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Attrition in NRG Oncology's Radiation-Based Clinical Trials

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Summary

Little is known about the factors that influence attrition in radiology cancer clinical trials. The results of this retrospective review found that those who were younger, female and whose performance status was ≥ 0 were more likely to be lost to attrition as were those in trials with a fixed endpoint. Loss to attrition was also found to be greater in differing geographical regions of the country.

Introduction

Cancer clinical trials, essential to the development of new treatments, are dependent on the voluntary participation of human subjects. It is well known, however, that only 3–5% of all adult cancer patients enroll in clinical trials and many trials document ethnic and racial disparities.^{1–5} Although a growing body of literature describes the facilitators and barriers of recruitment into clinical trials, much less is known about factors contributing to successful retention of subjects within these trials, especially in the National Clinical Trials Network. Similar to recruitment concerns, patient-participants who withdraw from trials (for various reasons) or who are lost to follow-up impact the ability to achieve the overall goals of a study. Participant loss from trials can be costly in terms of resources and threatens both internal and external validity. In fact, subjects who are lost to study follow-up may be very different with respect to the outcomes under study. Equally important, the systematic loss of study participants in randomized controlled trials reduces statistical power, biases measures

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Conflicts of interest:

Nothing to disclose, Dr. Bruner, Dr. Curran, Ms. Deshmukh, Dr. Grady, Dr. Hanlon and Dr. Ulrich. Dr. Pugh reports grants from State of Pennsylvania Department of Health, during the conduct of the study; grants from PCORI and the State of Pennsylvania Department of Health, outside the submitted work.

of interventional effectiveness, and hampers the translation of research to practice and the development of effective treatments.⁶ To better inform our understanding of attrition in controlled cancer trials, the factors that influence attrition, and the disparities that may exist, we conducted a retrospective analysis of XXXX's radiation-based clinical trials.

Methods

All XXXX's radiation-based clinical trials that were open to accrual and had primary efficacy results published from 1985–2011 were eligible for inclusion. XXXX symptom management trials, intergroup trials not led by XXXX, endorsed trials, and trials for which electronic patient follow-up data were not available were excluded. The XXXX Institutional Review Board approved the study.

Attrition Definition

Attrition was defined differently for two sets of trials: 1) event driven trials, and 2) fixed time trials. An example of an event driven trial is XXXX YYYY, a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. The primary endpoint was overall survival. For this type of trial, a patient was considered lost to follow up if his/her assessments were missing immediately prior to the time of the primary endpoint analysis. An example of a fixed time point trial is XXXX YYYY, a phase II trial of stereotactic body radiation therapy in patients with medically inoperable stage I/II non-small cell lung cancer. The primary endpoint was the local control rate at 2 years. For these trials, attrition occurred if a patient was not assessed at the time point of interest (i.e. 2 years). Additionally, if a patient withdrew consent prior to the time of the primary endpoint analysis or the time point of interest, that patient experienced attrition for event driven trials and time trials, respectively.

Statistical Analyses

Descriptive statistics by type of trial were run to describe patient-level, institution-level, and study-level characteristics. Time to attrition was calculated from the date of randomization or registration (for non-randomized trials) to the date of attrition, the date of death (which was treated as a competing risk), or the last known follow-up for alive patients still being followed. It should be noted that this is opposite of what is typically seen in a time-to-event trial. The event of interest in this analysis, attrition, is usually censored in time-to-event trials, such as those with overall survival as a primary endpoint. Patients were censored in this analysis if complete information was provided on a fixed time trial or at the time of analysis of an event driven trial. The cumulative incidence approach was used to estimate time to attrition and cause-specific Cox proportional hazards models were built to assess the predictive value of covariates on time to attrition.^{7,8,9} Stepwise selection with an entry criteria of 0.25 and exit criteria of 0.15 was used to narrow down the number of predictor variables. Due to the large sample size and number of attrition events, the hazard ratio, rather than the p-value, was used to determine the variables to remain in the multivariable models. Remaining variables with hazard ratios between 0.90 and 1.1 were removed from the multivariable model at one time. Hazard ratios, along with their 95% confidence intervals and p-values, were calculated. Patient-level characteristics considered for inclusion in the

