Competing Risk of Death in Elderly Patients with Newly Diagnosed Stage I Breast Cancer

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BACKGROUND: The majority of newly diagnosed breast cancers in the US are in women aged older than 65 years who can have additional comorbidities. Balancing the risks and benefits of treatment should take into account these competing risks of death.

STUDY DESIGN: The Surveillance, Epidemiology, and End Results Program-Medicare database was used to identify women with stage I breast cancer undergoing operations from 2004-2012. Using neural network analysis, comorbidities associated with mortality were grouped into clinically relevant categories. Cumulative incidence graphs and Fine and Gray competing risk regression analyses were used to study the association of age, race, comorbidity groupings, and tumor variables with 3 competing mortality outcomes: dead of disease (DOD), dead of other cancers (DOC), and non-cancer death (NCD).

RESULTS: The overall cumulative incidence of mortality was 4.9% for DOD, 3.7% for DOC, and 21.3% for NCD for the 47,220 patients studied. For all patients, the 5- and 8-year probability of DOD was 3% and 4.7%, for DOC 1.9% and 3.5%, and for NCD 9.8% and 18.9%, respectively. The presence of any major comorbidity (eg cardiovascular or neurologic disorders) significantly increased the probability of NCD, and estrogen receptor status was the strongest predictor of DOD. Given patient age, comorbidity, and estrogen receptor status, an estimate of competing risks of death from DOD, DOC, and NCD can be calculated.

CONCLUSIONS: To aid clinical decision making, we quantify competing risks of death in patients with stage I breast cancer by taking into account patient age, comorbidity, and estrogen receptor status. (J Am Coll Surg 2019;229:30–37. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

One in 8 women will be diagnosed with ductal carcinoma in situ or stage I breast cancer during their lifetime. With current multimodality treatment, the cure rate with early diagnosis approaches 100%.[1] As mortality becomes less of a concern, more attention has been directed to quality of life issues, especially the side effects of therapy. Instead of a "one size fits all" approach, treatment is being tailored according to individual patient and tumor characteristics to optimize the risk to benefit ratio for each treatment modality.

Patient factors, such as comorbidity and life expectancy, are increasingly being considered in therapeutic decision making. The routine use of adjuvant radiation therapy in women older than 70 years undergoing breast conservation is being questioned because any benefit from reduction of local recurrence is unlikely to be seen during the patient's remaining lifespan.[2] Similarly, the routine use of SLNB for patient's older than 70 years does not improve cancer outcomes or lead to significant changes

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Abbreviations and Acronyms
DOC = dead of other cancers
DOD = dead of disease
ER = estrogen receptor
NCD = non-cancer death
SEER = Surveillance, Epidemiology, and End Results Program

in management of early-stage breast cancer.[3] In clinically node-negative patients with hormone-positive invasive breast cancer, the latter was incorporated as one of the recommendations of the *Choosing Wisely* campaign by the Society of Surgical Oncology.[4]

Timely diagnosis coupled with advances in multimodality treatment means most patients with early-stage breast cancer are now at a higher risk of dying from a cause other that breast cancer. This is especially true for elderly patients (aged 65 years or older) in whom the majority of new-onset breast cancer is diagnosed, and who also have the additional burden of comorbidity from other diseases. These other causes of mortality can be considered competing risks and have not been studied extensively in the context of breast cancer.

The goal of this study is to quantify competing risks of mortality in elderly patients diagnosed with stage I breast cancer and use these data to develop a predictive model for mortality using patient, comorbidity, and tumor characteristics.

METHODS

Surveillance, Epidemiology, and End Results Program-Medicare database

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) tumor registry linked to the Medicare database was used for this study. The SEER-Medicare data link 2 national databases to provide detailed information about Medicare beneficiaries with cancer. To link SEER with Medicare data, the registries participating in the SEER program send individual identifiers for all persons in their files. These identifiers are matched with identifiers contained in Medicare's master enrollment file. For each of the linkages, 95% of persons aged 65 years or older in the SEER files are matched to the Medicare enrollment file.[5] Quality control is an important component of the SEER program. The current standard for accuracy of data is an error rate <5%. Data for the years 2004 to 2012 was requested for this study. As a population-based study with no patient identifiers involved, our investigation was exempt from IRB approval.

