Clinical Trial Accrual at Initial Course of Therapy for Cancer and Its Impact on Survival

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ABSTRACT

Background: This retrospective cohort study sought to characterize the accrual of patients with cancer into clinical trials at the time of diagnosis and analyze the impact of accrual on survival. **Methods:** The National Cancer Database (NCDB) was queried for patients enrolled in clinical trials at their initial course of treatment for 46 cancers from 2004 through 2015. Descriptive statistics were used to characterize the accrual of patients with cancer in clinical trials at diagnosis, and Kaplan-Meier graphical displays, log-rank tests, odds ratios, and stratified Cox proportional hazards models were used to analyze the impact of accrual on overall survival (OS). Strata were defined using 10 variables. Model-based adjusted survival curves of 2 groups were reverse-generated based on a Weibull distribution. **Results:** Of 12,097,681 patients in the NCDB, 11,576 (0.1%) were enrolled in trials. Patients in clinical trials typically had metastatic disease (30.9% vs 16.4%; $P < .0001$), were white (88.0% vs 84.8%; $P < .0001$), had private/managed care insurance (56.4% vs 41.8%; $P < .0001$), had fewer comorbidities (Charlson-Deyo score 0: 81.9% vs 75.7%; $P < .0001$, and Charlson-Deyo scores 1–3: 18.1% vs 24.3%; $P < .0001$) compared with those not in trials. At a median follow-up of 64 months, enrollment in a clinical trial was associated with improved OS in univariate and stratified analyses, with a median survival of 60.0 versus 52.5 months (hazard ratio, 0.876; 95% CI, 0.845–0.907; $P < .0001$). Stratified analysis with matched baseline characteristics between patients enrolled and not enrolled in a clinical trial showed superior OS at 5 years (95.0% vs 90.2%; $P < .0001$). **Conclusions:** Enrollment in clinical trials at first line of therapy in the United States is exceedingly low and favors young, healthy, white patients with metastatic disease and private insurance who are treated at academic medical centers. Patients with cancer treated in clinical trials live longer than those not treated in trials.

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Background

A clinical trial is defined by the NIH¹ as “a research study in which one or more human subjects are prospectively assigned to one or more interventions...to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.” NCCN believes that the best management for any patient with cancer is in a clinical trial.² Only 2% to 4% of patients diagnosed with cancer participate in clinical trials in the United States,³ with most enrolled at recurrence and not at initial therapy. Several barriers to clinical trial accrual have been proposed. Lara et al⁴ reported that, compared with patients in clinical trials, those who declined trial enrollment were more likely to desire other treatment, live farther from the cancer center, or have private insurance (vs government-funded insurance). It is currently unknown whether accrual onto clinical trials provides a survival benefit for patients and whether the healthcare system should focus on overcoming these barriers, such as by opening trials in more rural and underserved areas or by providing some form of government insurance that would cover costs for patients in a trial.

A systematic review published in 2004 found “little high-quality evidence to support the pervasive belief that cancer trial participation leads to improved outcomes.”⁵ Of 24 included studies, approximately half provided some evidence for a trial effect, and none found trial participation to be harmful, but methodological difficulties with most studies suggested the need for cautious interpretation. The investigators noted that most of the included studies did not adjust for potential confounders, including sex, socioeconomic status, and comorbidity.

The rate of patients being enrolled in a clinical trial at the first course of therapy and predictors of clinical trial accrual are unknown; moreover, it is unknown whether enrollment in a trial offers a survival benefit to patients.

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The purpose of our study was to characterize accrual of patients with cancer in clinical trials at the time of diagnosis and analyze the impact of accrual on survival. We hypothesized that patient accrual in clinical trials is associated with improved survival.

Methods

We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement in the design and reporting of the present analysis (supplemental eTable 1, available with this article at JNCCN.org).⁶ The National Cancer Database (NCDB) is a hospital-based cancer registry that collects data from American College of Surgeons Commission on Cancer (CoC)-accredited facilities. The NCDB is sponsored by the American College of Surgeons and the American Cancer Society and includes 70% of all malignant cancers diagnosed in the United States. The NCDB⁷ records demographics, comorbidities, tumor characteristics, and overall survival (OS), and contains information regarding therapies delivered during the first course of treatment (ie, surgery, radiation therapy [RT], chemotherapy, hormone therapy, immunotherapy, and palliative care).

