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Comparative effectiveness of postoperative chemotherapy among older patients with non-metastatic rectal cancer treated with preoperative chemoradiotherapy

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Abstract

Background—Postoperative chemotherapy is standard following preoperative chemoradiation therapy (CRT) and curative resection for clinically staged II/III rectal cancer. Recent trials have questioned whether postoperative chemotherapy improves overall survival. We evaluated the comparative effectiveness of postoperative chemotherapy following CRT or radiation therapy (RT) with specific attention on the impact of age on postoperative chemotherapy effectiveness.

Methods—Patients treated with CRT or RT then resection of pathologically staged 0-III rectal cancer diagnosed from 2004-2009 were identified from the Surveillance, Epidemiology and End Results program-Medicare database. Propensity score weighted Cox proportional hazards models and Kaplan Meier methods were used to compare the effectiveness of 1) postoperative 5-fluorouracil (5-FU) or capecitabine to no treatment and 2) postoperative oxaliplatin+5-FU/capecitabine to 5-FU/capecitabine alone on mortality. Results were stratified by age.

Results—We identified 1,316 patients; 49% received postoperative chemotherapy, 341 (52%) included oxaliplatin. After weighting, postoperative 5-FU/capecitabine alone was associated with decreased mortality in patients aged 66-74 (adjusted hazard ratio (aHR)=0.46, 95% CI: 0.30,0.72), corresponding to a 5-year risk difference of -0.23, (95% CI: -0.33,-0.12). No further mortality reduction from adding oxaliplatin to 5-FU/capecitabine was seen in patients aged 66-74

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(aHR=1.57, 95%CI: 0.93,2.65). No mortality reduction for 5-FU/capecitabine alone was observed among patients aged 75+ (aHR=1.11, 95%CI: 0.76,1.63).

Conclusions—Among patients<75 years, postoperative 5-FU/capecitabine was associated with reduced mortality after preoperative CRT/RT and surgical resection; however, addition of oxaliplatin was not associated with further mortality reduction. Decisions regarding postoperative chemotherapy after age 75 warrants consideration of individual patient risks and preferences, as benefits may be limited.

Keywords

rectal cancer; chemotherapy; aging; comparative effectiveness research

Introduction

For over 30 years the standard curative approach for stage II and III rectal cancer has included surgical resection, chemoradiotherapy (CRT), and 5-fluoruracil (5-FU) based postoperative chemotherapy. This approach is based on results of randomized controlled trials (RCTs) conducted in the 1980s-90s where patients treated with all three modalities had the lowest rates of local and distant recurrence and the longest survival.[1, 2] Rectal cancer treatment has since evolved. Total mesorectal excision is now standard with resultant lower rates of local recurrence.[3-6] CRT is administered preoperatively, providing better functional outcomes and possibly better local control and DFS.[7, 8] In 2004, the addition of oxaliplatin to 5-FU or capecitabine was shown to offer incremental survival benefit for patients with stage III colon cancer,[9-12] and its use was rapidly incorporated into treatment guidelines for rectal cancer and disseminated into routine clinical practice.[13]

While the best outcomes have been observed in patients treated with all modalities, early trials were not designed to test the individual contribution of each component of the preoperative CRT and postoperative chemotherapy platform on rectal cancer outcomes. The Cochrane Collaboration conducted a meta-analysis of 21 RCTs to examine whether the postoperative chemotherapy component in isolation reduces mortality over observation.[14] The meta-analysis reported a 17% reduction in the relative risk of all-cause mortality associated with postoperative chemotherapy; however, only a single trial, EORTC 22921, specifically evaluated chemotherapy following modern preoperative CRT. Now after 10 years of follow-up, 5-FU only marginally reduced mortality compared with observation (hazard ratio (HR)=0.91, 95%CI: 0.77,1.09); however, fewer than half of patients in EORTC 22921 were able to complete postoperative therapy at the planned dose and schedule.[15, 16] A second multi-trial analysis in which individual patient data from EORTC 22921 were combined with that of three additional trials of chemotherapy following preoperative treatment showed no benefit of postoperative chemotherapy (HR=0.97, 95%CI: 0.81,1.17). [17]

