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ORIGINAL ARTICLE

Patients' rationale for declining participation in a cancer-associated weight loss study

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Abstract
Background Fewer than 5 % of cancer patients participate in clinical research. Although this paltry rate has led to extensive research on this topic, previous studies have not sought verbatim comments in a real-time, comprehensive manner to understand why patients decline.
Methods This study used a low-risk, non-interventional parent study that focused on cancer-associated weight loss to understand patients' reasons for declining research participation. A research assistant wrote down the name and verbatim reason of all patients who declined to participate. These comments with accompanying patient demographic data are the subject of this report.
Results Of the 334 patients, 51 (15 %) declined parent study enrollment; three comment-related themes emerged: (1) a repelling sense of too much institutional research, (2) overwhelming personal health issues, and (3) a low likelihood of returning to the institution. In univariate and multivariate analyses, only age (older) and gender (female) were associated with non-enrollment. Interestingly, 41 patients with fatigue scores of 7 or worse and 26 with pain scores of 7 or worse were enrolled.
Conclusions Although many factors were associated with declining to participate in research, symptom severity was not. Upfront education might help cancer patients better prioritize their participation in research, particularly as some patients felt overwhelmed by too much research in the institution; and for now, investigators should continue to keep asking patients for their participation.

Keywords Clinical research · Clinical trial · Weight loss · Nutrition · Patient enrollment · Accrual · Decline

1 Introduction

A paltry 5 % of cancer patients participate in clinical research [1]. Yet, clinical research plays a pivotal role in improving cancer outcomes. Hence, a growing literature has sought to understand why so few cancer patients participate in it. Factors that detract from accrual include a limited number of relevant studies, healthcare providers' time constraints, patients' age (older) or gender (female), financial or logistical concerns on the part of the patient or institution, patients' limited education, patients' unwillingness to participate in interventions that could entail pain or adverse events, stable malignant disease with no apparent need to intervene, patient's ethnic minority status coupled with a mistrust of research, and a recent end-of-life discussion [2–12].

Is this list comprehensive? Likely, it is not. First, this list was derived largely from cancer therapeutic/palliative interventional trials, which often require a higher degree of patient commitment, can pose side effects, and may not capture the same patients as non-interventional trials. Yet, the latter also serve an important role in augmenting our understanding of cancer and its management. For example, preliminary research in cancer angiogenesis began with non-interventional studies that culminated in the availability of a relatively new

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class of commonly prescribed, life-prolonging cancer drugs [13, 14]. Understanding why patients decline to enroll in these non-interventional studies is especially timely because nationwide accrual is dropping [15]. Second, previous studies have often relied on retrospective data or patient surveys to assess accrual barriers. Few have relied on word-for-word patient comments. Capturing and analyzing verbatim comments might improve our understanding of patients' reluctance to participate. Third, few studies have acquired patients' reasons for declining study enrollment in a real-time manner. Patients often must make 'on-the-spot' decisions about research, and thus, it is important to study this issue at the point of decision-making. Finally, even fewer studies have comprehensively included patients. Including all patients obviates reliance on the recruitment of a patient who just declined a study and would be unlikely to participate in a second study, thus side stepping a chasm in our understanding of decision-making.

Hence, the current study used a single-institution, non-interventional research endeavor, which focused on cancer-associated weight loss, as a platform to probe into why cancer patients decline to participate in research. Focusing on a study that examined cancer-associated weight loss was particularly appealing because a large number of mechanism-based previous studies on this topic have relied on non-clinical models, underscoring the need for more clinically based, translational research in this field. In response to the comments above on research non-participation, the current study (1) focused on patients asked to enroll in a low-risk, non-interventional research study, (2) relied on direct patient quotes to explain reasons for declining, (3) utilized a real-time approach for data collection; and (4) comprehensively included all patients, including those who declined enrollment to the parent study. These approaches, coupled with a reassessment of other relevant variables, were undertaken to better understand issues related to lack of participation in low-risk, non-interventional cancer research.