models were age, gender (male vs. female), Zubrod performance status (0 vs. 1+), race/ethnicity (white, non-Hispanic vs. other), marital status (married/live-in partner vs. single/divorces/separated/widowed), education (at most completed high school/GED vs. education after high school/GED), type of insurance (private vs. other), and employment status (employed full- or part-time vs. other). Trial specific factors were comprised of year of trial activation, disease site (brain/CNS vs. gastrointestinal vs. head and neck vs. sarcoma/lung vs. bladder/prostate vs. gynecological/breast), and type of trial endpoint (fixed vs. event driven). Institutional factors consisted of institution type (full member vs. CCOP/affiliate/satellite/not XXXX member) and institution region (US New England/Midwest vs. US South/West vs. international). Variables in which more than 20% of cases were missing were excluded. Models were run first using a subgroup of patients with complete baseline data (n=22,660) then repeated using imputed data to include all patients (n=27,443). An additional complete-case analysis was run incorporating marital status and education as these variables had more than 20% of the data missing (n=17,881). Multiple imputation was performed for missing baseline covariates remaining using the Markov Chain Monte Carlo (MCMC) method with 50 imputations.¹⁰ Statistical analyses were accomplished using SAS Version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Follow-up data including attrition status was available for 27,443 patients representing 134 clinical trials. Overall, there were 8,634 patients (31%) enrolled on fixed time trials and 18,809 patients (69%) enrolled on event driven trials. A total of 22,660 patients had complete baseline and follow-up data. Since patient follow-up time depends heavily on the type of trial (4.1 months for fixed time point trials and 37.2 months for event driven trials), stratified analyses were used to determine the patient related and organizational factors of attrition. Due to the short follow-up time for fixed time point trials, attrition estimates were conducted for patients enrolled on studies with < 6 months of follow-up vs. patients enrolled on studies with ≥ 6 months of follow-up.

Fixed Time Trials

Patients (n=8,634) on fixed time studies were primarily treated for gastrointestinal (18%), lung (18%), prostate (17%), and head & neck (17%) cancers. The median age of patients was 62 years (range 18–93). Patients were primarily male (64%), had private insurance (35%), Zubrod performance status of 0 at study entry (70%), were Caucasian and not Hispanic (66%), and were married or had a live-in partner (52%). Many patients did not report education completed (29%) and employment status (90%), as several studies did not ask for this information. Of those who did report, about 43% had attended at least some college and 43% worked full-time outside of their home. Patients were primarily treated at X full member institutions (49%) and were treated most frequently in the US Midwest (28%) and US South (27%) [Table 1, Supplemental Table 1]. The median follow-up time for fixed time trials was 4.1 months (range 0.03 – 110.2) [Table 2], where most commonly patients were evaluated for a toxicity endpoint (45%) on a phase II study (44%) [Supplemental Table 2]. The 1- and 5-month attrition rates were 0.5% (95% confidence interval [CI]: 0.3%, 0.7%) and 4.3% (95% CI: 3.4%, 5.5%) for trials with <6 months of follow-up while the 1- and 5-

year attrition rates were 1.6% (95% confidence interval [CI]: 1.2%, 2.1%) and 25.1% (95% CI: 22.7%, 27.6%) for trials with 6 months of follow-up [Table 2, Figure 1].

Event Driven Trials

Patients on event driven trials (n=18,809) were primarily treated for prostate (35%), head & neck (20%), and brain (19%) cancers. The median age of patients was 63 years (range 18–91). Patients were primarily male (70%), had private insurance (27%), Zubrod performance status of 0 at study entry (61%), were Caucasian and not Hispanic (68%), and were married or had a live-in partner (46%). Again, some patients did not report education completed (36%) or employment status (48%). Of the remainder, 34% had attended at least some college and 49% were retired. Patients were primarily treated at X full member institutions (42%) and were treated in the US Midwest (27%) or US South (24%) [Table 1].