The Patient Entitlement and Diagnosis Summary Files contain the data elements collected by the SEER registries, as well as information pertaining to Medicare eligibility and enrollment. Cancer-related variables in Patient Entitlement and Diagnosis Summary Files include demographic characteristics, previous cancer diagnoses, date of cancer diagnosis, stage at diagnosis, and date of death if applicable. The National Claims History, Outpatient Claims, and Medicare Provider Analysis and Review files were used to find diagnosis codes for each patient up until the date of cancer diagnosis given in the Patient Entitlement and Diagnosis Summary Files.

Case selection

Case selection was performed by identifying patients with a biopsy-proven diagnosis of invasive ductal adenocarcinoma (ICD-9 histology codes 8500, 8521, 8230, 8522, 8523, and behavior code 3) who underwent operation for the primary tumor between 2004 and 2012. Our cohort was restricted to patients with stage I disease (as defined by the American Joint Committee on Cancer's Cancer Staging Manual, 7th edition) who were enrolled in Medicare during the year of their diagnosis.

The exclusion criteria ruled out ductal carcinoma in situ, stage other than I or unstaged cancer, cases identified by autopsy only, and patients not enrolled in both Medicare parts A and B or without enrolment in an HMO. Patients aged younger than 65 years enrolled in Medicare because of end-stage renal disease or chronic disability also were excluded from the study.

Outcomes

The cause of death variable code was used to identify our 3 primary outcomes of interest: death due to breast cancer (DOD), death due to other cancers (DOC), and death due to non-cancer causes (NCD). The cause of death variable in SEER is derived from death certificates, and although concerns have been expressed about the accuracy and use of this variable, it has been shown to be a valid estimate of cancer-specific survival.[6,7] For all survival analyses, time zero was the date of diagnosis of breast cancer. Last follow-up is the date of the last time the patient was seen in a clinical setting for which Medicare was charged, that is, the final Medicare claim.

Neural network analysis

Using ICD-9-CM diagnosis and procedure codes, relevant comorbid conditions in all medical claims (inpatient, outpatient, and physician claims) for the index breast cancer claim were identified for each patient. To produce clinically meaningful analyses, the comorbidities were grouped together into distinct categories associated with mortality

outcomes of interest and based on earlier work in the field.[8] After grouping the diagnoses codes, a neural network model was used to explore the predictive ability of these diagnosis groups on the mortality modes, with each mortality mode being an output node classification. This approach was used to recognize underlying relationships in the data without making a priori assumptions about comorbidities and the association with mortality. Because there were 3 different outcomes of interest and multiple comorbidity groupings, the associations between the 2 groups could best be explored by using this technique rather than traditional multivariable regression analysis. The input variables for the neural network analyses were the diagnosis codes and the output variables; the 3 mortality outcomes of interest—DOD, DOC, and NCD (Fig. 1).

Statistical analyses

Output from the neural network analysis was used to identify comorbidity groupings associated with our mortality outcomes of interest, which were then used in the subsequent analyses detailed here. The association of age, race, comorbidity groupings, and tumor variables with mortality risk was studied using Fine and Gray multivariable competing risk regression to predict the probability of DOD, taking into account the competing risks of DOC and NCD. Competing risk analysis is a special form of survival analysis in which a competing risk (dead of other cancer, non-cancer death) is an event whose occurrence precludes the occurrence of the primary event of interest (DOD).[9] Variables included in both models were age, race, psychiatric disorders, injuries, neurologic disorders, infectious disorders, neoplasms, cardiovascular disorders, and estrogen receptor (ER) status. The assumptions of the Fine-Gray model were tested using the 'crskdiag' package in R, version 3.1.3 (R Foundation for Statistical Computing), based on cumulative sums of residuals.[10] Competing risk analyses were also used to generate cumulative incidence graphs for our mortality outcomes of interest and construct a 5- and 8-year risks of death probability table. Validation of the Fine-Gray model was performed by pulling an 80% training sample, stratified by mortality mode, and testing the models on the remaining 20% test sample. Deciles (10 estimates) at the 8-year time point were chosen. Calibration plots were constructed with the "predicted" risk score on the x-axis is and the "observed" risk score, or actual mortality prevalence from the test sample on the y-axis.[11] A p value of <0.05 was set as our threshold for statistical significance and 95% CIs were used unless otherwise indicated. The analysis was performed using SAS, version 9.4 (SAS Institute) and R, version 3.1.3 (package 'cmprsk' and "finegray").

