Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2017 October ; 26(10): 1558–1563.

doi:10.1158/1055-9965.EPI-17-0277.

Mediating effect of post-surgical chemotherapy on presence of dementia and survival among patients 65 and older with Stage III colon cancer

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Abstract

Introduction—Both colon cancer and dementia are prevalent among the elderly and have a high risk of co-occurrence. Previous studies found that patients with dementia were treated less aggressively. In this study, we hypothesized that presence of pre-existing dementia was associated with worse survival for stage III colon cancer patients, and that post-operative chemotherapy was on the causal pathway.

Methods—We defined pre-existing dementia in SEER-Medicare data through either a formal diagnosis or a prescription for dementia drugs or both, before the diagnosis of cancer. We applied multivariable Cox regression to estimate the effect of pre-existing dementia on survival, adjusting for demographic factors, tumor characteristics, and receipt of chemotherapy. We assessed mediating effects in the context of the counterfactual framework using the accelerated failure time model.

Results—4,573 patients diagnosed with stage III colon cancer between 2007 and 2009 were identified. A pre-existing diagnosis of dementia significantly increased the risk of death by 45% (HR=1.45, 95% CI: 1.29–1.63). Patients with either a formal diagnosis of dementia or a related prescription had significantly lower cause-specific survival than their cognitively healthy counterparts. Receipt of chemotherapy was a significant mediator on the causal pathway. The effect of presence of dementia was mediated by receipt of chemotherapy by 13% for pre- existing dementia.

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Conclusions—Pre-existing dementia is significantly associated with worse survival for stage III colon cancer patients, and its deleterious effect is partially explained by decreased likelihood of postoperative chemotherapy receipt.

Introduction

Both dementia and colon cancer are prevalent among people aged 65 and older. Colon cancer is the third most common and the second leading cause of cancer-related death in the U.S. According to national statistics, there will be a total of 95,270 new colon cancer cases diagnosed and 49,190 attributable deaths in 2016.(1) According to the World Health Organization (WHO), 1 in every 8 people aged 65 and over and 1 in every 2.5 people aged 85 and over on average will be affected by dementia.(2) The incidence of both colon cancer and dementia increases with age, resulting in a high age-related probability of co-occurrence that complicates both outcomes and treatment decisions.

Survival after the diagnosis of colon cancer has improved continuously since the 1970s. This improvement is prominent among those with regional stage disease, where it reflects improvement in adjuvant chemotherapy for colon cancer that has spread to regional lymph nodes (stage III).(3) While large clinical trials demonstrate that adjuvant fluoropyrimidine and oxaliplatin-based chemotherapy reduces the risk of recurrence and subsequently improves survival in patients with stage III colon cancer,(4, 5) these treatments are associated with significant toxicities that result in challenging risk versus benefit assessments for older patients.(6) Nonetheless, the provision of fluoropyrimidine-based adjuvant chemotherapy for eligible patients with stage III colon cancer has been strongly recommended since at least 1990.(7)

Between 1990 and 2040, the United States elderly population is expected to grow from 31.6 to 68.1 million. (8) Demographic projections estimate that by 2030, 22% of the US population will be aged 65 and older (9), which will contribute a 60% increase in cancer incidence. (10) As the population ages, oncologists will increasingly encounter cancer patients with cognitive impairment. Given the high prevalence of cognitive impairment in older adults with cancer, understanding the overall extent to which dementia adversely affects colon cancer survival outcomes in this elderly group holds particular clinical and public health relevance.

There have been a number of studies on cancer treatment and outcomes of these cognitively impaired cancer patients. For example, cognitively impaired cancer patients are more likely to have lower treatment tolerance (11) and receive less curative treatment, both of which contribute to a 20%−50% increase in mortality risk. (10, 12–15) However, variations in study sample, methodology, and case definitions limit the generalizability of findings from all these existing studies to the U.S. elderly population. Moreover, there is no study to our knowledge that has examined the relationship between dementia and survival after diagnosis of non-metastatic colon cancer, with treatment choice as a possible mediating factor.