The median follow-up time for event driven trials was 37.2 months (range 0.1 – 172.4) [Table 2], where most patients were evaluated for an overall survival endpoint (71%) [Supplemental Table 1]. The 1- and 5-year attrition rates were 0.5% (95% CI: 0.4%, 0.6%) and 13.6% (95% CI: 13.1%, 14.1%) [Table 2, Figure 1].

Multiple Regression Models

Variables excluded due to large amounts of missing data overall were marital status (30% missing), education completed (34% missing), employment status (61% missing), and insurance (34% missing). Significant trial-related covariates for decreased hazard of attrition in the complete case analysis were recently activated trials (HR=0.44, 95% CI: 0.40, 0.48), disease site, specifically brain/CNS and bladder/prostate cancers, and those with an event driven endpoint (HR=0.54, 95% CI: 0.48–0.61) [Table 3]. Full member sites (HR=1.10, 95% CI: 1.03–1.18) and sites located in the US New England/Midwest (vs. international sites HR=1.13, 95% CI: 1.02–1.25) were associated with decreased attrition. Patient-level characteristics that were significantly associated with decreased attrition were Zubrod performance status 0 (HR=3.66, 95% CI: 3.33, 4.03), and male gender (HR=0.84, 95% CI: 0.77, 0.92). Incorporation of marital status and education into this model had similar results with the addition of marital status being significantly associated with attrition (HR=1.12, 95% CI: 1.04, 1.22) but not education [Supplemental Table 3].

Cause-specific hazard multiple regression models using imputed data showed similar results [Table 4]. Recently activated trials (HR=0.43, 95% CI: 0.40, 0.47), certain disease sites, specifically bladder/prostate cancer (HR=0.75, 95% CI: 0.65–0.86), and those with an event driven endpoint (HR=0.56, 95% CI: 0.51, 0.62) were associated with a decreased attrition. Full member sites were associated with decreased attrition (HR=1.16, 95% CI: 1.09–1.23) and institution region where patients from institutions in the US South/West had an increased attrition compared to US New England/Midwest (HR=1.12, 95% CI: 1.05, 1.19). Patient-level characteristics that were significantly associated with decreased attrition were Zubrod performance status 0 (HR=2.99, 95% CI: 2.75, 3.25) and male gender (HR=0.90, 95% CI: 0.82, 0.98).

Discussion

This is one of the first studies to expansively focus on attrition in the National Clinical Trials Network's radiation oncology based clinical trials. As expected, the attrition rates for both fixed and event trials in this secondary data analysis increased significantly over the duration of the trial. Generally, attrition rates were overall higher for fixed-time trials in comparison to event driven trials given the high rates for fixed time trials with follow-up < 6 months. This may be expected for several reasons. First, a quarter of the fixed trials were Phase I (25.4%) and 44% Phase II, whereas the majority of event-driven trials were Phase III (92.5%). Second, most participants in fixed trials had diagnoses of lung, gastrointestinal, brain, prostate, gynecologic, and head and neck cancers, cancers for which the survival prognosis is variable based on the aggressive nature of these types of cancer (e.g., non-small lung cancer). Estimates of attrition over time in these clinical trials as well as the factors associated with increased or decreased rates of attrition are important data that can help in trial design, and in developing strategies for recruitment and retention. Concerns about attrition and trial retention are significant due to the possible impact on study validity and completion. Moreover, patients lost to attrition in fixed trials, for example, may not be included in the primary analysis whereas for event-driven trials, the patient might be censored at their last known follow-up and included in the analysis. Attrition in event-driven trials steadily increased over time as well, with 13.6% attrition at 5 years, 29.9% at 10 years, and 47.5% at 15 years, respectively. However, without comparative data about attrition or details about statistical assumptions and trial specifics, it is difficult to assess the possible impact of this level of attrition on the studies themselves.

