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Brief Opinion

Financial Toxicity as an End Point in Prospective Clinical Trials Involving Radiation Therapy

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Abstract

Prior research, predominately retrospective, has increased awareness that patients with cancer are at elevated risk for financial toxicity (FT). Radiation therapy (RT) can be particularly disruptive due to weeks of daily treatments. Yet, FT in patients receiving RT is less studied, and the extent to which FT has been incorporated as an end point in prospective clinical trials involving RT is unknown. Clinicaltrials.gov was queried to identify all observational or interventional studies from 2001 to 2020 wherein RT was administered for cancer. Studies with primary, secondary, or exploratory FT end points were identified through keyword search. For trials incorporating FT outcomes, pertinent study characteristics were collected. Detailed information regarding FT measures was recorded. Descriptive statistics, including frequency counts and proportions, were performed. The overall rate of inclusion of FT end points was calculated, and rates over 5-year intervals were compared using the χ^2 test ($\alpha = 0.05$). Overall, 10,550 studies involving RT were identified, of which 88 reported FT end points (0.8%). Included FT end points were typically secondary (78%), with just 15 studies (17%), including primary end points. Notably, only 19 studies (22%) reported a standalone FT end point. The majority measured FT as part of a larger quality of life (QoL) questionnaire. The rate of inclusion of FT end points significantly increased over time from 0.1% from 2001 to 2005 to 1.5% from 2016 to 2020, ($P < .0001$). FT is a major stressor for patients with cancer, yet even after a relative increase over time, the absolute rate of inclusion of FT end points remains low among RT-based trials. When included, FT outcomes were typically a single question within a QoL assessment not validated as a standalone measure of FT, preventing meaningful study and inference. To characterize and mitigate this burden more accurately, future prospective studies should include FT end points with greater frequency.

Introduction

Prior research, predominately retrospective, has led to increasing awareness that patients with cancer are at elevated risk for financial toxicity (FT): the "harmful personal financial burden faced by patients receiving cancer treatment."[1-7] Radiation therapy (RT) can be particularly challenging, as patients may have their personal and professional lives disrupted by weeks of daily treatments.[5-9] Despite this, FT in patients receiving RT is less studied,[5-7]

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and the extent to which FT has been incorporated as an end point in prospective clinical trials involving RT merits investigation.

Methods and Materials

Clinicaltrials.gov was queried to identify all observational or interventional studies from 2001 to 2020 wherein RT was administered for cancer. FT was defined as above to encapsulate a wide range of potential financial consequences including, but not limited to, loss of job or income, bankruptcy, or even homelessness—economic issues that have been previously attributed to RT.[5,7] Studies with primary, secondary, or exploratory FT end points were identified through keyword search using the broad term "economic OR financial" and manually verified. Trials with health care economic end points, such as macroeconomic comparisons between treatment techniques, but lacking planned end points assessing personal financial metrics were excluded. For trials incorporating FT outcomes, pertinent study characteristics, such as cancer type, phase, inclusion of systemic therapy or surgery, date listed, planned enrollment, and study location were collected. Detailed information regarding FT measures was recorded. Descriptive statistics, including frequency counts and proportions, were performed. The overall rate of inclusion of FT end points was calculated, and rates over 5-year intervals were compared using the χ^2 test ($\alpha = 0.05$).

Results

Overall, 10,550 studies involving RT were identified, of which 88 reported FT end points (0.8%, Fig 1). Table 1 depicts pertinent characteristics for these studies with FT end points. Nineteen percent, 18%, and 14% of these trials were in breast, gastrointestinal, and prostate cancers, respectively. The majority (75%) were latter phase (2/3), included systemic therapy (89%) or surgery (56%), enrolled <500 patients (84%), and were conducted in the United States, Canada, or Europe (81%). Of the included studies, 24 (27%) had completed accrual with 15 having resulted in at least one publication; 32 were currently recruiting (36%); 15 (17%) were active but not recruiting; and 3 (3%) had not yet begun recruiting. Of the remaining studies, 7 (8%) were of unknown status, 1 (1%) was suspended, 2 were terminated (2%), and 4 (5%) were withdrawn.

FT end points were typically secondary (78%) with just 15 studies (17%) including FT as a primary end point. Notably, while only 19 of all 88 studies (22%) reported a standalone FT end point, 40% of studies with a primary FT end point (6/15) also had a standalone FT end point. Many studies with standalone end points (10 of 19) did not specify how FT would be measured. When specified, the COmprehensive Score for financial Toxicity (COST) questionnaire was most used (3 studies) followed by an adaptation of items from the National Health Interview Survey and the Cancer Care Outcomes Research and Surveillance study (2 studies). Additional tools used were the Time Off Work Questionnaire, ENRICH Questionnaire, Economic Strain and Resilience in Cancer Financial Toxicity Questionnaire, and Patient-Reported Skin Toxicity Cost Questionnaire. Of the remaining 69 studies, the majority measured FT as part of a larger QoL questionnaire, most commonly question 28 of the European Organization for Research and Treatment of Cancer Core QoL (EORTC QLQ-C30) questionnaire. Figure 2 demonstrates that the rate of inclusion of FT end points significantly increased over time from 0.1% from 2001 to 2005 to 1.5% from 2016 to 2020 ($P < .0001$).