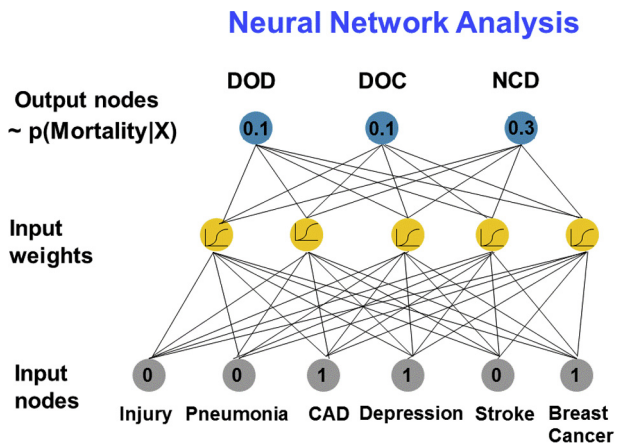

Figure 1. Neural Network Analysis for comorbidity groupings of interest: death due to breast cancer (DOD), death due to other cancers (DOC), and death due to non-cancer causes (NCD). CAD, coronary artery disease.

RESULTS

Demographics

Our study population consisted of 47,220 female patients with stage I adenocarcinoma of the breast. The mean and median age was 74.6 ± 6.7 years and 74 (range 65 to 114) years, respectively. The majority of patients were classified as white (87%) and most of the tumors were ER^+ (84%). At last follow-up, the majority of the patients were alive (86%), and 3% had died of breast cancer, 2% of other cancers, and 10% from other causes.

Cumulative incidence of mortality

The overall cumulative incidence of mortality was 4.9% for DOD, 3.7% for DOC, and 21.3% for NCD. With a median follow-up of 50 months, the cumulative incidence graph depicting probability of death from breast cancer, other cancers, and non-cancer causes is shown in Figure 2. Although the probability of mortality from any 1 of these 3 causes increases with time from diagnosis, that from non-cancer causes does so precipitously.

Probability of death table

The 5- and 8-year probability of breast cancer death (DOD), other cancer death (DOC), and non-cancer death (NCD) is depicted in Table 1. For all patients, the 5- and 8-year probability of DOD was 3% and 4.7%, for DOC 1.9% and 3.5%, and for NCD 9.8% and 18.9%, respectively. As expected, with increasing age the probability of DOC and NCD rises. However, an increase in the probability of DOD with age is also seen with patients older than 81 years having a 7.4% chance of DOD at 8 years compared with 3.1% in patients 65 to 70 years old. Patients classified as black had a higher probability of DOD compared with white or

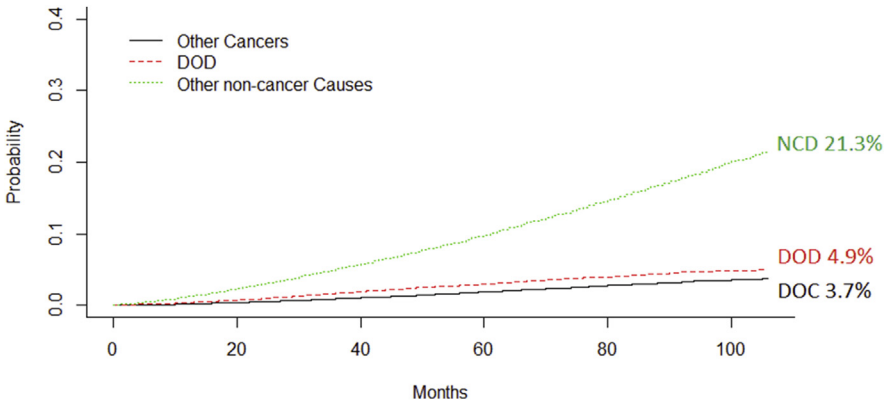

Figure 2. Cumulative incidence of mortality graph. DOC, death due to other cancers; DOD, death due to breast cancer; NCD, death due to non-cancer causes.

other patients. The presence of any major comorbidity (eg cardiovascular or neurologic disorders) significantly increased the probability of an NCD. Estrogen-receptor status was the strongest predictor of DOD for cancer related variables (5- and 8-year mortality 2.4% vs 6.8% and 4.0% vs 9.2%, respectively, for ER^+ vs ER^-).