The attrition rates and death rates raise important questions surrounding the role of palliative care in clinical trials.^{11–12} Much theoretical work has outlined the therapeutic benefit of palliative care but an article by Temel and colleagues¹¹ found that early integration of palliative care for patients with metastatic lung cancer significantly improved survival and quality of life; and importantly, less than 1% of their sample dropped out of the study. Brunetto and colleagues¹³ reported several patient baseline characteristics (age greater than 60 years, 3 or more metastatic sites, high serum LDH, and albumin <35 g/dL trending to significance) were associated with 21% of unplanned patient hospitalizations in Phase I trials and contributed to an early risk of attrition (6.7%). The majority of unplanned admissions were for disease-related treatments and symptom management while 22% were for management of treatment-related toxicities. XXXX, and colleagues¹¹ argue that palliative care is often not perceived as compatible with clinical trial participation yet can provide significant benefits for trial participants in terms of pain control, spiritual needs, and overall mental health support. It would be important to document how often XXXX trials include palliative care and symptom management for participants in their clinical trials, and whether and how inclusion of such services affects attrition rates over time.

The results from this analysis show that attrition rates vary by disease site, with sarcoma and lung cancers having an increased rate of attrition and brain and bladder and prostate cancers having decreased rates of attrition. With any type of cancer diagnosis, symptom burden is a concern. In fact, Bubis and colleagues reported that cancer site was significantly associated with higher odds of symptom burden, particularly for those with respiratory and

oropharyngeal cancers.¹⁴ Patients might suffer from a constellation of emotional, cognitive, and physical symptoms that affect their ability to participate in research. A more in-depth analysis as well as additional data is needed to appreciate the specific issues for participants with cancers in different disease sites who were lost to attrition and the types of formal and informal support mechanisms they might need to remain actively enrolled on a trial. Better understanding is needed of the different types of symptoms that might lead to attrition based on disease site and the type of treatment modalities that participants are receiving, including participation in cancer clinical trials. In-depth qualitative data could begin to explore these issues, particularly as they relate to symptom burden and distress.

The enrollment of women in research continues to be an issue of concern for all researchers despite establishment of federal guidelines for their inclusion in human subjects research in 1993.¹⁵ A report from the National Institutes of Health (NIH), however, suggests that a larger percentage of women are participating in NIH clinical research and Phase III trials since 1993.¹⁶ Yet, these data do not specify the percentage of women enrolled in cancer clinical trials, which seem to be lagging behind. In our sample, slightly more than a third of participants in fixed trials were women, while approximately 29.5% of participants in event-related trials were women. This is consistent with the findings of Jargisi and colleagues who reported that women remained underrepresented in published clinical cancer research studies; in their work, an average of 38.8% of women participated in non-sex-specific studies and there was a lower proportion of women included in the 7 non-sex specific cancer types that they assessed (e.g., lung, head and neck, gastrointestinal, hematological).¹⁷ To some degree, it is not surprising to find that women are more likely than men to be lost to attrition. Today, many women are financially self-sufficient, raising children on their own, taking care of older parents, and involved in other life/care-giving role activities. A better picture is needed of how women's caregiving role and gender differences affect clinical trial participation and retention and the amount of support that women need once enrolled in a trial.

In the cohort that we analyzed, attrition was also higher in X institutions in the West and in the South. Both of these areas in the country generally have higher percentages of minority populations. The number of minority participants in our sample was lower than Caucasians overall, however, we don't have data on the breakdown by region. For example, Hispanics now comprise about 17% of the U.S. population and more than 50% of the Hispanic population resides in three states, including California, Texas, and Florida.¹⁸ More process oriented data on the experiences of minorities participating in research within these particular XXXX sites is clearly needed. Real-time data capture of minority participants' day-to-day experiences of participating in clinical trials may provide us with insights on factors influencing retention.

The main strength of this study includes the extensive review of XXXX radiation-based cancer trials over an extended period of time. Nonetheless, there are several limitations. First, a measure of toxicity was not included because of the variability in measuring toxicity throughout the years. Future studies need to take this into consideration as symptom-related distress and toxicity could be a significant predictor of attrition. Patients experience various degrees of symptom burden associated with cancer and cope differently depending on their

degree of tolerance and what experimental side effects they are willing to accept to extend their life or remain hopeful for a cure. However, the relationship between disease status, symptom burden, toxicity and attrition is not known. As symptoms progress or remain unabated, it could significantly impact retention in a clinical trial and would be important to assess in future work. Because of the retrospective review of our data and the limitations associated with collecting certain demographic variables in earlier time periods, we don't know, for example, what role social support networks or the support of a loving partner, spouse, or friend might play in retention. When we assessed marital status using a subgroup of patients with complete data, however, we found that those who were married or had a live-in-partner were more likely lost to attrition. Future research should also examine these types of issues.