Patients

Eligibility criteria included all patients with a cancer diagnosis among the 46 disease sites with the highest global incidence.⁸ Treatment coding in the NCDB is limited to the first course of treatment, defined as all methods of therapy recorded in the treatment plan and administered before disease progression or recurrence. Data regarding specific agents of systemic therapy administered were not available. Clinical trial participation was assessed using the variable "RX_SUMM_OTHER," which is defined by the CoC as identifying "other treatment that cannot be defined as surgery, radiation, or systemic therapy according to the defined data items in this manual."⁹ In our study, cases were defined as those with a value of "2, participation in institution-based clinical trials," and "3, a patient is involved in a double-blind clinical trial." For these codes, once the patient has been unblinded, they are coded with the treatment that they were known to have received (eg, surgery, chemotherapy, and RT); however, this variable is not independent or mutually exclusive of other treatment-related details. Thus, it should be noted that the coding of treatments for patients in a trial versus those not in a trial is relatively similar (Table 1).

When the coded variables were 8 or 9, which are unknown variables, they were excluded from the analysis. All other variables (no trial, refusal of trial) were considered as not being enrolled in a clinical trial and were coded as controls. Because the NCDB is limited to the

first course of treatment, patients enrolled in clinical trials after the first course (ie, at the time of disease progression) are not coded in the NCDB and therefore were not identified in our analysis.

Outcome Measures

The primary objective of our study was to characterize the accrual of patients with cancer in clinical trials at the time of diagnosis. The secondary objective was to analyze the effect of trial enrollment on survival.

Statistical Analysis

Descriptive statistics were used to evaluate the primary objective. Predictors of clinical trial enrollment were calculated using odds ratios (ORs) and 95% CIs. For the secondary objective, the OS of patients diagnosed with one of the top 10 cancers with the highest trial enrollment was analyzed using Kaplan-Meier graphical displays, log-rank tests, and hazard ratios (HRs) derived from stratified Cox proportional hazards models with 95% CIs. For survival estimates, we reverse-generated the model-based adjusted survival curves of 2 groups based on a Weibull distribution.

Strata were defined with 10 variables:

1. Ten cancer subtype levels, based on the disease sites with the greatest absolute number of patients in trials: breast, non-small cell lung cancer (NSCLC), pancreas, acute myeloid leukemia, brain, prostate, melanoma, kidney, myeloma, and colorectal
2. Two facility levels: community and academic
3. Four age group levels, based on quartile of age
4. Twelve years of diagnosis levels, 2004–2015
5. Three race levels: white, black, and other
6. Four Charlson-Deyo comorbidity score levels: 0–3
7. Five insurance levels: none, private, Medicaid, Medicare, and other government/unknown
8. Six disease stage levels: 0–4 or unknown
9. Two surgery levels: yes or no
10. Two chemotherapy levels: yes or no

Facility treatment volume may be positively correlated with clinical trial accrual, and there may be collinearity between these 2 variables. We considered also adjusting for facility volume, but given the large number of strata ($n=4,748$), incorporation of treatment volume was not possible for our analysis because it significantly decreased the number of patients. Similarly, approximately 60% of patients received RT at some point in their disease course, but only 27% received external-beam RT and 5% received radioactive implants or isotopes. We would ideally want to stratify for the use of RT, but this would have created too many strata, limiting the analysis.

