Phase 1 Trial Participation and Hospice Enrollment During End-of-Life Care

Background: Hospice care seeks to improve pain management and quality of life at the end of life. Some patients with incurable cancer are enrolled in Phase 1 clinical trials, which are designed to determine medication dosing. Their participation benefits experimental cancer therapies but may not have a direct benefit to the patients themselves. Patients enrolled in Phase 1 clinical trials are not eligible for hospice care. There is concern that enrollment in Phase 1 clinical trials has the potential to lead to decreased quality of life. Therefore, the purpose of our analysis was to examine the relationship between enrollment in Phase I trials and enrollment in hospice, adjusting for potential confounders and precision variables.

Study Design: The study used a retrospective cohort design. Data was obtained at a single cancer treatment center from deceased individuals with a diagnosis of thoracic or head/neck cancer. 203 individuals were selected based on exposure status, enrolled or not enrolled in a Phase 1 trial. All deceased individuals who were enrolled in a Phase 1 trial were included (n=64) as well as 139 deceased individuals who were not enrolled in a Phase 1 trial.

Statistical Methods: To explore the relationship between enrollment in Phase 1 clinical trials and hospice, we conducted model-based standard error estimates of multivariate logistic regression analyses. The model treated the binary indicator of enrollment in a Phase 1 trial as the predictor and the binary indicator of enrollment in hospice as the outcome, adjusting for potential confounding variables including age at metastatic diagnosis, insurance coverage (Government/ Non-Government), lines of therapy, cancer type, and disease stage at metastatic diagnosis. We considered referral to hospice and whether patients had an advanced care planning POLST form in place at time of death (ACP POLST) as precision variables. Based on this model, a Wald test was performed to test the null hypothesis that enrollment in hospice is not associated with enrollment in a Phase 1 trial and the minimum statistical significance level was set at $\alpha = 0.05.$ Covariates were selected a priori. We considered that patients who were older or had fewer lines of therapy may be more likely to be enrolled in Phase 1 trial and hospice. Also, insurance, cancer type, and disease stage may be related to

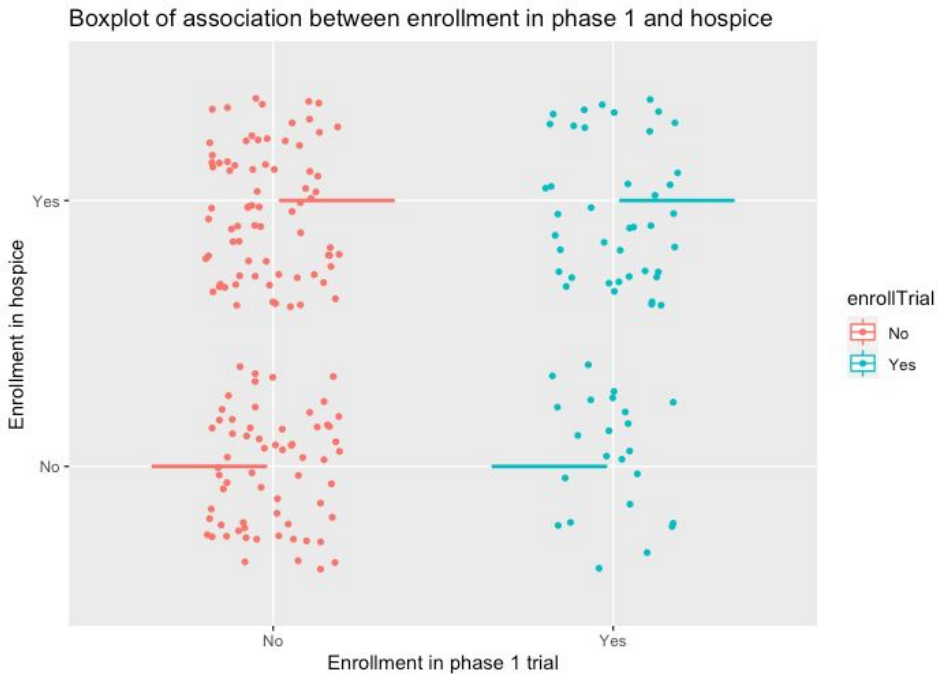
opportunities to be enrolled in Phase 1 clinical trials as well as hospice, and may, thus, be a source of confounding. Independent of clinical trial enrollment, patients who were referred to hospice or had ACP POLST may be more likely to be enrolled in hospice. We treated age at diagnosis as a continuous confounder. The remaining covariates were binary or categorical and adjusted using indicator variables.