2 Methods

2.1 Description of the parent study

The current study was spawned from a Mayo Clinic Institutional Review Board approved study that sought to understand the mechanisms underlying the cancer-associated weight loss syndrome. Herein, this study is referred to as the 'parent' study. Eligible patients had a diagnosis of metastatic lung cancer or metastatic exocrine pancreas cancer with no chemotherapy in the preceding week. A clinical research assistant (TW) approached patients deemed eligible based on prior medical record review, explained the rationale and procedure requirements for the parent study and asked if they would like to enroll. Patients who chose to participate had to be willing to (1) complete a 2-minute appetite questionnaire, (2) give two tubes of blood (20 ml total), and (3) repeat completion of the questionnaire and blood draw no sooner than 3 weeks later. If a patient declined, the clinical research assistant wrote down that patient's name, clinic number, and verbatim reason for declining so as not to approach that same patient again.

2.2 Overview of the current study

The Mayo Clinic Institutional Review Board separately approved the current study, which did not require patient consent. This approval was based on the importance of the research question and the innocuous nature of the confidentially retrieved clinical data. The primary goal of the current study was to understand patients' reasons for declining study enrollment based on the verbatim comments they had provided to the clinical research assistant. Secondary goals were to examine patient demographics and symptoms as potential predictors of parent study enrollment and to explore whether patients who declined enrollment manifested worse survival. This survival endpoint explored the possibility that non-enrolled patients might have accurately sensed their impending demise and was thought important to assess in the context of a non-interventional study, particularly one that focused on cancer-associated weight loss, which carries a poor prognosis, and, where, to our knowledge and in contrast to interventional trials, such analyses had not been previously undertaken [16, 17].

The medical records of all patients—regardless of whether they declined or enrolled—were reviewed for age, gender, and cancer type (lung or pancreas). Ethnicity was not retrieved because of the homogeneity of our patient population. Patients' baseline responses to a fatigue and pain question were also extracted from the medical record [18]. These two questions required patients to respond to a 0–10-point linear analog scale (for example, 10='worst fatigue you can imagine') at the time of each clinic visit, as a routine part of clinical care. Information on vital status and date of death or last follow-up was also extracted.

2.3 Qualitative methods

Two investigators (TW and AJ) independently reviewed all word-for-word comments from patients who declined to participate in the parent study to identify themes related to non-participation. Both investigators resolved initial discrepancies in theme identification with further discussion, using well-established qualitative research methods [19–21]. No third-party adjudication was necessary. Specific patient comments were used to substantiate theme selection.

Accrual to the current study was halted at the present sample size for three reasons: theme saturation, the parent study was nearing its target accrual, and the extant data set captured a full year of accrual.

2.4 Quantitative analyses

Demographic and accrual data are presented descriptively. Univariate and multivariate logistic regression models were used to assess associations between patient demographics and non-enrollment to the parent trial. Odds ratios with 95 % confidence intervals are reported. Survival data were censored when appropriate, and a log rank test was used to explore differences in survival between patients based on enrollment status to the parent trial. A Cox proportional hazards model was constructed also to explore well-established predictors of survival to show validation of the data set. A P-value of <0.05 was judged statistically significant.

3 Results

3.1 Demographics

A total of 334 patients were approached for enrollment to the parent trial. Only 51 patients (15 %) declined. Demographics on all patients appear in Table 1. This study sought to enroll patients regardless of whether they had suffered weight loss, so demographic data on this variable are not included.

3.2 Reasons for declining enrollment to the parent trial

From patients' verbatim comments, we identified three themes: (1) a repelling sense of too much research in the institution ($n=10$), (2) an overwhelming set of personal medical health issues that made it too difficult to participate ($n=10$), and (3) a high unlikelihood of being able to return for the second blood draw and survey because primary oncology care was being rendered elsewhere ($n=16$). Some overlap occurred in themes among patients. Representative word-for-word patient quotes appear in Table 2. Fifteen patients answered with a quick, 'no', and provided minimal, if any, other comments.