Cause-specific Cox regression analyses

For each mortality category the association between age, race, comorbidity, and ER status and the hazard of mortality is shown in Table 2. For DOD increasing age, black race, and psychiatric comorbidity were associated with increased risk. Other and Asian race, as well as ER^+ status were associated with decreased risk. The most significant variable associated with an increasing hazard of DOC was increasing age. The NCD risk was higher with increasing age and psychiatric, neurologic, as well as cardiovascular morbidity, and lower with ER^+ status.

Fine-Gray competing risk regression

The sub-distribution hazards of the risk for DOD after competing risk analysis are shown in Table 3. Age continues to have a strong association with increased risk of DOD, as does black race and psychiatric comorbidity. Asian and other race, as well as positive ER status, are associated with decreased risk of DOD.

Risk calculator

A risk calculator incorporating probabilities of mortality given patient age, comorbidity, and tumor characteristics generated from the cumulative incidence graph gives an estimate of competing risks of death from DOD, DOC, and NCD. For example, a 70-year-old woman with no comorbidity, Other race designation and an ER^+ stage I breast cancer has an 8-year probability of 2.0% for DOD, 2.4% for DOC, and 7.5% of NCD. For a 70-year-old woman with cardiac and neurologic comorbidity, White race and an ER^- tumor these probabilities are 9.3% for DOD, 4.2% for DOC, and 15.3% for NCD (risk calculator available in Appendix 1). Calibration plots showed that the risk models were fairly accurate, with estimates generally falling on the dashed diagonal lines, indicating that the predicted scores are generally reflective of the actual risk (eFig. 1).

DISCUSSION

A justifiable focus of patients with cancer and their treating physicians is mortality. For cancers such as stage I breast cancer, in which the vast majority of patients are cured, quality of life and risks vs benefits of treatment recommendations are becoming more relevant than an exclusive focus on mortality. Effective decision making in these patients requires tradeoff calculations by the physician and buy-in from the patient. To better inform such discussions, we quantify competing risks of death in elderly patients with breast cancer. In our study, we show that age, race, comorbidity grouping, and ER status of the patient have significant influence on the probability of death from breast cancer, other cancers, and non-cancer causes for any given patient. We believe these data are important because breast cancer and the impact on a patient's life does not occur in a vacuum, but in the context of age, race, and other comorbidity. Traditional cancer survival statistics often do not account for these competing risks of death.

Similar to our study, Mell and colleagues[12] used institutional data to show that competing mortality in patients with stage I and II breast cancer is associated with increasing age, black race, and comorbid disease. The 10-year cumulative incidence of competing mortality was 7.2% in the low risk vs 30.6% in the high-risk group

Table 1. Five- and 8-Year Probability of Death

		Breast cancer death, %		Other cancer death, %		Non-cancer death, %	
Characteristic	**n**	**5 y**	**8 y**	**5 y**	**8 y**	**5 y**	**8 y**
All patients	47,220	3.0	4.7	1.9	3.5	9.8	18.9
Race							
White	40,967	2.9	4.6	1.9	3.4	10.0	19.1
Black	2,975	5.1	8.5	2.0	4.6	10.7	20.1
Other	3,278	2.0	3.4	1.6	2.7	6.6	14.8
Age at dx							
65 to 70 y	15,684	1.8	3.1	1.3	2.6	2.9	6.0
71 to 80 y	21,700	2.7	4.6	2.0	3.8	7.9	16.5
81 y and older	9,836	5.3	7.4	2.5	3.9	24.7	43.5
Psychiatric dx							
Yes	15,830	3.5	5.4	1.9	3.2	14.5	27.2
No	31,390	2.7	4.4	1.9	3.6	7.4	14.5
Injury dx							
Yes	26,007	3.0	4.8	1.9	3.4	11.4	21.8
No	21,213	2.9	4.6	1.9	3.5	7.7	15.0
Neurologic disorder dx							
Yes	32,363	3.1	5.0	2.0	3.6	11.2	21.0
No	14,857	2.6	4.2	1.6	3.2	6.8	14.0
Infectious disorder dx							
Yes	32,007	3.0	4.9	1.9	3.6	11.0	20.8
No	15,213	2.9	4.4	1.8	3.2	7.2	14.8
Neoplasm dx							
Yes	36,079	3.0	4.8	1.9	3.4	10.1	19.1
No	11,141	2.9	4.5	1.9	3.6	9.0	18.2
Cardiovascular dx							
Yes	36,634	3.0	4.9	1.9	3.5	10.7	20.2
No	10,586	2.7	4.3	1.8	3.4	6.7	14.5
Estrogen receptor							
Positive	39,485	2.4	4.0	1.9	3.4	9.6	18.7
Negative	5,658	6.7	9.2	1.9	3.8	9.5	17.7
Unknown	2,077	3.5	5.9	1.9	3.1	14.5	25.1

Dx, diagnosis.