Results: Demographic and clinical characteristics of the study sample were presented in *Table 1*. Overall, 73% of patients were diagnosed with lung cancer, 27% diagnosed with head and neck cancer, and 45% had at least 3 lines of therapy. Proportion given a hospice referral was similar in exposure groups, overall 71% of patients received a hospice referral. The mean age at metastatic diagnosis was 61 in the group who enrolled in a Phase 1 trial and 65 in the group who did not. There was substantial missing data (about 40%) for disease stage at metastatic diagnosis. We excluded this co-variate from our logistic regression analysis. We found no statistically significant association between enrollment in a Phase I clinical trial and hospice enrollment after adjusting for confounders and precision covariates (model-based Wald test: p= 0.94) (*Table 2*). Among patients of the same age at diagnosis, insurance, cancer type, stage, treatment, the odds ratio of hospice enrollment comparing patients enrolled or not enrolled in a clinical trial was 1.04 (95%CI: 0.32 - 3.38).

Discussion: The strength of the study was that adjusting for covariates associated with the response variable can improve the precision of estimates by reducing the residual variance; however, covariate adjustment in logistic regression models always leads to a loss of precision. Nonetheless, this loss of precision does not always result in a loss of power[1]. Inclusion of precision variables in a cohort study can offset the loss of precision by increasing the power of the main effect size. However, this study had several limitations. Data was obtained from a single cancer treatment center and may not be generalizable to other clinical settings. Due to limited data collected, we were not able to account for temporal relationships between Phase I trial and hospice enrollment which may have confounded the association. We found no statistically significant relationship between enrollment in a Phase I Clinical Trial and enrollment in hospice care. Additional research is needed to determine if the relationship between enrollment in a Phase I Clinical Trial and enrollment in hospice is clinically significant.

Tables and Figures

Figure 1. Boxplot of association between enrollment in phase 1 trial and hospice.



The boxplot with jittered plots was drawn as exploratory analysis. There was no obvious trend shown in the relationship between enrollment in phase 1 trial and hospice.

Table 1. Key demographic and clinical characteristics of study sample

	Enrolled in phase 1 trials (N=64)	Not enrolled in phase 1 trials (N=139)	Total (N=203)
Enrolled hospice			
No	23 (35.9%)	64 (46.0%)	87 (42.9%)
Yes	41 (64.1%)	75 (54.0%)	116 (57.1%)
Cancer Types			

Head and Neck	28 (43.8%)	26 (18.7%)	54 (26.6%)
Lung Cancer	36 (56.2%)	113 (81.3%)	149 (73.4%)
Government Insurance			
Both	24 (37.5%)	56 (40.3%)	80 (39.4%)
Government Aid/Charity	19 (29.7%)	43 (30.9%)	62 (30.5%)
Non-Government Aid	21 (32.8%)	40 (28.8%)	61 (30.0%)
Age at Metastatic			
Mean (SD)	60.8 (11.6)	65.4 (10.5)	64.0 (11.0)
Median [Min, Max]	62.0 [23.0, 85.0]	66.0 [34.0, 94.0]	65.0 [23.0, 94.0]
Disease Stage at Metastatic Diagnosis			
IB	0 (0%)	1 (0.7%)	1 (0.5%)
III	0 (0%)	1 (0.7%)	1 (0.5%)
IIIA	3 (4.7%)	8 (5.8%)	11 (5.4%)
IIIB	2 (3.1%)	6 (4.3%)	8 (3.9%)
IV	37 (57.8%)	59 (42.4%)	96 (47.3%)
IVA	2 (3.1%)	2 (1.4%)	4 (2.0%)
IVB	2 (3.1%)	0 (0%)	2 (1.0%)
Missing	18 (28.1%)	62 (44.6%)	80 (39.4%)
Lines of therapy (ordinal)			
1	7 (10.9%)	50 (36.0%)	57 (28.1%)
2	7 (10.9%)	46 (33.1%)	53 (26.1%)
>3	50 (78.1%)	41 (29.5%)	91 (44.8%)
Missing	0 (0%)	2 (1.4%)	2 (1.0%)
Referred to Hospice			
No	17 (26.6%)	42 (30.2%)	59 (29.1%)
Yes	47 (73.4%)	97 (69.8%)	144 (70.9%)

ACP POLST			
No	42 (65.6%)	99 (71.2%)	141 (69.5%)
Yes	22 (34.4%)	40 (28.8%)	62 (30.5%)

Table 2: Coefficients or adjusted odds ratios (95% CIs) from the logistic regression model to explore association between Enrollment in Phase 1 Clinical Trial and Enrollment in Hospice