The results suggest several areas for consideration. First, because attrition of women in XXXX cancer clinical trials remains a considerable issue, further dialogue, research, and targeted efforts are needed to understand the specific concerns of diverse groups of women. Additionally, the limited research on gender differences and retention in clinical trials demands more work on life-balance issues that arise during the course of study participation, especially for women. Indeed, in some cases women continue to be underrepresented in clinical trials yet these clinical trials are used to formulate women's health guidelines.¹⁹ Second, many patients recognize that they have an incurable disease yet still choose to participate in research for a variety of reasons. Integrating palliative care within clinical trials can allow patients to participate in research and simultaneously address their symptoms, psychological or other immediate individual, family, and health-related needs. Innovative models of care are needed that provide a seamless transition from clinical trial participation to quality end-of-life care. Third, for trials with a time-to-event endpoint, (i.e. longer follow-up times), general efforts to keep patients engaged such as scheduling the next visit at the time of the last visit and telephone contact may benefit from additional electronic contact using text and email messages or other types of social media.

In conclusion, this data suggest more research is needed to examine the rates of attrition in different kinds of trials, reasons for higher attrition in women, younger individuals, those enrolled in geographically diverse institutions as well as further dialogue on the role of palliative care within clinical trials given the attrition rates for fixed trials. In addition, it would be useful to begin a dialogue among the different cooperative groups on the development of innovative strategies to address retention issues specific to each network group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Patients at Risk											
Fixed	8634	2767	1280	768	374	233	122	68	29	5	0
Event Driven	18809	15013	12017	9755	7674	5326	3643	2578	1988	1458	1007

Figure 1.
Time to Attrition

Table 1

Descriptive Statistics by Type Of Endpoint

	Fixed Time (n=8634)	Event Driven (n=18809)
<i>Institution Characteristics</i>		
Institution Type		
Full	4191 (48.5%)	7818 (41.6%)
Affiliate	2572 (29.8%)	5815 (30.9%)
CCOP	1023 (11.8%)	2269 (12.1%)
Satellite	553 (6.4%)	1096 (5.8%)
Not an RTOG Member	288 (3.3%)	1811 (9.6%)
Not Reported	7 (0.1%)	0 (0.0%)
Institution Region		
New England	1827 (21.2%)	3970 (21.1%)
Midwest	2431 (28.2%)	4982 (26.5%)
South	2295 (26.6%)	4462 (23.7%)
West	1398 (16.2%)	2939 (15.6%)
International	676 (7.8%)	2456 (13.1%)
Not Reported	7 (0.1%)	0 (0.0%)
<i>Trial Characteristics</i>		
Disease Site		
Bladder	389 (4.5%)	0 (0.0%)
Brain	1105 (12.8%)	3556 (18.9%)
Breast	150 (1.7%)	589 (3.1%)
Gastrointestinal	1581 (18.3%)	2051 (10.9%)
Gynecological	874 (10.1%)	416 (2.2%)
Head & Neck	1460 (16.9%)	3708 (19.7%)
Lung	1516 (17.6%)	1939 (10.3%)
Prostate	1474 (17.1%)	6550 (34.8%)
Sarcoma	85 (1.0%)	0 (0.0%)
<i>Patient Characteristics</i>		
Age (years)		
Median	62	63
Min – Max	18 – 93	18 – 91
Q1 – Q3	53 – 70	54.7 – 71
Zubrod		
0	6023 (69.8%)	11440 (60.8%)
1	2495 (28.9%)	6904 (36.7%)
2–3 *	113 (1.3%)	463 (2.5%)
Unknown	3 (0.0%)	2 (0.0%)
Gender		
Male	5507 (63.8%)	13245 (70.4%)