($p < 0.001$). With regard to comorbid conditions, Bayliss and colleagues[13] looked at patients with cancer and multimorbidity to show that the influence of cancer prognosis was greatest in year 1, and the effect of comorbidities increased long term, especially in patients with good prognosis cancers. In an older study using just SEER data, Schairer and colleagues[14] showed that non-cancer mortality exceeds breast cancer mortality for patients older than 50 years with localized breast cancer. An important implication of these data are that the 5-year overall survival statistic used as a "benchmark" for reporting prognosis in cancer can be misleading, especially in older and sicker patients.[15] For example, this statistic can be improved, not due to any underlying improvements in cancer care but rather better treatment of comorbid conditions.

Studies looking at other cancer types report similar results. In particular, prostate cancer is the archetype of a cancer with low long-term mortality and treatment options with the potential to adversely impact quality of life. In a study by Daskivivh and colleagues,[16] older men with low- or intermediate-risk prostate cancer with major comorbidity were at high risk for other-cause mortality within 10 years of diagnosis. The authors suggest that these patients and their treating physicians take this information into consideration when deciding between conservative management and aggressive treatment. For localized renal carcinoma, a nomogram was developed incorporating commonly available clinical information to help make tradeoff calculations about treatment.[17] Another approach was to use competing mortality to

Table 2. Adjusted Cause Specific Hazard Ratios

Variable	Breast cancer death, HR (95% CI)	Other cancer death, HR (95% CI)	Non-cancer death, HR (95% CI)
Age at diagnosis, y	1.07 (1.07−1.08)	1.05 (1.04−1.06)	1.12 (1.12−1.12)
Race			
White*			
Black	1.65 (1.37−1.97)	1.15 (0.88−1.51)	1.11 (0.99−1.25)
Other	0.57 (0.36−0.93)	0.76 (0.46−1.24)	0.74 (0.58−0.94)
Asian	0.58 (0.37−0.89)	0.71 (0.44−1.14)	0.72 (0.59−0.88)
Hispanic	1.11 (0.70−1.77)	1.30 (0.75−2.24)	0.73 (0.54−0.98)
Native American	1.82 (0.68−4.87)	1.77 (0.97−3.23)	1.71 (1.01−2.89)
Comorbidity			
Psychiatric	1.24 (1.10−1.41)	0.90 (0.77−1.05)	1.62 (1.52−1.73)
Injury	0.82 (0.71−0.95)	0.86 (0.72−1.12)	0.99 (0.92−1.08)
Neurological	1.08 (0.89−1.32)	1.33 (1.04−1.69)	1.14 (1.02−1.29)
Infectious	0.86 (0.72−1.03)	0.99 (0.79−1.24)	1.05 (0.95−1.17)
Neoplasm	1.13 (0.89−1.43)	0.97 (0.72−1.29)	0.59 (0.52−0.67)
Cardiovascular	0.96 (0.76−1.20)	0.95 (0.72−1.25)	1.31 (1.15−1.49)
Estrogen receptor			
Negative*			
Positive	0.35 (0.31−0.40)	0.86 (0.70−1.05)	0.89 (0.81−0.97)
Unknown	0.47 (0.37−0.60)	0.83 (0.59−1.18)	1.05 (0.92−1.21)

HR, hazard ratio.
*Referent.

risk stratify patients with head and neck cancers into categories most likely to benefit from treatment intensification.[18] Finally, for patients with early-stage endometrial cancer an increasing competing mortality risk score was associated with a diminishing likelihood of benefit from treatment intensification.[19]

There are several limitations to this study that we would like to acknowledge. For the sake of analytic feasibility and ease of presentation, we incorporated a reductionist approach in conducting our analyses. A more expansive approach, by including all possible variables, might have yielded different probabilities. In addition, refinement of our model, for example, by using ICD-10 instead of ICD-9 codes, has the potential to ferret out the individual codes rather than comorbidity groupings, which have the largest influence on mortality. In addition, interactions between comorbid conditions (eg obesity) and the risk of dying from breast cancer were not examined in this model. We limited our patient population to stage I breast cancer and it is quite likely that our calculated probabilities of competing risks of death would change with increasing breast cancer stages. We did not consider the influence of adjuvant chemotherapy, radiation treatment, or hormone treatment on our calculated probabilities. Our data are retrospective and therefore subject to selection bias, misclassification bias, and missing variables. In particular, the use of the cause of death variable, although validated by studies, is only as good as the information available on the death certificate.