	Enrolled in Hospice		
	Adjusted OR*	95%CI	p-value
Enrolled in Phase 1 Trial	1.04	0.32 – 3.38	0.94
Government insurance			
Both (referent group)	1.00	-	-
Government Aid/Charity	0.99	0.34 – 2.93	0.99
Non-Government Aid	0.51	0.16 – 1.69	0.27
Cancer types			
Head and Neck (ref)	1.00	-	-
Lung cancer	0.37	0.09 – 1.50	0.16

Age at metastatic diagnosis (for each additional year)	0.946	0.898 – 0.998	0.041**
Lines of therapy			
>3 (ref)	1.00	-	-
1	0.39	0.12 – 1.32	0.13
2	0.54	0.17 – 1.76	0.31
Referred to hospice	2.00	0.00 – Inf***	0.99
ACP POLST form in place	2.03	0.75 – 5.48	0.16

*Adjusted for age, insurance coverage, lines of therapy, type of cancer, disease stage at metastatic diagnosis, hospice referral, and POLST form in place at death

**Statistically significant P-Values compared with 0.05.

***Beta estimate for this parameter was 21.3 and model-based standard error was 1.31e+03

Reference

[1] Xing G, Xing C. Adjusting for covariates in logistic regression models. Genet Epidemiol. 2010;34(7):769-772. doi:10.1002/gepi.20526

Codes

```
library(boot)

library(table1)

library(ggplot2)


## Read dataset

hospice <- read.csv("~/Desktop/hospice.csv")


## Descriptive statistics ###################################


## predictor of interest

hospice$enrollTrial <- ifelse(hospice$Enrolled.in.a.phase.1=="Yes",1,0)

hospice$enrollTrial<-factor(hospice$enrollTrial,

                            levels=c(1,0),

                            labels=c("Enrolled in phase 1 trials",

                                     "Not enrolled in phase 1 trials"))

## outcomes

hospice$enrollHospice <- ifelse(hospice$Enrolled.in.Hospice.=="Yes",1,0)

hospice$enrollHospice<-factor(hospice$enrollHospice,
```

```
                levels=c(0,1),

                labels=c("No","Yes"))

## Government insurance

hospice$insureGov<-as.factor(hospice$Insurance.Coverage..Government.Non.Government.)

## cancer diagnosis

hospice$diag21 <- as.factor(hospice$Diagnosis.Simplified)

## Age

hospice$ageDiag <- hospice$Age.at.Metastatic.Locally.Advanced.Diagnosis

## Disease stage

hospice$diseaseStage <- as.factor(hospice$Disease.Stage.at.Metastatic.Diagnosis)

## Lines of therapy

hospice$linesTx <- as.factor(hospice$Lines.of.therapy..ordinal.)

## Referred to hospice

hospice$hospiceRefer <- ifelse(hospice$Referred.to.Hospice.=="Yes",1,0)

hospice$hospicerefer_cha <- as.factor(hospice$Referred.to.Hospice.)

## ACP polst

hospice$ACP <- ifelse(hospice$ACP.polst=="Yes",1,0)

hospice$ACP_cha <- as.factor(hospice$ACP.polst)
```

```
#label variables

label(hospice$enrollTrial)<-"Enrolled Phase 1 Trial"

label(hospice$enrollHospice)<-"Enrolled hospice"

label(hospice$insureGov)<-"Government Insurance"

label(hospice$diag21)<-"Cancer Types"

label(hospice$ageDiag)<-"Age at Metastatic"

label(hospice$diseaseStage)<-"Disease Stage at Metastatic Diagnosis"

label(hospice$linesTx)<-"Lines of therapy (ordinal)"

label(hospice$hospicerefer_cha)<-"Referred to Hospice"

label(hospice$ACP_cha)<-"ACP polst"


## Table 1

a<-table1(~enrollHospice+diag21+insureGov+ageDiag+diseaseStage+linesTx

        +hospicerefer_cha+ACP_cha|enrollTrial,data=hospice,overall="Total")

print(a)


## exploratory analysis ##################################

boxplot(hospice$enrollHospice~hospice$enrollTrial)

p <- ggplot(hospice, aes(x=enrollTrial, y=enrollHospice,color=enrollTrial)) +
geom_boxplot()
```

```
p <- p+ggtitle("Boxplot of association between enrollment in phase 1 and hospice")

p <- p+xlab("Enrollment in phase 1 trial")

p <- p+ylab("Enrollment in hospice")

p

# 0.2 : degree of jitter in x direction

p + geom_jitter(shape=16, position=position_jitter(0.2))



## Analysis ################################################

## omit missing values

na.omit(hospice$linesTx)

## logistics regression

mod <- glm(enrollHospice~enrollTrial+insureGov+diag21+ageDiag

        +linesTx+hospiceRefer+ACP,data=hospice,family="binomial")

summary(mod)
```