The three recently completed randomized trials comparing postoperative 5-FU/capecitabine with and without oxaliplatin have done little to elucidate the role of postoperative oxaliplatin, as in two trials the addition of oxaliplatin resulted in an improvement in disease free survival (DFS) of a similar magnitude as is seen in stage III colon cancer, but the third

reported no DFS benefit.[18-20] Though long-term follow-up is immature, it seems unlikely that these results will markedly change given the close relationship between DFS and overall survival in colorectal cancer.[21]

While expert guidelines from the National Comprehensive Cancer Network,[22] European Society of Medical Oncology,[23] and the National Institute for Health and Care Excellence [24] continue to include the recommendation to at least consider postoperative chemotherapy, there is insufficient data about the effectiveness of postoperative chemotherapy (with or without oxaliplatin) to reduce recurrence or cancer mortality in preoperatively-treated patients.[25, 26] Because older adults tend to be underrepresented in trials,[27] there are even less data regarding the effectiveness of postoperative chemotherapy approaches in this population.

We evaluated the effectiveness of postoperative chemotherapy with 5-FU or capecitabine alone - and the incremental effectiveness of oxaliplatin - following preoperative CRT and surgery for rectal cancer in routine care settings in the US. With over half of all patients with rectal cancer diagnosed over the age of 65, [28] we also specifically evaluated the impact of age on the comparative effectiveness of postoperative chemotherapy approaches.

Methods

Data sources

Cancer cases were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program which collects demographic and tumor data for individuals diagnosed with cancer residing within one of the 18 SEER regions.[29] The linkage of persons in SEER with their Medicare enrollment and claims data allows for the identification of cancer treatments [30, 31] and extended mortality follow-up.

Study population

We included patients diagnosed with pathologically confirmed, first primary cancer of the rectum/rectosigmoid junction from 2004-2009, with continuous Medicare Parts A and B fee-for-service and no managed care enrollment for the 12-months before and 6-months following the cancer diagnosis date, ensuring complete claims capture and to define covariates and treatments. Patients with American Joint Commission on Cancer (AJCC) 6th Edition stage 0-III were included to ensure inclusion of patients with clinical stage II and III rectal cancer (for which CRT is standard) who were down staged by preoperative therapy because pathologic stage (e.g. ypT and ypN stage) supersedes clinical stage in SEER. Patients who underwent complete surgical resection within 180 days from diagnosis and received preoperative CRT or radiation therapy alone (RT) between the date of diagnosis and surgery date were included in the study.

Ascertainment of treatment

Administrative codes identified cancer-directed treatments (Appendix A) and have high validity for identifying specific chemotherapy agents.[30-32] Postoperative chemotherapy was assessed from the date of surgery through the following 122 days (4 months). Specific

chemotherapeutic agents administered within the 60 days of the first chemotherapy administration were used to define the initial postoperative chemotherapy group (i.e., 5-FU/capecitabine alone or in combination with oxaliplatin).[30, 33-35]

Ascertainment of all-cause and cancer-specific mortality

The primary outcome of interest was all-cause mortality ascertained through December 2011 from the Medicare enrollment database.[36] Follow-up began 122 days from the surgery date (i.e., the landmark). The secondary outcome of cancer-specific mortality was defined from the death certificate cause of death reported to SEER; however, ascertainment was limited through December 2009.

Ascertainment of covariates

The diagnosis year, sex, age at diagnosis, race/ethnicity, marital status, region of residence, county and census tract level socioeconomic data were obtained from SEER.[37] Comorbidity was measured using conditions from Klabunde's adaptation of the Charlson Comorbidity Index (CCI).[38] Hospitalization within 30 days following surgical resection was a proxy for surgical complications, shown to be associated with both chemotherapy receipt and all-cause mortality.[39] For each patient, we estimated the predicted probability of activities of daily living dependence (ADL-D) as a proxy for frailty using a previously validated model.[40]