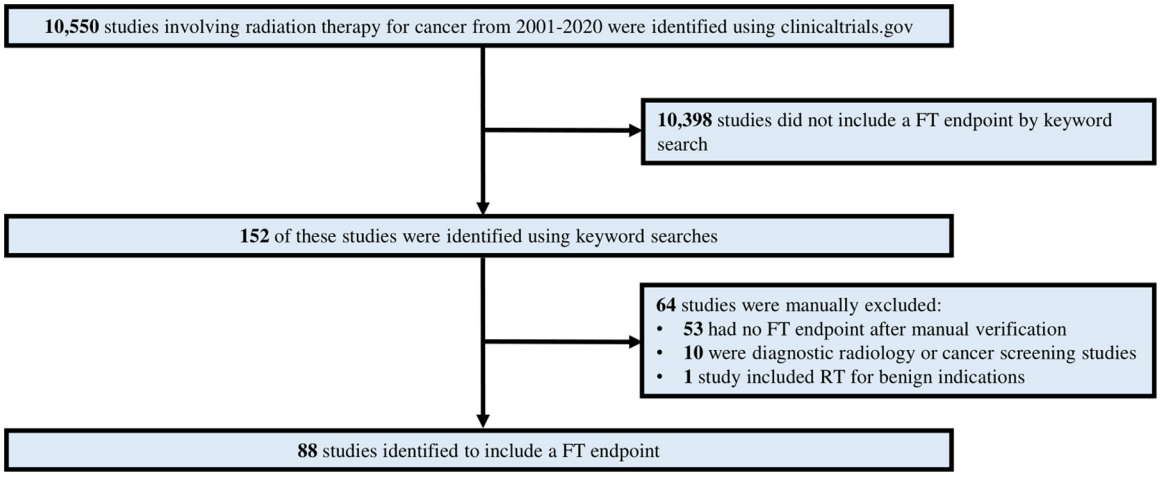

Figure 1 Schema demonstrating the process for identifying studies including radiation therapy that contained financial toxicity end points. *Abbreviations*: FT = financial toxicity, RT = radiation therapy.

Table 1 Pertinent characteristics of studies involving radiation therapy that incorporated financial toxicity end points

Trial characteristic	No. (%)
Trials	88 (100)
Cancer type	
Breast	17 (19)
Gastrointestinal	16 (18)
Prostate	12 (14)
Central nervous system	12 (14)
Head and neck	10 (11)
Gynecologic	7 (8)
Lung	6 (7)
Skin	2 (2)
Multi-site/other	6 (7)
Phase	
Observational	11 (13)
1	11 (13)
2/3	66 (75)
Financial end point	
Primary	15 (17)
Secondary	69 (78)
Exploratory	4 (5)
Type of financial end point	
Standalone	19 (22)
EORTC QLQ-C30 questionnaire	63 (72)
Other QOL questionnaire	6 (7)
Systemic therapy	
Yes	78 (89)
No	10 (11)
Surgery	
Yes	49 (56)
No	39 (44)
Date listed	
2001-2005	2 (2)
2006-2010	11 (13)
2011-2015	19 (22)
2016-2020	56 (64)
Planned enrollment	
<99	36 (41)
100-499	38 (43)
500-999	7 (8)
1000 +	7 (8)
Location	
Europe	39 (44)
US	27 (31)
Canada	5 (6)
Asia/Africa/South America	9 (10)
Australia/New Zealand	1 (1)
Global	7 (8)
Institution	
Single	46 (52)
Multi	42 (48)
Recruitment status	
Completed accrual	24 (27)
Currently recruiting	32 (36)
Active, but not recruiting	15 (17)
Not yet recruiting	3 (3)
Unknown	7 (8)
Suspended	1 (1)
Terminated	2 (2)
Withdrawn	4 (5)

(*continued on next page*)

Table 1 (*Continued*)

Abbreviations: EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Core Quality of Life; QoL = quality of life.

Discussion

The National Cancer Institute has prioritized "measuring, understanding, and addressing" FT,[3] yet <1% of modern studies involving RT included a FT end point. Additionally, of the few studies including FT end points, 16% were terminated, withdrawn, suspended, or of unknown status, representing an additional barrier to adequately assessing FT in RT populations. Furthermore, the few RT studies addressing FT were concentrated in Europe and North America, limiting generalizability to other populations, particularly lower income countries. This issue is critically important, because FT is highly burdensome for the majority of patients.[10] It is correlated with decreased QoL,[1,2] dissatisfaction with the health care system,[11] and detrimental coping and cost-saving behaviors such as treatment nonadherence.[11,12] Additionally, several studies have noted an association between financial insolvency and increased mortality in patients with cancer,[13,14] including one study noting that patients who experienced bankruptcy were nearly twice as likely to die as those who did not.[13] Potential explanations include decreased quality of life and global well-being, increased stress, and treatment