A prior study used SEER-Medicare data for patients diagnosed from 1993 to 2005 to address the effect of dementia on treatment and survival for colon cancer patients; (12)

however, because Medicare Part D data were not available during the study period, the authors could not use medication history as supplemental data to identify patients with dementia. So far there are four Federal Drug Administration (FDA) approved drug treatments for dementia that may temporarily improve symptoms (Donepezil, Galantamine, Memantine, Rivastigmine). Tacrine was also approved for dementia treatment during the study period but withdrawn in 2013 in the U.S. All of them can be prescribed to patients with symptoms of cognitive impairment with or without a formal diagnosis of dementia. There are no other currently recognized indications for the use of these drugs. Therefore, we believe that by combining medication data with diagnosis code, the sensitivity for physician-recognized dementia or cognitive impairment would be increased, while retaining specificity. In this study, we evaluated the effect of dementia on survival among stage III colon cancer patients who had received initial surgical treatment using the improved algorithm in dementia identification, and then examined the causal relationship between adjuvant chemotherapy and survival outcome for these cognitively impaired colon cancer patients.

Materials and Methods

This was a retrospective cohort study that identified patients who were diagnosed with Stage III colon cancer in 2007–2009 using the SEER-Medicare linked databases (described in detail elsewhere (16)). Because the data was de-identified, the project was exempted from the UC Davis IRB. With permission from the IMS Health, Medicare files received and used for this study included the Medicare Provider Analysis and Review (MedPAR) file, the inpatient, outpatient, NCH (physician/supplier), HHA (home health agency), and DME (durable medical equipment) claims files, and the Medicare Part D file, in accordance with their requirements for data protection and confidentiality. By signing the Data Use Agreement (DUA) with the IMS, the data was allowed to be released without obtaining authorization from individual patients. Only patients for whom colon cancer was the first or only cancer diagnosis and those who were aged 65 years or above were eligible. Patients with death certificate only or diagnosis at autopsy were excluded from the analysis.

The primary predictor was the presence of pre-existing dementia, which was identified through either a formal diagnosis in the claims data (inpatient, outpatient, physician files, and HHA files) or a medication record in the Part D data. In the claims data, the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes were used. Codes for Alzheimer's disease and related dementia were 290.40 to 290.43, 331.0, 331.1, 331.11, 331.19, 331.82, 046.11, 046.19, 292.82, 333.4, 290.10 to 290.13, 290.0, 290.20, 290.21, 290.3, 331.2, 331.9, 290.8, 290.9, 294.10, 294.11, 294.20, 294.21, 294.1, 294.8, and 797, and 331.83 for mild cognitive impairment (12). In the Part D data, patients with a prescription for any of the four FDA-approved dementia drugs (donepezil, galantamine, memantine, rivastigmine) plus tacrine were identified as dementia cases.

Covariates include patient's demographic characteristics (age, gender, race, marital status, insurance types, median income for census tract, percentage of persons 25+ with less than 12 years of education in the census tract, and urban/rural recode), tumor grade, and

comorbidities. Marital status was categorized into three levels, ”married” included patients who were married, ”single” included patients who were never married, separated, divorced, or widowed, and ”other” marital status included patients who had a domestic partner or with unknown marital status. Insurance coverage was defined as private or government (including managed care and Medicare with supplement), Medicaid or low income, Medicare, insured not otherwise specified, and uninsured. The median income for census tract and the percentage of persons 25+ with less than 12 years of education in the census tract were used as criteria for evaluation of patient’s social economic status, and they were categorized as tertiles. Comorbidity was derived from diagnosis codes in outpatient and inpatient claims during a time window of 1 year before the diagnosis of colon cancer for comorbidity computation. (17) Number of comorbidities was measured using Charlson Comorbidity Index (CCI) (18, 19), modified to exclude dementia. CCI was categorized into “none”, “one”, and “two or more”. Receipt of chemotherapy was identified by HCPCS codes 964XX, 96500 to 96549, Q0083 to Q0085, J9000 to 9999, G0345 to G0351, G0353 to G0363, J0640, 51720, or ICD-9 codes V581, V662, V672 or 99.25. The 11-digit National Drugs Codes (NDCs) in the Durable Medical Equipment (DME) file was used to capture the usage of orally administered chemotherapy, including 000041100xx, 000041101xx, 548684143xx, 548685260xx, and 545695717xx.

Chi-square tests were used to determine if the distributions of covariates were significantly different between patients with and without presence of dementia. The primary analysis compared the survival of patients with pre-existing dementia (defined as either formal diagnosis or prescribed medication or both) to those with no evidence of dementia before the diagnosis of cancer. Time from the diagnosis of tumor to death or the end of 2009 was considered as time to event. A person was considered censored if he or she died of other diseases during the study period. Multivariable Cox regression analyses were performed to assess the cancer-specific risk of death, assuming an independent censoring mechanism. Two models were constructed for distinct comparison purposes. Model 1 aimed to estimate the overall effect of pre-existing dementia on survival. Model 2, a sensitivity analysis, aimed to further confirm the effect of pre-existing dementia on survival but among a more restrictive group of patients who had both a formal diagnosis of and a medication prescription for dementia, as well as to assess the independent effects of source of dementia diagnosis. Covariates included demographic characteristics and tumor grade, receipt of chemotherapy, and number of comorbidities. Secondary analyses examined the effect of co-existing dementia on cancer survival (that is, the evidence of dementia could present before, concurrent with, or after the diagnosis of cancer).