	Fixed Time (n=8634)	Event Driven (n=18809)
Female	3121 (36.1%)	5554 (29.5%)
Not Reported	6 (0.1%)	10 (0.1%)
Ethnicity/race		
White, non-Hispanic	5712 (66.2%)	12778 (67.9%)
Hispanic	293 (3.4%)	522 (2.8%)
Black, non-Hispanic	769 (8.9%)	2086 (11.1%)
Native Hawaiian/Pacific Islander	6 (0.1%)	25 (0.1%)
Asian	105 (1.2%)	152 (0.8%)
Native American/Alaskan Native	29 (0.3%)	64 (0.3%)
Other	54 (0.6%)	86 (0.5%)
Not Reported	1666 (19.3%)	3096 (16.5%)
Marital Status		
Married/Live-In Partner	4475 (51.8%)	8723 (46.4%)
Single/Divorced/Separated/Widowed	1973 (22.9%)	4037 (21.5%)
Not reported	2186 (25.3%)	6049 (32.2%)
Education Completed		
None	142 (1.6%)	243 (1.3%)
Grade 1–8	641 (7.4%)	1754 (9.3%)
Grade 9–11	1299 (15.0%)	2466 (13.1%)
Completed HS/GED	1335 (15.5%)	2959 (15.7%)
Vocational School	35 (0.4%)	0 (0.0%)
Some College/Associate Degree	2055 (23.8%)	4098 (21.8%)
Bachelor's Degree	331 (3.8%)	314 (1.7%)
Advanced Degree	218 (2.5%)	197 (1.0%)
Other	54 (0.6%)	50 (0.3%)
Not Reported	2524 (29.2%)	6728 (35.8%)
<i>Trial Characteristic</i>		
Year Trial Activated		
Mean	1995	1996
Std. Dev.	6.160	5.690
Median	1995	1994
Min – Max	1985 – 2008	1985 – 2006
Q1 – Q3	1991 – 2001	1992 – 2000

*
Only 1 patient with Zubrod performance status 3

Table 2

Attrition Estimates

Time (Years)	All trials		Event Driven Trials		Fixed Time Trials Trial Duration 6 months		Fixed Time Trials Trial Duration <6 months	
	% Lost to Attrition (95% CI)	# at Risk	% Lost to Attrition (95% CI)	# at Risk	% Lost to Attrition (95% CI)	# at Risk	% Lost to Attrition (95% CI)	# at Risk
0	0% (N/A)	27443	0% (N/A)	18809	0% (N/A)	3552	0% (N/A)	5082
1	1.0% (0.9, 1.1)	17780	0.5% (0.4, 0.6)	15013	1.6% (1.2, 2.1)	2767	0.5% (0.3, 0.7)	4847
2	3.1% (2.9, 3.4)	13297	1.9% (1.8, 2.2)	12017	8.8% (7.7, 10.0)	1280	0.6% (0.4, 0.9)	4266
3	6.2% (5.8, 6.5)	10523	4.7% (4.4, 5.0)	9755	14.8% (13.2, 16.3)	768	0.8% (0.6, 1.1)	3912
4	9.6% (9.2, 10.0)	8048	8.2% (7.8, 8.6)	7674	18.6% (16.8, 20.5)	374	3.0% (2.3, 3.7)	946
5	15.0% (14.5, 15.6)	5559	13.6% (13.1, 14.1)	5326	25.1% (22.7, 27.6)	233	4.3% (3.4, 5.5)	288
6	19.5% (18.8, 20.1)	3765	18.0% (17.4, 18.6)	3643	30.8% (27.9, 33.7)	122	7.2% (4.3, 11.1)	0
7	23.1% (22.4, 23.8)	2646	21.5% (20.8, 22.3)	2578	36.9% (33.5, 40.3)	68	-	-
8	26.1% (25.3, 26.8)	2017	24.5% (23.7, 25.2)	1988	42.8% (39.1, 46.5)	29	-	-
9	28.9% (28.1, 29.7)	1463	27.2% (26.4, 28.0)	1458	49.5% (45.5, 53.4)	5	-	-
10	31.5% (30.7, 32.4)	1007	29.9% (29.0, 30.8)	1007	-	-	-	-
11	34.1% (33.2, 35.0)	656	32.5% (31.6, 33.5)	656	-	-	-	-
12	37.8% (36.8, 38.8)	356	36.4% (35.4, 37.4)	356	-	-	-	-
13	41.8% (40.7, 42.8)	143	40.6% (39.5, 41.7)	143	-	-	-	-
14	46.0% (44.7, 47.4)	11	45.0% (43.6, 46.4)	11	-	-	-	-
15	48.5% (46.3, 50.6)	0	47.5% (45.3, 49.8)	0	-	-	-	-
Patients Lost to Attrition/Total	4519/27443		3915/18809		500/3552		104/5082	
Median Follow-up time (range)	22.2 months (0.03–172.4)		37.2 months (0.07–172.4)		15.9 months (6.02–110.3)		3.5 months (0.03–5.99)	

