigation, Writing – review & editing. **Melanie Schneider:** Investigation, Writing – review & editing. **Elo-die Bockelmann:** Investigation, Writing – review & editing. **Martin Treppner:** Conceptualization, Investigation, Methodology, Writing – review & editing. **David Krug:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Nils H. Nicolay:** Conceptualization, Investigation, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AR received speaker honoraria from Merck KGaA and research funding, consulting fees and reimbursements for travel expenses from Novocure GmbH. DK received honoraria from Merck Sharp & Dohme and Pfizer as well as research funding from Merck KGaA, outside of the submitted work. GW received funding by the “Clinician Scientist”-program of the Interdisciplinary Center for Clinical Research, Jena University Hospital (grant-No.: CSP-11). LK received honoraria from AMGEN outside of the mentioned study. NHN received speaker honoraria from Merck KGaA and research funding from Novocure GmbH. The other authors have no competing interests to declare that are relevant to the content of this article.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2023.109604>.

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