Statistical Analysis

We evaluated the association between postoperative chemotherapy with 5-FU/capecitabine alone versus observation and all-cause and cancer-specific mortality. We constructed a rich propensity score (PS) model that estimated the probability that each patient received postoperative 5-FU/capecitabine alone versus observation to control for measured confounding.[41] This model drew upon prior work,[13] including age, sex, race/ethnicity, marital status, metropolitan area, the proportion of individuals living below the poverty line within the same census tract, pathologic stage, cancer site, receipt of preoperative CRT or RT, specific comorbidities, hospitalization within 30 days from surgery, and the predicted probability of ADL-D. To control for measured confounders, we balanced the covariates across treatment groups using standardized mortality ratio (SMR)-weighting, assigning a weight of 1 for patients treated with postoperative 5-FU/capecitabine alone and a weight of the propensity odds $[(PS)/(1-PS)]$ for patients who did not receive postoperative chemotherapy, creating a "pseudo-population" of patients who did not receive postoperative chemotherapy with the same covariate distribution as that observed in patients who received postoperative chemotherapy with 5-FU/capecitabine alone.[42, 43] Covariate balance was evaluated using standardized absolute mean difference (SAMD); adequate balance was considered as $SAMD < 0.1$.[44]

The same analytic approach was implemented among all patients receiving postoperative chemotherapy in order to evaluate the association between the addition of oxaliplatin to postoperative 5-FU/capecitabine alone and all-cause and cancer-specific mortality. However, this analysis was restricted to patients aged 66-74 years in an effort to further reduce the potential for residual confounding by frailty among the oldest patient subgroups (where

oxaliplatin treatment is least likely). We constructed a separate PS model to estimate the probability that each patient was treated with postoperative oxaliplatin (compared with 5-FU or capecitabine alone).

Cox proportional hazards models with SMR weights and robust standard errors (to account for the lack of independence due to weighting) were used to estimate adjusted hazard ratios (aHRs) and their 95% confidence intervals (CIs) for all-cause and cancer-specific mortality. Analyses of cancer-specific mortality accounted for non-cancer death as a competing risk. [45] The weighted cumulative incidence of all-cause and cancer-specific mortality was plotted for each postoperative treatment comparison and used to calculate adjusted 3- and 5-year risk ratios (aRRs) and risk differences (aRDs).[46] Ninety-five percent confidence intervals (CIs) were generated using the standard deviation of 200 bootstraps. Analyses for the comparison of postoperative chemotherapy versus observation were further stratified by age group (<75 vs. 75+ years, based on clinical input), pathologic stage (0-I, II, III) and preoperative treatment (CRT vs. RT only). Exploratory analyses evaluated treatment effect heterogeneity by age on all-cause mortality in greater detail using a 5-year age-stratified moving window approach. All data were analyzed in SAS, version 9.3 (SAS Institute, Cary, NC). The institutional review board at the University of North Carolina at Chapel Hill determined that this research was exempt from review.

Results

Patterns of postoperative chemotherapy

In total, 1,316 patients with non-metastatic rectal cancer 66 years and older were included (Figure 1). Approximately half of eligible patients received postoperative chemotherapy following preoperative CRT and resection (n=650, 49%) and 341 (52%) of these chemotherapy treated patients received oxaliplatin (Table 1). Older age, lower stage, metropolitan residence and 30-day post-surgical hospitalization were associated with lower use of postoperative chemotherapy with 5-FU/capecitabine alone (versus observation), while comorbid peripheral vascular disease and preoperative CRT receipt were associated with higher use (Supplemental Table 1a). Among patients age 66-74 years who received postoperative chemotherapy, older age, higher census tract poverty level, lower stage and 30-day post-surgical hospitalization were associated with lower oxaliplatin receipt (Supplemental Table 1b). After PS weighting, measured characteristics were well balanced across treatment groups (SAMD <0.1, Supplemental Tables 2a-b).

Effectiveness of postoperative 5-FU or capecitabine alone

Over a mean follow-up of 3.8 and 3.5 years for postoperative 5-FU/capecitabine groups and observation, respectively, all-cause mortality was significantly lower for those patients treated with postoperative 5-FU/capecitabine alone compared to observation (HR=0.68, 95% CI: 0.52, 0.88, Supplemental Table 3a). This survival benefit was not substantially altered by control for measured confounding (aHR=0.72, 95% CI 0.55, 0.96).