Table 1. Demographic and Clinical Characteristics

Characteristic	Enrolled n (%)	Not Enrolled n (%)
Patients, N	11,576	12,086,105
Age, median (IQR), y	59 (51–68)	65 (55–74)
Sex		
Male	5,931 (51.2)	6,499,323 (53.8)
Female	6,445 (48.8)	5,586,782 (46.2)
Race		
White	10,183 (88.0)	10,252,942 (84.8)
Black	823 (7.1)	1,266,023 (10.5)
Other	570 (4.9)	567,140 (4.7)
Insurance status		
Uninsured	260 (2.2)	364,901 (3.0)
Private/Managed care	6,528 (56.4)	5,054,019 (41.8)
Medicaid	636 (5.5)	668,601 (5.5)
Medicare	3,721 (32.1)	5,587,387 (46.0)
Other government	151 (1.3)	147,266 (1.2)
Unknown	280 (2.4)	263,931 (2.2)
Disease stage		
0	257 (2.2)	1,001,520 (8.3)
I	1,179 (10.2)	3,402,584 (28.2)
II	1,863 (16.1)	2,529,934 (20.9)
III	2,155 (18.6)	1,634,567 (13.5)
IV	3,573 (30.9)	1,981,020 (16.4)
Unknown/Other	2,549 (22.0)	1,536,480 (12.7)
Cancer type (top 11)		
Breast	2,252	2,437,408
Non–small cell lung cancer	1,324	1,385,960
Pancreas	1,088	336,690
Acute myeloid leukemia	845	97,770
Brain	709	202,765
Prostate	672	1,375,422
Melanoma	690	521,922
Kidney	944	462,370
Myeloma	397	148,934
Colon	338	829,581
Non-Hodgkin's lymphoma, nodal	284	339,399
Distance from facility, median miles (IQR)	16.8 (7.0–45.0)	9.6 (4.3–22.9)
Charlson-Deyo comorbidity score		
0	9,483 (81.9)	9,143,662 (75.7)
1	1,677 (14.5)	2,152,368 (17.8)
2	296 (2.6)	556,732 (4.6)
3	120 (1.0)	233,343 (1.9)

(continued)

Abbreviation: IQR, interquartile range.

Table 1. Demographic and Clinical Characteristics (cont.)

Characteristic	Enrolled n (%)	Not Enrolled n (%)
Treatment		
Hormone therapy	2,348 (20.3)	2,059,561 (17.0)
Immunotherapy	953 (8.2)	303,153 (2.5)
Surgery	7,353 (63.5)	8,140,516 (67.4)
Radiation therapy	3,690 (31.9)	3,850,799 (31.9)
Palliative therapy	751 (6.5)	463,753 (3.8)
Chemotherapy	7,269 (62.8)	3,883,532 (32.1)

Abbreviation: IQR, interquartile range.

We considered using propensity score matching and adjusting for other variables as well, but given our large sample size and number of patients not enrolled in trials, a stratified analysis provided the best statistical assessment. With stratification, all individuals within a stratum are perfectly matched in terms of the set of covariates. However, propensity scores could yield individuals with similar propensity scores who have very different values for the set of covariates. Stratification is preferred if it does not cause too much loss of data (strata that consist of members of one group only).

Additionally, the unadjusted and adjusted 30-day readmission rates for the 2 groups were calculated using ORs and 95% CIs. The adjusted model was fit using a mixed-effects logistic regression model, stratified based on the 10 predictors, and a random intercept was introduced to the model to represent the heterogeneity between strata.

Results

Primary Objective

From 2004 through 2015, of 12,097,681 patients in the NCDB, 11,576 (0.1%) were enrolled in institutional or double-blind trials in the United States (Figure 1). Patient demographics in the unadjusted analysis are shown in Table 1. Figure 2 shows the patients in clinical trials versus those diagnosed with cancer. Among those in trials versus not in trials, the median age was 59 years (interquartile range [IQR], 51–68 years) versus 65 years (IQR, 55–74 years), respectively, and 51.2% versus 53.8% were male. The most common disease sites of patients enrolled in clinical trials were breast cancer (n=2,252; 0.09%) and NSCLC (n=1,324; 0.10%) compared with those not enrolled. Patients in clinical trials versus those not in trials more typically had metastatic disease (30.9% vs 16.4%; $P<.0001$), were white (88.0% vs 84.8%; $P<.0001$), had private insurance (56.4% vs 41.8%; $P<.0001$), had fewer comorbidities (Charlson-Deyo score 0: 81.9% vs 75.7%; $P<.0001$, and Charlson-Deyo scores

Figure 1. Patient groups included in analysis. First, 11,576 patients on trial and 12,086,105 patients not on trial were identified, and these were used to compute patient characteristics (Table 1). To perform the survival analysis of patients on clinical trial versus not on a clinical trial with a stratified approach (Figure 2), we included 7,903 versus 1,707,620 patients, respectively.