Table 3. Competing Risk Sub-Distribution Hazards for Breast Cancer Death

Variable	Hazard ratio	95% CI	p Value
Age at diagnosis	1.06	1.05−1.07	<0.001
Race			
White*	—	—	—
Black	1.63	1.38−1.95	<0.001
Asian	0.60	0.39−0.92	0.020
Hispanic	1.18	0.74−1.87	0.480
Other	0.58	0.36−0.94	0.026
Comorbidity			
Psychiatric	1.20	1.06−1.36	0.005
Injury	0.83	0.72−0.95	0.008
Neurologic	1.08	0.90−1.30	0.420
Infectious	0.86	0.72−1.03	0.110
Neoplasm	1.16	0.92−1.45	0.210
Cardiovascular	0.94	0.75−1.17	0.550
Estrogen receptor			
Negative*	—	—	—
Positive	0.36	0.32−0.41	<0.001
Unknown	0.47	0.37−0.60	<0.001

*Referent.

CONCLUSIONS

Quantifying competing risks of mortality, primarily those of breast cancer death, death from other cancers, and non-cancer death, in patients with stage I breast cancer is possible using registry data. This information can be used to develop a predictive mortality model using patient age, comorbidity groupings, and ER status to aid in clinical decision making. Risk stratification of patients in clinical trials for efficacy should also consider incorporating comorbidity information. In addition, reporting of long-term cancer survival when censoring patients who die from comorbid conditions has the potential to artificially inflate disease-free survival estimates.[15] Additional development of this model, including incorporation of treatment variables, such as adjuvant chemotherapy or ICD-10 codes and external validation, can be used to develop online calculators that take into account competing risks of death when calculating survival benefits from treatment.

Author Contributions

Study conception and design: Wasif, Neville, Pockaj
Acquisition of data: Wasif, Neville, Pockaj
Analysis and interpretation of data: Wasif, Neville, Gray, Cronin, Pockaj
Drafting of manuscript: Wasif, Neville, Gray, Cronin, Pockaj
Critical revision: Wasif, Neville, Gray, Cronin, Pockaj

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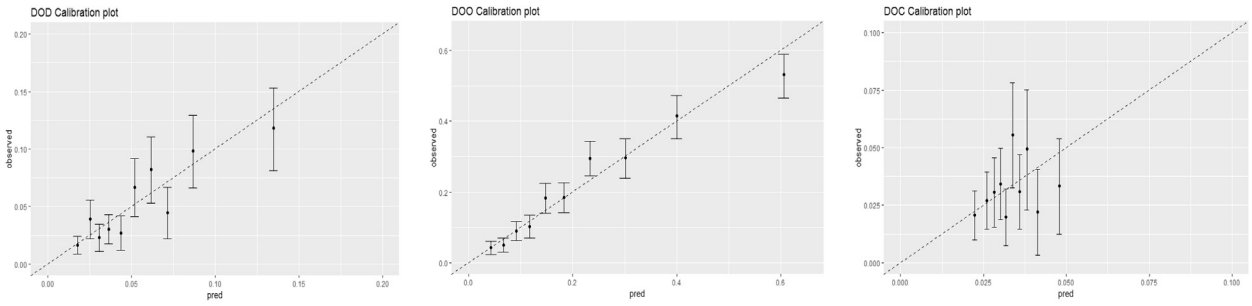
Discussion

DR DAVID WINCHESTER (Evanston, IL): Individualized patient care, particularly in cancer, is becoming an important goal to decrease unnecessary side effects, mortality, risk of recurrence, and health care costs. This study is another example of many efforts underway to achieve this goal. The authors have appropriately targeted an older population of breast cancer patients for which there have been randomized clinical data confirming equivalent outcomes for patients treated with and without radiation therapy, and non-randomized data showing equivalent outcomes for patients older than 70 years with axillary dissection or observation.

This study does not help us tailor treatments, but does help us to make estimations regarding competing causes of mortality in



eFigure 1. Death due to breast cancer (DOD) calibration plot. Pred, predicted.