The benefit of postoperative 5-FU/capecitabine over observation was restricted to patients aged 66-74 years (aHR=0.46, 95% CI: 0.30, 0.72, Figure 2, Supplemental Table 3a). This

translates to an absolute risk reduction in all-cause mortality of 14% at 3 years (aRD=-0.14, 95%CI: -0.23, -0.04) and 23 % at 5 years (aRD=-0.23, 95%CI: -0.33, -0.12), leading to a 3- and 5-year number needed to treat (NNT) of 7 and 4 (Table 2), assuming a causal effect. In contrast, patients aged 75+ years did not appear to benefit from postoperative 5-FU/capecitabine alone compared with observation (aHR=1.11, 95%CI: 0.76, 1.63, Figure 2, Supplemental Table 3a).

The substantial mortality reduction associated with postoperative 5-FU/capecitabine alone does not seem largely related to unmeasured confounding based on treatment selection as cancer-specific mortality was similarly better in the postoperative 5-FU/capecitabine treated patients compared to untreated patients in the entire cohort (aHR=0.81, 95%CI 0.50-1.31, Supplemental Table 3a) and in patients aged 66-74 (aHR=0.41, 95%CI 0.19, 0.86, Figure 2, Supplemental Table 3a) though not in patients over 75 (aHR=1.03, 95%CI 0.57, 1.87, Figure 2, Supplemental Table 3a). Stratified results did not indicate effect measure modification by pathologic stage, although associations by preoperative treatment receipt were imprecise (Supplemental Figure 1).

The exploratory analysis of treatment effect heterogeneity revealed a pattern of attenuating aHRs with increasing age (Figure 3), with the aHR reaching 1.0 at the age midpoint of 74 years (aHR=1.00, 95%CI: 0.59, 1.69). This analysis confirms the approximate clinical selection of age 75 years as a cutpoint for stratified analyses.

Comparative effectiveness of postoperative oxaliplatin versus 5-FU/capecitabine alone—Because of the observed lack of benefit of postoperative chemotherapy and the small number of patients over the age of 75 treated with oxaliplatin, we only evaluated the comparative effectiveness of adding oxaliplatin to 5-FU/capecitabine alone on all-cause and cancer-specific mortality in patients aged 66-74 years. Overall, there were 79 deaths; 29 in the 5-FU or capecitabine alone group and 50 in the postoperative oxaliplatin group with a median follow-up of 4.1 and 3.6 years, respectively. Oxaliplatin was not associated with an improvement in all-cause mortality compared with 5-FU/capecitabine alone in patients aged 66-74 years (aHR=1.57, 95%CI: 0.93, 2.65, Figure 2, Supplemental Table 3b). This translated into a non-significant increase in absolute risk at 3 years (aRD=0.04, 95%CI: -0.03, 0.11, Table 3), and significant increase in the risk of death at 5 years (aRD=0.10, 95%CI: 0.03, 0.18), leading to a 5-year number needed to treat to harm (NNT_H)[47] of 10. The lack of observed mortality reduction and potential harm of oxaliplatin among patients aged 66-74 was also seen in cancer-specific mortality analyses, although these results were imprecise.

Discussion

Postoperative 5-FU/capecitabine alone following preoperative CRT and surgical resection was associated with lower all-cause and cancer-specific mortality compared with observation in this large cohort of Medicare beneficiaries. However, the benefits of postoperative chemotherapy on mortality reduction appear to be attenuated with advancing age, with no clear benefit observed in patients 75 years or older. We found no evidence that

oxaliplatin incrementally reduced mortality compared with 5-FU/capecitabine alone among patients aged 66-74 years old.

Multiple European trials have specifically addressed the role of postoperative chemotherapy versus observation following CRT for rectal cancer.[17] In the analysis of patient data from four of these trials, three of which used 5-FU and leucovorin and one which used oxaliplatin with capecitabine, there was no suggestion of benefit from postoperative chemotherapy on survival (HR 0.97, 95% CI 0.81-1.17) or DFS (HR 0.91, 95% CI 0.77-1.07).[17] Low adherence to the protocol prescribed postoperative chemotherapy (where most patients were randomized at diagnosis and not after surgery) is a key limitation that has prevented these results from changing the long accepted belief that postoperative chemotherapy improves outcomes in resected rectal cancer. While seemingly contradictory, our study was designed to specifically address the role of postoperative chemotherapy among patients treated with timely preoperative CRT and surgery, rather than the entire CRT and chemotherapy program and therefore may better represent the isolated impact of postoperative chemotherapy among patients able to initiate treatment following surgical resection.