Abbreviation: NCDB, National Cancer Database.

1–3: 18.1% vs 24.3%; $P<.0001$), and lived farther from the treatment center (median, 16.8 [IQR, 7.0–45.0] vs 9.6 miles [IQR, 4.3–22.9]).

A significant proportion of disease staging was recorded as unknown/other for patients enrolled in trials (22.0%)—much higher than that for patients not enrolled (12.7%), because more of the enrolled patients were diagnosed with cancers for which staging was not applicable (eg, myeloma, leukemia, liver), representing 60% of the unknown cases, or because the cancers were unknown (eg, melanoma, rectum, breast, colon). Furthermore, in the unadjusted analysis, patients in trials versus not in trials were less likely to receive surgery (63.5% vs 67.4%; $P<.0001$), equally likely to receive RT (31.9% vs 31.9%; $P=.6$), and more likely to receive chemotherapy (62.8% vs 32.1%; $P<.0001$), hormone therapy (20.3% vs 17.0%; $P<.0001$), immunotherapy (8.2% vs 2.5%; $P<.0001$), and palliative care (6.5% vs 3.8%; $P<.0001$). After adjustment for all variables in our model (ORs shown in Table 2), predictors of clinical trial enrollment included having acute myeloid leukemia, treatment at an academic facility, young age, more recent year of diagnosis, white race, fewer comorbidities, and receipt of chemotherapy and surgery.

Secondary Objective

Among patients with the top 10 tumors with the highest trial enrollment rates, without stratification, median survival for those not enrolled in a trial versus those enrolled was 5.70 (95% CI, 5.70–5.71) versus 5.00 years (95% CI, 4.87–5.12). The 5-year OS for those in trials versus not in trials was 0.57 versus 0.50, and the 10-year

OS was 0.13 versus 0.11. After stratification based on 10 variables and removing strata without case or control patients, there were a total 1,715,523 patients, with 1,707,620 not in trials (control patients) and 7,903 in trials (cases), leaving 4,748 strata (Figure 1). At a median follow-up of 64 months, patients enrolled in a clinical trial versus those not enrolled had improved OS in univariate and stratified analyses, with median survival time of 60.0 versus 52.5 months (HR, 0.886 (95% CI, 0.845–0.907; $P<.0001$) (Figure 3). The hazard for patients enrolling in trials was significantly less than that for patients not enrolling in trials (12% less), matching on the 10 variables. In addition, patients treated in trials had a significantly lower rate of readmission (adjusted OR, 0.715; 95% CI, 0.563–0.910; $P=.006$).

We performed further analyses using a stratified Cox model fitted for each disease site or stage. HRs for all sites and stages are summarized in Table 3. The largest benefit for survival was noted for patients with brain cancer (HR, 0.684; 95% CI, 0.557–0.839), NSCLC (HR, 0.693; 95% CI, 0.603–0.796), and kidney cancer (HR, 0.789; 95% CI, 0.712–0.874).

Discussion

This is the first contemporary study to assess accrual of patients with cancer in clinical trials at the initial course of treatment and the impact of accrual on survival. We report 3 important findings. First, enrollment in clinical trials at the first line of therapy in the United States is exceedingly low, at 0.1% of patients. Second, clinical trial enrollment favors young, healthy, white patients with metastatic disease and private insurance who are treated at academic medical centers. Third, patients with cancer treated in clinical trials live longer than those not treated in trials, with an HR of 0.876 (95% CI, 0.845–0.907). Our findings support the recommendation by NCCN, which states that the best management for any patient with cancer is in a clinical trial,² and the Canadian Cancer Research Alliance, which states that the outcomes of patients with cancer will not continue to improve without clinical trials. Further efforts are needed to increase clinical trial accrual, particularly for underserved minority patients.