The mediating effect of chemotherapy was estimated through a Weibull accelerated failure time (AFT) model, to allow estimation of as well as testing for mediation, through a counterfactual approach.(20) In the AFT model, the estimated effect is the proportionate change in the mean survival time: a reduction, or less than 1, for a deleterious covariate, and an increase, or greater than 1, for a protective covariate. This is in contrast to the proportional hazards model, where the effect of a deleterious covariate is to increase the hazard of death (effect greater than 1). The Weibull distribution offers flexibility to allow for hazards that may increase, decrease, or remain constant after diagnosis. The mediation effect is estimated from two quantities that can be computed through the AFT: the natural direct

effect (NDE) and natural indirect effect (NIE). The NDE is the estimated impact on the mean survival time of a person simply having dementia but treated just like a person without dementia, compared to a person without dementia. The NIE is the estimated effect on the mean survival time of current chemotherapy practice for people with dementia, compared to the hypothetical situation where a person with dementia is as likely to get chemotherapy as a person without dementia (effect is less than 1 if current practice is deleterious). The NDE thus captures decrease in survival due to having dementia, while the NIE captures the decrease in survival time due to someone with dementia potentially not receiving more aggressive treatment. The mediation effect of decreased use of chemotherapy in the presence of dementia was estimated by the following formula (21):

$$\text{Proportion mediated} = \frac{\text{NDE}-\text{NDE}*\text{NIE}}{1-NDE*NIE}$$

The denominator represents the total impact of having dementia on survival, while the numerator represents that portion just due to being more likely to receive chemotherapy. A well-established SAS macro for estimation of NDE and NIE was implemented in this study (22) (its manual can be accessed at http://links.lww.com/EDE/A877). Standard errors were estimated by the delta method.

Results

A total of 4,573 patients diagnosed with stage III colon cancer from 2007–2009 were identified in SEER-Medicare data, of whom 3,903 had valid dates associated with both diagnosis of dementia and cancer, and were included for the following analyses. We identified 575 patients with pre-existing dementia using either a recorded diagnosis or a prescribed anti-dementia medication. Patient demographics, number of comorbidities, tumor grade and receipt of chemotherapy are described in Table 1. About 22% of the patients were over age 84. More than half of the patients were female. A majority of the patients were non-Hispanic whites, with smaller numbers of Hispanics, Asian/Pacific Islanders, and non-Hispanic blacks. Almost all patients resided in a metropolitan area (61% for big metro area and 25% for metro area). A majority of the patients were married and fully covered by either Medicare (62%) or private or government-based insurance (33%). Forty percent of the patients had no comorbidities. Fewer than half of the patients received chemotherapy.

Cancer-specific survival for patients with pre-existing dementia was significantly worse than for their cognitively healthy counterparts regardless of the algorithms used for dementia identification (shown in Table 2). Being younger (65–84 years old) was associated with better cancer-specific survival. Patients residing in areas with residents attaining higher levels of education had better survival outcomes, whereas median income showed no significant effect. The risk of cancer-related death increased significantly as tumor grade advanced. Receipt of chemotherapy was significantly associated with better cancer-specific survival.

The mediating effect analysis used AFT models, with dementia was identified through either a formal diagnosis or a drug prescription. For patients who received no chemotherapy, the

average mean survival time for those with pre-existing dementia was 63% that of patients with no pre-existing dementia. The odds of receiving chemotherapy was reduced by 9% for patients with pre-existing dementia compared to patients with no dementia (as shown in Table 3).

The average mean survival time of Stage III colon cancer patients with presence of pre-existing dementia is 57% that of patients with no evidence of dementia. Chemotherapy was a statistically significant mediator for presence of dementia on survival for Stage III colon cancer patients. The effect of presence of dementia was mediated by receipt of chemotherapy by 13% for pre-existing dementia (shown in Table 4).