Although we used SMR-weighting methods with validated, novel measures of frailty to address measured confounding, it is likely that our estimate of an approximately 50% reduction in the risk of death following postoperative 5-FU/capecitabine alone versus observation among patients aged 66-74 is an overestimate of the actual treatment effect. In observational studies estimating treatment effectiveness, a key limitation is the inability to directly measure a number of key prognostic factors, notably frailty, performance status, and pretreatment clinical staging. This is particularly problematic in the comparison of postoperative 5-FU/capecitabine alone to observation, as the reasons that underlie the decision to forgo chemotherapy (e.g. frailty) are likely also related to increased mortality, thus failure to adequately control for these factors would lead us to overestimate the benefit of postoperative chemotherapy. Our study design, however, inherently decreases the potential for residual confounding by frailty, as all patients had to undergo active preoperative CRT or RT followed by curative surgical resection (e.g. not just local excision), thereby excluding patients deemed ineligible for aggressive treatment based on frailty or comorbidity. This type of restriction strategy has been found to be effective in reducing residual confounding by frailty.[48, 49] Bias related to treatment selection would be likely to have the greatest effect on all-cause mortality, yet we also observed a substantial reduction in cancer-related mortality associated with 5-FU/capecitabine alone. Thus, while it is unlikely that we could estimate the exact magnitude of the effect of 5-FU/capecitabine alone, we believe the design and findings of this study support the conclusion that postoperative 5-FU/capecitabine alone compared with observation likely reduces mortality following preoperative CRT/RT and surgery in patients with rectal cancer under 75 years.

While postoperative 5-FU/capecitabine alone reduced mortality among the entire cohort, there was no reduction observed among patients over age 75 at diagnosis. This decreasing benefit of postoperative therapy with increasing age among the elderly has been reported in subgroup analyses of patients with colon cancer treated in clinical trials. The landmark pooled analysis of patient data from randomized adjuvant 5-FU trials by Sargent in 2001 confirmed a similar benefit of 5-FU on freedom from recurrence in patients 70 years and

over; however while there was no statistical evidence of interaction of age and survival, the survival difference between treated and untreated patients diminished with increasing follow up, presumably due to the higher rates of death from other causes.[50] Limitations of our data preclude us from evaluating the effect on recurrence specifically, and the follow-up time for cancer-specific survival is too short to make definitive conclusions based on those results.

The balance of evidence from the three recently reported trials supports the benefit of postoperative oxaliplatin versus 5-FU/capecitabine alone on DFS.[18, 20] In the one negative trial, patients were randomized at diagnosis and the resultant low completion rates make it difficult to interpret the postoperative chemotherapy effect (only 52% of patients randomized to oxaliplatin and 66% of patients randomized to capecitabine completed planned postoperative therapy).[19] Limitations of our data did not allow us to incorporate therapy completion into our analyses, which could mask the potential benefits of postoperative oxaliplatin. However, our analysis was designed to estimate the association of starting oxaliplatin versus 5-FU/capecitabine alone as an initial strategy, which answers a clinically relevant, but different question.

If oxaliplatin likely improves DFS in patients following resection of preoperatively treated rectal cancer, the pattern of benefit in rectal cancer may be akin to what is seen in colon cancer where oxaliplatin unequivocally works in younger patients but not in older patients. Just as we found no mortality reduction attributable to postoperative oxaliplatin in patients 66-74 years old, a pooled analysis of oxaliplatin in patients 70 and older with stage III colon cancer found oxaliplatin was associated with a slight improvement in time to recurrence over 5-FU alone, but there was no improvement in DFS or overall survival.[51] In the pooled analysis in colon cancer and our evaluation of patients aged 66-74 in SEER-Medicare, there was a slight suggestion that the addition of oxaliplatin may actually lead to harm. Because of the short follow-up for cancer-specific mortality and lack of information on recurrence, it is premature to conclude that oxaliplatin increases mortality. The possibility for harm should, however, be considered when counseling older patients about the addition of oxaliplatin to 5-FU/capecitabine alone following preoperative CRT and surgical resection of rectal cancer.