In the United States, >60% of children with cancer are enrolled in clinical trials; however, for those aged >20 years, accrual decreases to 2% to 4%, raising concerns about the generalizability of trial results to the general population.^{10–12} Notably, these rates are for a clinical trial at any point in the disease course (including at time of recurrence) and do not focus on clinical trial accrual at the initial course of treatment. Our findings showed that patients diagnosed with the top 10 cancers with the highest clinical trial accrual at initial course of treatment tended to be healthy and white and to have metastatic disease and private insurance (Table 1).

Figure 2. Patients enrolled in a clinical trial at first course of treatment versus patients diagnosed with cancer. The log-transformed number of patients diagnosed with the top 46 cancers is shown on the x-axis and of those entering a clinical trial at first course of treatment is shown on the y-axis.

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; NOS, not otherwise specified; SCLC, small cell lung cancer.

Although a previous systematic review concluded that enrollment in clinical trials was not associated with a survival benefit,⁵ it did not account for potential confounders, including socioeconomic status, age, race, comorbidity, or treatment year. Since that review, modern studies have been published showing a survival benefit for patients enrolled in trials,^{13–15} after adjusting for confounders. Similarly, we found a benefit for survival among patients enrolled in a trial. The impact of trial accrual on survival may be secondary to the increased care received by patients, such as improved quality assurance¹⁶ or early palliative care referral.¹⁷ We recommend that the healthcare system focus on alleviating known barriers⁴ to improve clinical trial accrual.

The impact of clinical trial accrual on survival has been assessed in several cancers, and the results of our work (Table 2, Figure 3) support the findings of these prior studies. For example, Wuthrick et al¹³ assessed the survival of patients with head and neck cancer treated at low- versus high-accruing centers and found that patients at low-accruing centers had better Zubrod performance status (0: 62% vs 52%; $P=.04$) and lower T stage

(T4: 26.5% vs 35.3%; $P=.002$), but were otherwise similar. RT protocol deviations were higher at low-accruing than at high-accruing centers (18% vs 6%; $P<.001$). Compared with patients at high-accruing centers, those at low-accruing centers had worse OS (5 years, 51.0% vs 69.1%; $P=.002$). Treatment at low-accruing centers was associated with increased risk of death of 91% (HR, 1.91; 95% CI, 1.37–2.65) after adjustment for prognostic factors and 72% (HR, 1.72; 95% CI, 1.23–2.40) after RT compliance adjustment. Similarly, Arrieta et al¹⁴ reported a retrospective review of 1,042 patients with NSCLC in Mexico treated from 2007 through 2014 and concluded that enrollment in a clinical trial was associated with better OS (HR, 0.47–0.74), independent of other confounders.

Few other studies have assessed the impact of clinical trial accrual on survival among many cancers. Chow et al¹⁵ queried the California Cancer Registry and identified 555,469 patients with cancer. Enrollment in cancer trials was associated with a lower hazard of death. However, after stratification by disease site, survival benefit was observed only in lung, colon, and

Table 2. Predictors of Enrollment in a Clinical Trial

Predictor	Odds Ratio (95% CI)
Cancer type	
Acute myeloid leukemia	Ref
Brain	0.497 (0.446–0.553)
Breast	0.108 (0.091–0.128)
Colon	0.037 (0.030–0.045)
Kidney and renal pelvis	0.221 (0.185–0.265)
Non-small cell lung cancer	0.072 (0.060–0.086)
Melanoma	0.178 (0.148–0.215)
Myeloma	0.340 (0.300–0.385)
Pancreas	0.213 (0.177–0.255)
Prostate	0.058 (0.048–0.071)
Treatment facility	
Community	Ref
Academic	3.484 (3.304–3.674)
Age group quartile (range, 40–90)	
<0.25 (40–54; youngest)	Ref
0.25–<0.50 (55–64)	0.854 (0.807–0.904)
0.50–<0.75 (65–73)	0.786 (0.726–0.851)
≥0.75 (74–90; oldest)	0.482 (0.438–0.529)
Year of diagnosis	
2004	Ref
2005	0.657 (0.577–0.749)
2006	0.538 (0.469–0.617)
2007	0.563 (0.493–0.643)
2008	0.804 (0.713–0.905)
2009	0.871 (0.775–0.978)
2010	0.804 (0.714–0.905)
2011	1.157 (1.038–1.289)
2012	1.208 (1.085–1.345)
2013	1.212 (1.089–1.348)
2014	1.280 (1.153–1.422)
2015	1.424 (1.284–1.579)

(continued)

breast cancers. Unger et al¹⁸ reviewed the SWOG national clinical trials consortium. Among 5,190 patients enrolled in trials from 1987 through 2007, participation was not associated with improved OS for all 11 good-prognosis studies but was associated with better survival for 9 of 10 poor-prognosis studies ($P<.001$). Our analysis found the survival impact to be present for all cancers.