Table 1 Baseline demographics ($n=334$)*

Demographics**	Declined	Enrolled
	$n=51$ (%)	$n=283$ (%)
Age, mean (standard deviation)	68 (12)	65 (11)
Gender		
Male	21 (41)	163 (58)
Female	30 (59)	120 (42)
Cancer		
Lung	41 (80)	208 (73)
Pancreas	10 (20)	75 (27)
Fatigue score, mean (standard deviation)	3.9 (2.5)	3.9 (2.3)
Pain score, mean (standard deviation)	2.3 (2.4)	2.5 (2.5)

*Data on fatigue were available for 47 and 270 patients, who declined and enrolled, respectively; the same is the case for data on pain.

**Numbers - parentheses refers to percentages unless otherwise specified

3.3 Patient variables associated with enrollment to the parent trial

Examining gender, age, cancer type, fatigue score, and pain score, we observed in both univariate and multivariate analyses that only age (older) and gender (female) were associated with declining parent study enrollment. Although this inverse association with age was of borderline statistical significance in the multivariate analysis ($p=0.05$), it nonetheless appeared clinically significant: each year of advancing age yielded a 3 % greater chance that a patient would be unwilling to enroll. Women were less likely to enroll than men.

None of the other clinical variables was associated with trial enrollment (Tables 3 and 4). Of note, 41 patients with a fatigue score of 7 or worse and 26 patients with a pain score of 7 or worse were willing to enroll in the parent trial.

3.4 Survival of patients who declined and enrolled

At the time of this report, 241 patients remain alive, and the median follow-up of survivors is 20 weeks. The median survival of patients who declined and enrolled was 48 and 47 weeks, respectively ($p=0.70$) (data not shown). The Cox proportional hazards model confirmed the well-established, statistically significant findings that women and patients with less symptomatology (less pain and less fatigue) live longer, thus providing internal validation of our data set (data not shown).

4 Discussion

This study focused on a low-risk, non-interventional study on cancer-associated weight loss and observed that only 15 % of patients declined participation. This rate of decline is lower than that reported in the general literature and shows that cancer patients are very willing to participate in non-interventional research, particularly as relevant to the topic of cancer-associated weight loss [15]. Nonetheless, with 51 of the 334 patients declining, this study provides robust, real-time qualitative data to help us better understand how patients reach their decision [19–21]. Patients said they were being asked to participate in too much research, that they felt overwhelmed by their own health issues, and that, at times, they were seeking only a second opinion and would be unable to return to complete the study. Admittedly, it is unreasonable to expect all cancer patients to participate in all research, but the above findings do identify potential areas for improving accrual. Based on the subgroup who commented on the fact that too many studies were offered, there may be a role for providing

Table 2 Themes with comments from patients who declined parent trial participation

Themes		
Too much research at the institution and repelled by more	Overwhelmed by health issues	Unable to return for study completion, as primary oncology care rendered elsewhere
Comments		
'…so I don't want to sign up for another one.'	'I'm going into hospice and won't be back.'	'I would love to do the study but I'm only going to be coming once a year now.'
'No thanks. I'm already doing one.'	'I'm too sick. I'm just too sick. I'm sorry.'	'We won't be returning. Sorry.'
'Too much research.'	'Too much else to deal with and keep up with.'	
'There's just too much of it (research).'	'Just not up to it.'	
'I'm in a drug trial.'	'I don't have time. I don't have time for that.'	
'I've already done two studies.'	'I'm not sure how I'm doing or what's going to happen.'	
'…I agreed to another one once and received too much in the mail, and they were asking me to come in and give blood, and I just don't think so.'	'I don't think so. This is a little overwhelming. I'm trying to fight this, and I just don't need anything else to fill out or do.'	
'…I bet I've done 12 studies and someone is always asking me and I don't want to anymore…I don't even want to hear about it.'	'I don't think so today. Things haven't been going right for us…We signed up for hospice and they brought the wrong thing this morning and I had to refuse it. It's just not a good day.'	

cancer patients introductory educational materials on the depth and breadth of research endeavors within an academic cancer center, educating them on the importance of low-risk research, non-interventional research, particularly that which focuses on cancer-associated weight loss, and, thereby, helping them prioritize whether or not to participate in research, and if so, what types. This approach might eliminate the current first-come, first-serve tactic and instead enable patients to make decisions consistent with their own values.