In summary, postoperative 5-FU/capecitabine alone was associated with a considerable reduction in mortality following preoperative CRT and surgery for non-metastatic rectal cancer in patients younger than 75 years compared with observation. Patients over the age of 75 should be counseled that any potential benefit of postoperative therapy after resection is likely to be small and treatment decisions should consider individual risks and preferences. Similar to the colon cancer setting, our data do not support the addition of oxaliplatin to postoperative chemotherapy in older patients with resected rectal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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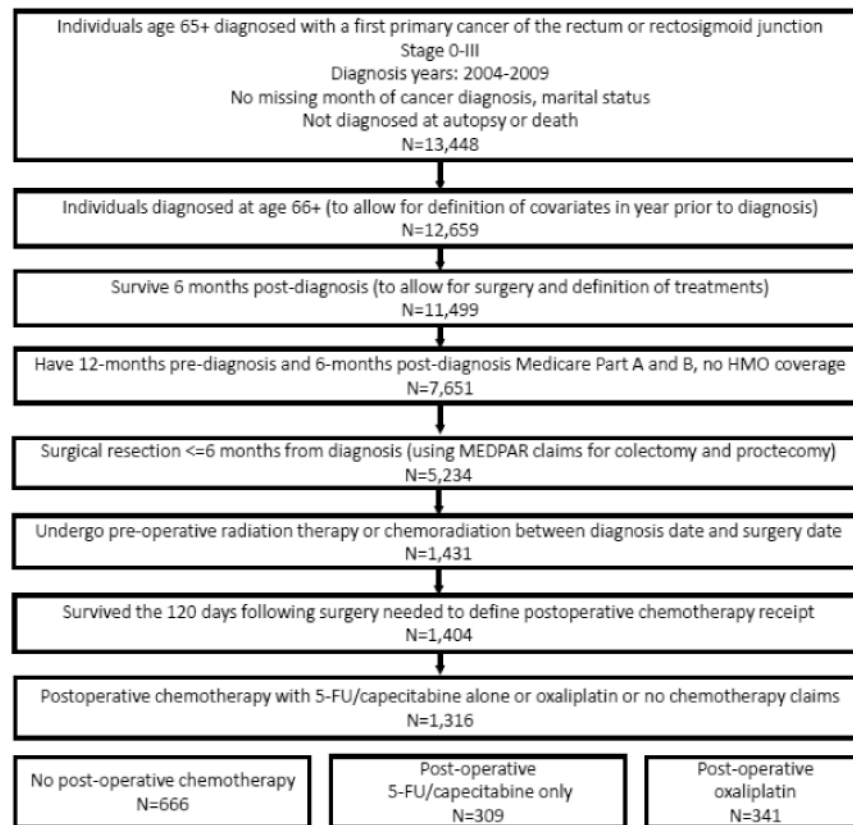
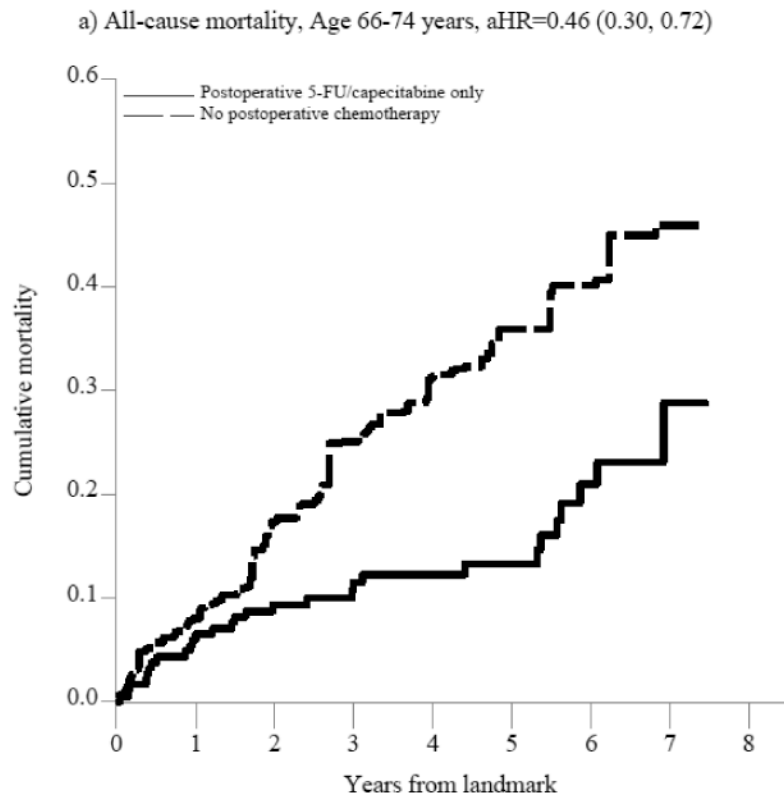
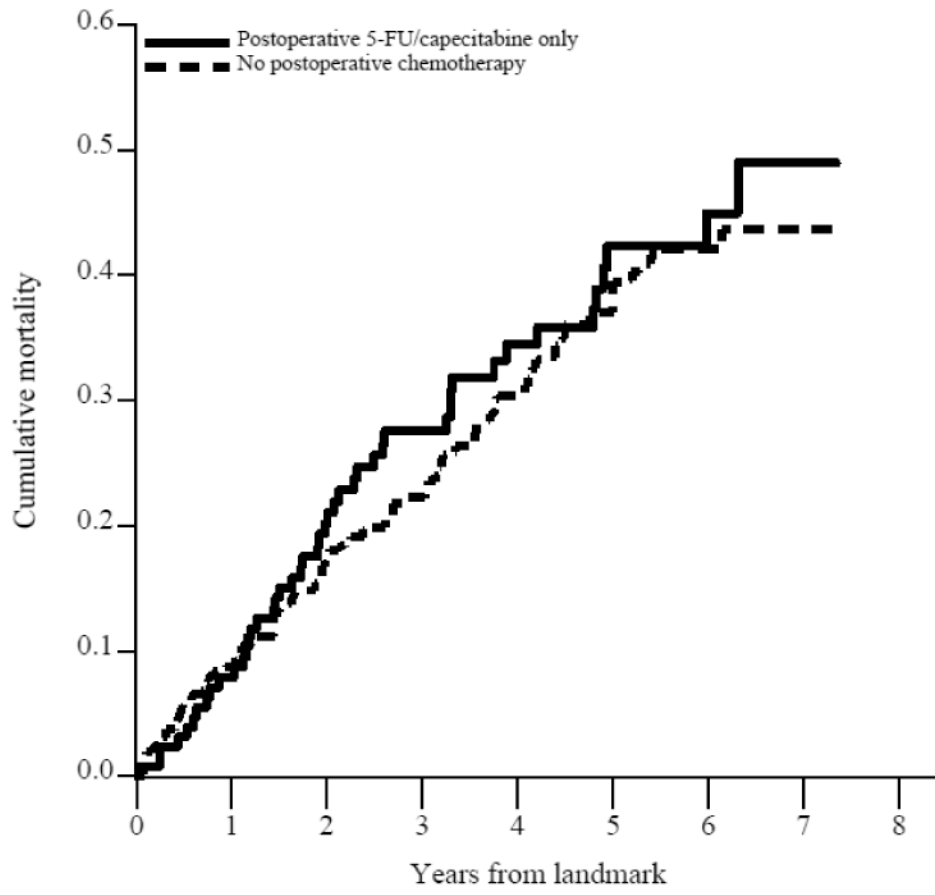