Our study has limitations. First, the definition of being on trial was limited to an institutional or a double-blind study, and single-arm studies may have been excluded. In addition, because data in the NCDB is limited to the first course of treatment, patients enrolled in clinical trials after their first course of therapy (ie, at

Table 2. Predictors of Enrollment in a Clinical Trial (cont.)

Predictor	Odds Ratio (95% CI)
Race	
White	Ref
Black	0.543 (0.498–0.593)
Other	0.830 (0.745–0.925)
Charlson-Deyo comorbidity score	
0	Ref
1	0.790 (0.742–0.841)
2	0.590 (0.515–0.676)
3	0.511 (0.406–0.644)
Insurance status	
None	Ref
Private	2.089 (1.782–2.449)
Medicaid	1.224 (1.016–1.474)
Medicare	1.683 (1.421–1.993)
Other government/unknown	1.696 (1.320–2.178)
Disease stage	
0	Ref
I	1.350 (1.154–1.581)
II	3.034 (2.596–3.547)
III	5.854 (5.00–6.853)
IV	8.590 (7.299–10.109)
Unknown/Other	2.082 (1.696–2.556)
Surgery	
No	Ref
Yes	1.128 (1.051–1.211)
Chemotherapy	
No	Ref
Yes	1.769 (1.666–1.879)

time of disease progression) are not coded in the NCDB and could not be identified in our analysis. An estimated 2% to 4%³ of patients with cancer in the United States are enrolled in clinical trials, and our study captures a fraction of these patients. Furthermore, the number of patients for whom a clinical trial was available (ie, eligible for screening but not necessarily enrollment) may be a more appropriate denominator. There are many patients with cancer for whom a clinical trial is not available, simply because no one is asking a specific question for that particular cancer subtype or stage or because no such trial was available at the specific institution where the patient was treated and had their NCDB coding. There are also trials available for patients with metastatic cancer, but they typically enroll patients at the first course of treatment or at the time of

Figure 3. Kaplan-Meier cumulative rates for stratified groups using a Weibull method.

recurrence/progression (which would not be captured by the NCDB). Even if we were to provide a list of open trials during the 2004–2015 period to determine the number of trials open for metastatic versus nonmetastatic disease, it would not provide an accurate estimate of eligible patients at any point in their disease course. Thus, our reported “rate” of 0.1% of patients being enrolled in a trial refers to only those who are eventually enrolled in a trial at the first course of treatment among all patients diagnosed with cancer.

Although we attempted to adjust for age, economic factors, and facility type, it is not clear that bias has been removed from the comparison. There is selection bias in patients enrolled in clinical trials; most had advanced cancer, were white, and had limited comorbidities and private insurance. The NCDB contains variables on comorbidities, but this captures primarily major differences in health, such as hospitalizations, and fails to represent performance status and multiple chronic illnesses. This limitation could lead to overestimation of the impact of clinical trial participation. Performance/functional status can affect a patient’s ability to be eligible for clinical trials, and those who need to start therapy urgently because of symptoms may not be enrolled in upfront clinical trials either. Patients in clinical trials may generally be more motivated and may be more likely to choose aggressive therapy that improves their overall lifespan even at the cost of toxicity. Finally, in a study by Ohri et al,¹⁶ implementation of good quality assurance scores was associated with survival, and the benefit of being in a clinical trial may actually have been due to having proper quality checklists in care.