In secondary analyses, we examined the impact of expanding the definition of dementia to include co-existing dementia, diagnosed at or after the diagnosis of cancer. Overall, the impact of a co-existing dementia diagnosis on cancer survival was less than that for pre-existing dementia. Mean survival was reduced by 70% for co-existing dementia compared to patients with no evidence of dementia; receipt of chemotherapy mediated this effect on survival by 18%.

Discussion

The main findings of this study can be summarized in two points. First, the presence of a pre-existing diagnosis of dementia, identified by either medical history or medication history-based algorithms, was significantly associated with worse cancer-specific survival for patients with Stage III colon cancer. Second, the receipt of chemotherapy was a significant mediator on the causal pathway of presence of dementia on survival outcome for Stage III colon cancer patients. In other words, nearly twenty percent of the worse survival in patients with dementia and stage III colon cancer could be explained by the decreased odds of receiving chemotherapy.

Consistent with another study, we found that patients with dementia had significantly worse survival than their cognitively healthy counterparts, even after adjusting for the receipt of cancer treatment.(15) Two possible explanations have been proposed: the physician may elect not to recommend chemotherapy, and, even if it is recommended, the patient and family may decline to pursue this option. From a physician’s perspective, depending on the specific degree and nature of the cognitive impairment, a variety of behavior issues may arise to complicate informed decision-making and consent for these cancer patients with dementia. Disorganized thinking may also hinder a person’s ability to follow medical recommendations, such as scheduling follow-up medical appointments or adhering to complex treatment regimens. (23) A further consideration for dementia patients is higher risk of chemotherapy-related toxicities,(24) especially those that might worsen cognitive impairment. Even if patients with dementia were prescribed a typical post-surgical chemotherapy, the course might be less aggressive to ensure the completion. (6) Thus physicians may hesitate to recommend chemotherapy, including enrollment in clinical trials, for patients with dementia. (23, 25, 26)

Secondly, individuals with a pre-existing dementia and their families must also weigh risks and benefits, even if they are informed about potential survival benefits of chemotherapy. Adherence to cancer care guidelines generated from populations with normal cognition may yield limited survival benefits for older patients with more advanced dementia.(15) Indeed, use of less invasive diagnostic and staging procedures in patients with cancer and dementia may reflect good clinical judgment on the part of caregivers and clinicians. (13) Older cancer patients or their families are more likely to choose less-invasive therapies or to forgo treatment if the patient has dementia or functional limitations or if life expectancy is perceived to be brief. (27) In particular, cancer patients diagnosed at later stages are among the most likely to refuse treatment. (28) Some patients and families, however, may still consider potentially curative cancer chemotherapy worthwhile. This is especially likely for patients with early-stage dementia, because median survival without chemotherapy is about 24 months, (29) while survival after initial dementia diagnosis may be as long as 4 to 8 years.(30)

There are two limitations of this study. The primary limitation is that the SEER-Medicare database does not include detailed information on the dementia diagnosis or functional status, so that we were not able to identify the extent of the dementia. A second limitation is that we do not know whether the choice of not using chemotherapy represented physician advice, or patient/family choice, and what other grounds either might have had for deciding against chemotherapy. It is possible that patients with dementia receive less screening, either due to diminished recommendation or diminished capacity to undergo screening. If this were the case, colon cancer would be diagnosed only when symptomatic and would on average be a more advanced/poorer prognosis case than those found incidentally on screening. Therefore, less aggressive cancer treatment is more likely to be a patient/family choice, because it would not be recommended by a physician to maintain patient’s overall quality of life.

Approaches to mediation analysis with uncorrelated survival data include Cox proportional hazard (PH) and accelerated failure time (AFT) models. The primary strength of this paper is that we employed AFT model and combined with the counterfactual approach for a rigorous causal interpretation for the mediation effect, while the Cox PH model can only provide a valid test for the presence of a mediator effect according to the product-coefficient method. [15]

Adjuvant chemotherapy is a standard component of treatment for patients diagnosed with stage III colon cancer. Previous studies have shown that chemotherapy can have a deleterious effect on cognitive function. (31, 32) Despite several research studies about the effect of dementia on cancer treatment and survival, the impact of diminished chemotherapy as a causative factor in these reduced survival outcomes was not previously known. Patients at a high risk for cognitive impairment have often been excluded from existing studies of cancer. (33) In the current study we provide the first estimate of the mediating effect of diminished chemotherapy in patients with stage III colon cancer and dementia, simultaneously demonstrating the cancer-specific survival benefit of chemotherapy in the presence of dementia. In this study, we were unable to determine the exact chemotherapy regimen delivered to patients. Nonetheless, diminished receipt of any adjuvant

chemotherapy was found to account for 18% of the diminished survival of stage III colon cancer patients with dementia. Currently, there is limited evidence showing that chemotherapy is associated with a measurable deterioration of cognitive function for cancer patients. (9, 34) However, whether this effect is greater with certain chemotherapy drugs or in patients with pre-existing dementia is unknown. Future studies should assess the effect of adjuvant chemotherapy on cognitive function in patients with pre-existing dementia and determine whether interventions that enhance the provision of standard adjuvant chemotherapy enhance the survival of patients with concomitant stage III colon cancer and dementia.