Table 3

Time to Attrition Cause-Specific Cox Proportional Hazards Multiple Regression Model Complete Case

Variables	Hazard Ratio	95%CI	P-value
Age (≥ 65 vs. <65 [RL])	0.876	(0.81–0.95)	0.0007
Year of Trial Activation (≥ 1994 vs. <1994 [RL])	0.440	(0.40–0.48)	<.0001
Institution Type (CCOP/ Affiliate/Satellite/Not an RTOG vs. Full Member [RL])	1.102	(1.03–1.18)	0.0054
Institution Region (US New England /Midwest [RL] vs.			
US South/West	1.069	(0.99–1.15)	0.0595
International)	1.126	(1.02–1.25)	0.0249
Zubrod Performance Status (≥ 1 vs. <1 [RL])	3.662	(3.33–4.03)	<.0001
Gender (Male vs. Female[RL])	0.840	(0.77–0.92)	0.0002
Type of Endpoint (Event Driven vs. Fixed [RL])	0.542	(0.48–0.61)	<.0001
Disease Site (Brain [RL] vs.			
Gastrointestinal	1.893	(1.63–2.20)	<.0001
Head & Neck	1.408	(1.22–1.63)	<.0001
Sarcoma & Lung	3.568	(3.03–4.21)	<.0001
Bladder & Prostate	0.919	(0.79–1.08)	0.2917
Gynecological & Breast	1.214	(1.03–1.44)	0.0238
Patients Lost to Attrition/Total	3788/22660		
Patients Lost to Death	8221		

RL = Reference Level

Table 4

Time to Attrition Cause-Specific Cox Proportional Hazards Multiple Regression Model Imputed Analysis

Variables	Hazard Ratio	95%CI	P-value
Year of Trial Activation (1994 vs. <1994 [RL])	0.434	(0.40–0.47)	<.0001
Institution Type (CCOP/ Affiliate/Satellite/Not an RTOG vs. Full Member [RL])	1.160	(1.09–1.23)	<.0001
Institution Region (US New England /Midwest [RL] vs.			
US South/West	1.118	(1.05–1.19)	0.0005
International)	1.097	(0.99–1.21)	0.0620
Zubrod Performance Status (1 vs. <1 [RL])	2.993	(2.75–3.25)	<.0001
Gender (Male vs. Female[RL])	0.898	(0.82–0.98)	0.0136
Type of Endpoint (Event Driven vs. Fixed [RL])	0.559	(0.51–0.62)	<.0001
Disease Site (Brain [RL] vs.			
Gastrointestinal	1.484	(1.29–1.71)	<.0001
Head & Neck	1.019	(0.89–1.16)	0.7846
Sarcoma & Lung	2.543	(2.19–2.95)	<.0001
Bladder & Prostate	0.75	(0.65–0.86)	<.0001
Gynecological & Breast	0.979	(0.84–1.14)	0.7938
Patients Lost to Attrition/Total	4519/27443	at each iteration of imputation	
Patients Lost to Death	9700		

RL = Reference Level