The NCDB does not collect certain demographic, treatment, and outcome variables, including pulmonary

Table 3. Hazard Ratios Derived From Stratified Cox Model

	Hazard Ratio (95% CI)	P Value
Cancer type		
Acute myeloid leukemia	0.956 (0.808–1.130)	.5980
Brain	0.684 (0.557–0.839)	.0003
Breast	0.897 (0.850–0.946)	.0001
Colon	0.881 (0.737–1.053)	.1650
Kidney and renal pelvis	0.789 (0.712–0.874)	.0000
Non–small cell lung cancer	0.693 (0.603–0.796)	.0000
Melanoma	0.841 (0.726–0.974)	.0207
Myeloma	0.929 (0.800–1.080)	.3380
Pancreas	0.908 (0.747–1.104)	.3320
Prostate	1.062 (0.961–1.175)	.2390
Disease stage		
0	0.739 (0.634–0.861)	.0001
I	0.854 (0.788–0.925)	.0001
II	0.947 (0.886–1.012)	.1070
III	0.882 (0.817–0.953)	.0014
IV	0.834 (0.749–0.929)	.0009
Unknown/Other	0.861 (0.786–0.943)	.0012
Age group quartile (range, 40–90)		
<0.25 (40–54; youngest)	0.889 (0.839–0.942)	<.0001
0.25–<0.50 (55–64)	0.919 (0.866–0.976)	.0058
0.50–<0.75 (65–73)	0.843 (0.779–0.913)	<.0001
≥0.75 (74–90; oldest)	0.722 (0.632–0.824)	<.0001

function tests, specific comorbidities, gene mutations in tumors, progression-free survival, cancer-specific survival, and toxicity. The database is hospital-based, not population-based, and it is meant to measure quality metrics of hospitals. It is limited to hospitals accredited by the CoC, which have more resources than unaccredited hospitals. Hospitals that are not included in the NCDB may have different characteristics regarding clinical trial accrual of patients, and we are unable to explain these characteristics in the current work.

Conclusions

Enrollment in clinical trials at the first line of therapy in the United States is exceedingly low (0.1% of patients at the first course of therapy) and favors young, healthy, white patients with metastatic disease and private insurance who are treated at academic medical centers. Patients with cancer treated in clinical trials live substantially longer than those not treated in trials.

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Supplemental online content for:

Clinical Trial Accrual at Initial Course of Therapy for Cancer and Its Impact on Survival

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eTable 1: STROBE Statement: Checklist of Items That Should Be Included in Reports of Cohort Studies

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	Item No.	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was performed and what was found.
Introduction		
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported.
Objectives	3	State specific objectives, including any prespecified hypotheses.
Methods		
Study design	4	Present key elements of study design early in the paper.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. (b) For matched studies, give matching criteria and number of exposed and unexposed.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.
Data sources/measurement	8 ^a	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.
Bias	9	Describe any efforts to address potential sources of bias.
Study size	10	Explain how the study size was arrived at.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. (e) Describe any sensitivity analyses.
Results		
Participants	13 ^a	(a) Report numbers of individuals at each stage of study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed. (b) Give reasons for nonparticipation at each stage. (c) Consider use of a flow diagram.
Descriptive data	14 ^a	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. (c) Summarize follow-up time (eg, average and total amount).
Outcome data	15 ^a	Report numbers of outcome events or summary measures over time.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% CI). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.
Other analyses	17	Report other analyses performed—eg, analyses of subgroups and interactions, and sensitivity analyses.

(continued on next page)

An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the internet sites of *PLOS Medicine* at <http://www.plosmedicine.org/>, *Annals of Internal Medicine* at <http://www.annals.org/>, and *Epidemiology* at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org/>.

Abbreviation: STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

^aProvide information separately for exposed and unexposed groups.

eTable 1. STROBE Statement: Checklist of Items That Should Be Included in Reports of Cohort Studies (cont.)		
	Item No.	Recommendation
Discussion		
Key results	18	Summarize key results with reference to study objectives.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.
Interpretation	20	Give a cautious overall interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.
Generalizability	21	Discuss the generalizability (external validity) of the study results.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the internet sites of *PLOS Medicine* at <http://www.plosmedicine.org/>, *Annals of Internal Medicine* at <http://www.annals.org/>, and *Epidemiology* at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org/>.

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