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Table 1:

Demographic factors, tumor characteristics, and receipt of post-operative chemotherapy for patients with Stage III colon cancer by their cognitive status (pre-existing dementia), 2007–2009, N (Percent)

Variables	Total (n=3,903)	Dementia		P-value
		No (n=3,328)	Yes (n=575)	
Age				<0.001
65–84	3,060 (78.4)	2,713 (81.5)	347 (60.4)	
84+	843 (21.6)	615 (18.5)	228 (39.7)	
Gender				0.023
Male	1,524 (39.1)	1,324 (39.8)	200 (34.8)	
Female	2,379 (60.9)	2,004 (60.2)	375 (65.2)	
Race				0.197
White	3,112 (79.7)	2,661 (80.0)	451 (78.4)	
Black	389 (10.0)	322 (9.7)	67 (11.7)	
Hispanic	73 (1.9)	62 (1.9)	11 (1.9)	
Asian	193 (4.9)	159 (4.8)	34 (5.9)	
Unknown/Other	136 (3.5)	124 (3.6)	12 (2.1)	
Marital status				0.002
Married	3,470 (88.9)	2,976 (89.4)	494 (85.9)	
Single	307 (7.9)	241 (7.2)	66 (11.5)	
Unknown	126 (3.2)	111 (3.3)	15 (2.6)	
Insurance types				<0.001
Insured, NOS	79 (2.0)	67 (1.9)	12 (2.1)	
Medicaid/Low income	40 (1.0)	33 (1.0)	7 (1.2)	
Medicare	2,409 (61.7)	1,985 (61.1)	424 (73.7)	
Private/Government	1,301 (33.3)	1,176 (34.0)	125 (21.7)	
Not insured	6 (0.2)	5 (0.2)	1 (0.2)	
Unknown	57 (1.5)	51 (1.8)	6 (1.0)	
Missing	11 (0.3)	11 (0.3)	0 (0.0)	
Median income				0.454
Low	1,331 (34.5)	1,124 (34.1)	207 (36.6)	
Median	1,239 (32.1)	1,068 (32.4)	171 (30.2)	
High	1,288 (33.4)	1,100 (33.4)	188 (33.2)	
Less than 12 years education				0.060
Low percentage	1,231 (31.9)	1,068 (32.4)	163 (28.8)	
Middle percentage	1,270 (32.9)	1,090 (33.1)	180 (31.8)	
High percentage	1,357 (35.2)	1,134 (34.5)	223 (39.4)	
Urban/Rural recode				0.930
Big Metro	2,361 (60.5)	2,020 (60.7)	341 (59.3)	
Metro	980 (25.1)	828 (24.9)	152 (26.4)	
Urban	168 (4.3)	142 (4.3)	26 (4.5)	

Variables	Total (n=3,903)	Dementia		P-value
		No (n=3,328)	Yes (n=575)	
Less Urban	317 (8.1)	271 (8.2)	46 (8.0)	
Rural	76 (2.0)	66 (2.0)	10 (1.7)	
Grade				0.689
Grade I	196 (5.0)	162 (4.9)	34 (5.9)	
Grade II	2,383 (61.1)	2,046 (61.5)	337 (58.6)	
Grade III	1,110 (28.4)	938 (28.2)	172 (29.9)	
Grade IV	119 (3.1)	101 (3.0)	18 (3.1)	
Unknown	95 (2.4)	81 (2.4)	14 (2.4)	
Charlson comorbidity index				<0.001
No comorbidity	1,608 (41.2)	1,443 (43.4)	165 (28.7)	
1	956 (24.5)	814 (24.5)	142 (24.7)	
2+	1,337 (34.3)	1,069 (32.1)	268 (46.6)	
Chemotherapy				<0.001
No	2,523 (64.6)	2,078 (62.4)	445 (77.4)	
Yes	1,380 (35.4)	1,250 (37.6)	130 (22.6)	

Table 2:

Effect of pre-existing dementia on cancer-specific survival for patients with Stage III colon cancer based on Cox proportional hazards models.