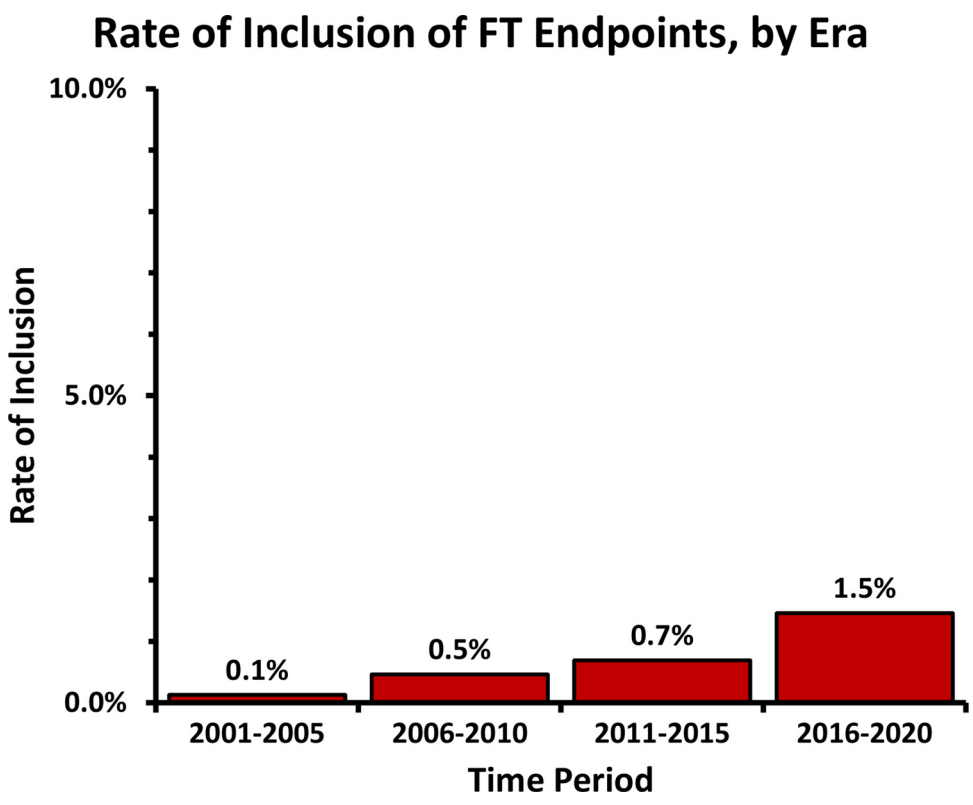

Figure 2 Inclusion of financial toxicity end points in studies involving radiation therapy, over time ($P < .001$). *Abbreviation*: FT = financial toxicity.

noncompliance due to loss of income or necessities, such as food, housing, or transportation.[11]

When included in the examined studies, FT outcomes were typically a single question within a QoL assessment, most commonly Q28 of the EORTC QLQ-C30, which was never intended to be or validated as a standalone measure of FT from RT. This represents a significant obstacle to in-depth study and meaningful inference. While about one-fifth of studies in our analysis used a dedicated, standalone FT end point, widely used screening tools for FT, such as the COST questionnaire,[4] should be cautiously applied to patients receiving RT. Because this tool was developed in populations receiving palliative chemotherapy (and not definitive RT), the unique nature of RT-related stressors such as the intensive nature of daily therapy may not be adequately captured.[5,7-9] One potential solution would be to adapt the COST questionnaire and validate it in a population receiving RT. However, one drawback of this approach is that the addition of questionnaires with double-digit item counts may be onerous for both study participants and administrators. An alternate strategy employing an intermediate approach would be to validate a short (2 to 3) item rapid screening tool in populations receiving RT.[7] Such an approach potentially offers richer data then relying upon a single, nonvalidated survey item, better sensitivity and specificity for FT after RT as it would be validated in the intended population,[7] and ease of implementation relative to the currently accepted but cumbersome and lengthy tools.[4]

Our analysis reveals that the rate of inclusion of FT measures has significantly increased over time, mirroring recent trends toward increasing publication of retrospective data characterizing FT in oncology. However, rates of inclusion of FT end points remain objectively low. Because we found that studies with primary FT end points were nearly twice as likely as studies with secondary or exploratory FT end points to include an in-depth, standalone FT measure, encouraging the incorporation of primary end points in future studies may be especially critical to ensuring robust characterization of FT in RT populations. Study limitations stem from the imperfect nature of published trial registry data.

In summary, patients receiving RT represent a unique population in which studying FT is imperative.[5-7] Yet, among prospective clinical trials involving RT, FT remains a rare end point despite being a major source of stress for patients with cancer and a primary focus of the National Cancer Institute. To more accurately characterize (and mitigate) this burden, future prospective studies should include FT end points with greater frequency.

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