Interestingly, although declining patients described that they felt overwhelmed by research and their own health issues, within the group as a whole, patient-reported fatigue and pain did not preclude participation in the parent study. Even patients with severe fatigue or severe pain were, in fact, willing to participate and did. Furthermore, no relationships were observed between research participation and overall survival. Taken together, these findings suggest that healthcare providers and study personnel should not be reluctant to approach patients because of their current symptomatology or because of fear that they might accurately be sensing their impending demise. All eligible patients should be allowed to make their own decisions about research participation.

Although one shortcoming of our study is that we report a single-institution experience that may not be applicable to other academic medical centers, the fact that women and older patients declined participation confirms what others have reported [3, 22, 23]. This confirmation validates the findings within our data set and suggests that our more novel observations could be relevant to other academic cancer centers. Moreover, the labor-intensive nature of screening all eligible patients for the parent trial, approaching them consecutively, and capturing all verbatim comments from those who declined enrollment may not be feasible within a multi-institutional study. Nonetheless, we acknowledge the single-institution nature of this study as a limitation, and we also acknowledge that some aspects of this study, such as the survival analyses, are exploratory.

Table 3 Univariate analyses of variables assessed for odds of declining enrollment

Variable	Odds ratio (95 % confidence interval)	*P*-value
Age (1-year increase)*	1.03 (1.00, 1.07)	0.03
Gender (female vs male)**	1.94 (1.06, 3.59)	0.03
Cancer (lung vs pancreas)	1.48 (0.73, 3.26)	0.29
Fatigue (one-unit increase)	1.00 (0.87, 1.14)	0.94
Pain (one-unit increase)	0.96 (0.84, 1.08)	0.49

*Older patients are 3 % more likely than younger patients to decline enrollment with each year of advancing age.

**Women have a 94 % increased likelihood of declining study participation than men.

Table 4 Multivariate analyses of variables assessed for odds of declining enrollment

Variable	Odds ratio (95 % confidence interval)	*P*-value
Age (1-year increase)*	1.03 (1.00, 1.06)	0.05
Gender (female vs male)**	2.24 (1.19, 4.35)	0.01
Cancer (lung vs pancreas)	1.21 (0.58, 2.73)	0.62
Fatigue (one-unit increase)	1.01 (0.87, 1.17)	0.93
Pain (one-unit increase)	0.95 (0.82, 1.10)	0.49

*Older patients are 3 % more likely than younger patients to decline study participation with each year of advancing age after adjusting for gender, cancer type, fatigue score, and pain score.

**Women have a 2.24 times greater likelihood of declining study enrollment than men after adjusting for age, cancer type, fatigue score, and pain score.

In summary, the current study provides two important observations. First, patients who declined research participation sometimes did so because they were repelled by too much research within the institution or were overwhelmed by their own health issues—and were not necessarily responding to the merit or relevance of the research itself. Perhaps, providing a patient education session prior to clinical appointments may help them make better-informed decisions about research participation, particularly with respect to nutrition-related issues, which patients might find appealing. Second, although some patients in this study declined because of health issues, healthcare providers should not assume that symptoms—such as fatigue and pain—are reasons not to ask patients to participate. In effect, the current study should prompt further investigation into how best to inform patients about cancer research in order to enable them to make the best decisions they can—and, in addition, investigators should keep asking patients to participate.

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Conflict of interest Tammy Wanger, Nathan Foster, Phuong Nguyen, and Aminah Jatoi declare that they have no conflict of interest.

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