Variables	Hazard Ratio (95% CI)	
	Model 1	Model 2
Presence of pre-existing dementia		
No dementia	Reference	Reference
Dementia (Any evidence)	1.45 (1.29, 1.63) [a]	-
Dementia (both diagnosis and prescription)	-	1.23 (0.99, 1.52) [b]
Dementia (diagnosis only)		1.59 (1.35, 1.87) [b]
Dementia (prescription only)		1.93 (1.14, 3.28) [b]
Age		
65–84	0.59 (0.53, 0.66)	0.58 (0.52, 0.65)
84+	Reference	Reference
Gender		
Male	1.00 (0.91, 1.10)	1.00 (0.91, 1.09)
Female	Reference	Reference
Race		
White	Reference	Reference
Black	0.94 (0.80, 1.10)	0.93 (0.79, 1.09)
Hispanic	0.88 (0.62, 1.25)	0.86 (0.61, 1.23)
Asian	0.7t6 (0.59, 0.96)	0.75 (0.59, 0.95)
Marital status		
Married	0.94 (0.80, 1.10)	0.94 (0.80, 1.11)
Single	Reference	Reference
Insurance types		
Insured, NOS	0.70 (0.48, 1.02)	0.69 (0.47, 1.01)
Medicaid/Low income	1.51 (0.98, 2.32)	1.49 (0.97, 2.29)
Medicare	1.14 (1.03, 1.26)	1.15 (1.04, 1.27)
Private/Government	Reference	Reference
Not insured	0.94 (0.35, 2.53)	0.94 (0.35, 2.52)
Median income		
Low	Reference	Reference
Median	1.03 (0.91, 1.16)	1.02 (0.91, 1.15)
High	1.07 (0.93, 1.24)	1.08 (0.93, 1.24)
Less than 12 years education		
Low percentage	0.78 (0.67, 0.90)	0.78 (0.68, 0.91)
Middle percentage	0.93 (0.83, 1.05)	0.94 (0.83, 1.06)
High percentage	Reference	Reference
Grade		
Grade I	Reference	Reference

Variables	Hazard Ratio (95% CI)	
	Model 1	Model 2
Grade II	1.10 (0.87, 1.39)	1.10 (0.88, 1.39)
Grade III	2.08 (1.65, 2.63)	2.10 (1.66, 2.65)
Grade IV	2.57 (1.91, 3.48)	2.56 (1.90, 3.46)
Unknown	2.39 (1.74, 3.29)	2.43 (1.76, 3.34)
Charlson comorbidity index		
No comorbidity	1.00 (0.90, 1.11)	0.99 (0.89, 1.10)
1	1.01 (0.90, 1.13)	1.00 (0.89, 1.13)
2+	Reference	Reference
Chemotherapy		
No	Reference	Reference
Yes	0.56 (0.50, 0.61)	0.55 (0.50, 0.61)

[a]The overall effect of pre-existing dementia on survival.

[b]The effect of source of evidence of pre-existing dementia on survival.

Table 3:

Mediation analysis with causal effects estimated for presence of dementia at the mean level of the covariates, based on accelerated failure time models (AFT).

	NDE [b] (95% CI)	NIE [c] (95% CI)
Pre-existing dementia	0.63 (0.55, 0.72)	0.91 (0.88, 0.94)
Co-existing dementia	0.76 (0.67, 0.85)	0.93 (0.91, 0.95)

[a]NDE (natural direct effect): estimated effect on the mean survival time of a person simply having dementia but treated just like a person without dementia, compared to a person without dementia. It captures decrease in survival due to having dementia.

[b]NIE (natural indirect effect): estimated impact on effect on the mean survival time of current chemotherapy practice for people with dementia, compared to the hypothetical situation where a person with dementia is as likely to get chemotherapy as a person without dementia. It captures the decrease in survival time due to someone with dementia potentially receiving more aggressive treatment.

Table 4:

Proportion of effect of presence of dementia mediated by receipt of chemotherapy

	Total effect [a] (95% CI)	Proportion mediated
Pre-existing dementia	0.57 (0.50, 0.66)	13%
Co-existing dementia	0.70 (0.62, 0.79)	18%

[a]Total effect is the product of NDE and NIE; combined effect on survival time of having dementia, then potentially having more aggressive treatment.