Figure 1. Study population flowchart

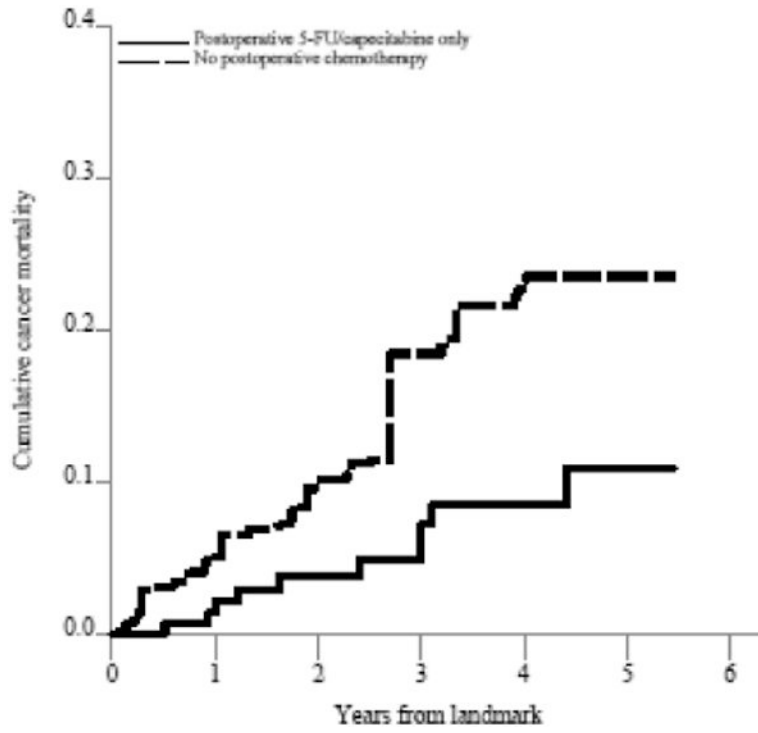
Cohort inclusion and exclusion criteria for older individuals diagnosed with pathologically staged, non-metastatic rectal cancer at age 66 years or older using the Surveillance, Epidemiology and End Results program (SEER)-Medicare linked data from 2003-2009.



b) All-cause mortality, Age 75+ years, aHR=1.11 (0.76, 1.63)



c) Cancer-specific mortality, Age 66-74 years, aHR=0.41 (0.19, 0.86)



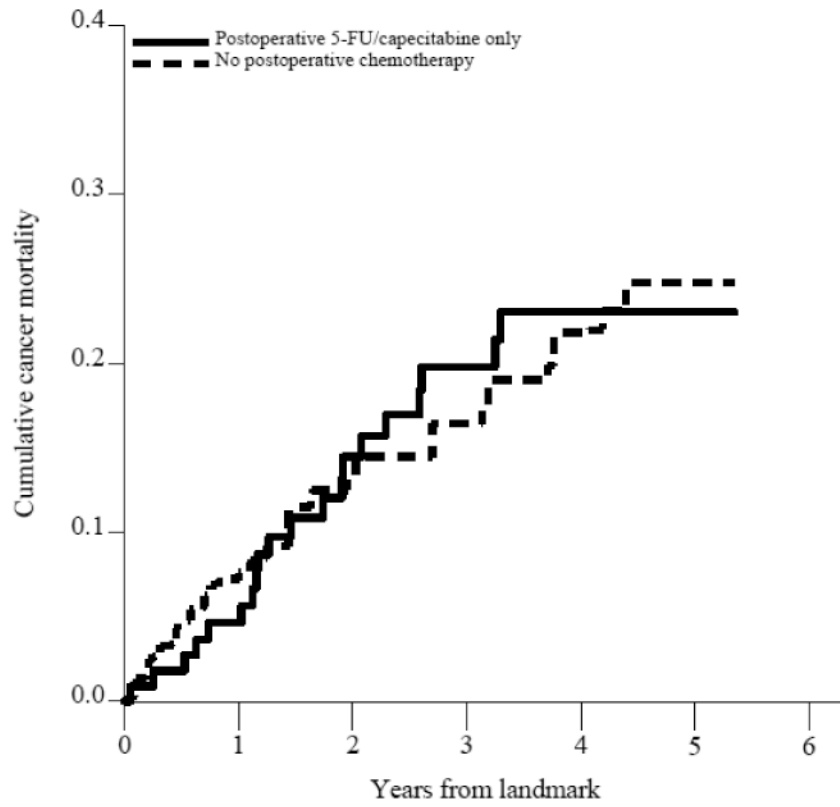
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d) Cancer-specific mortality, Age 75+ years, aHR=1.03 (0.57, 1.87)



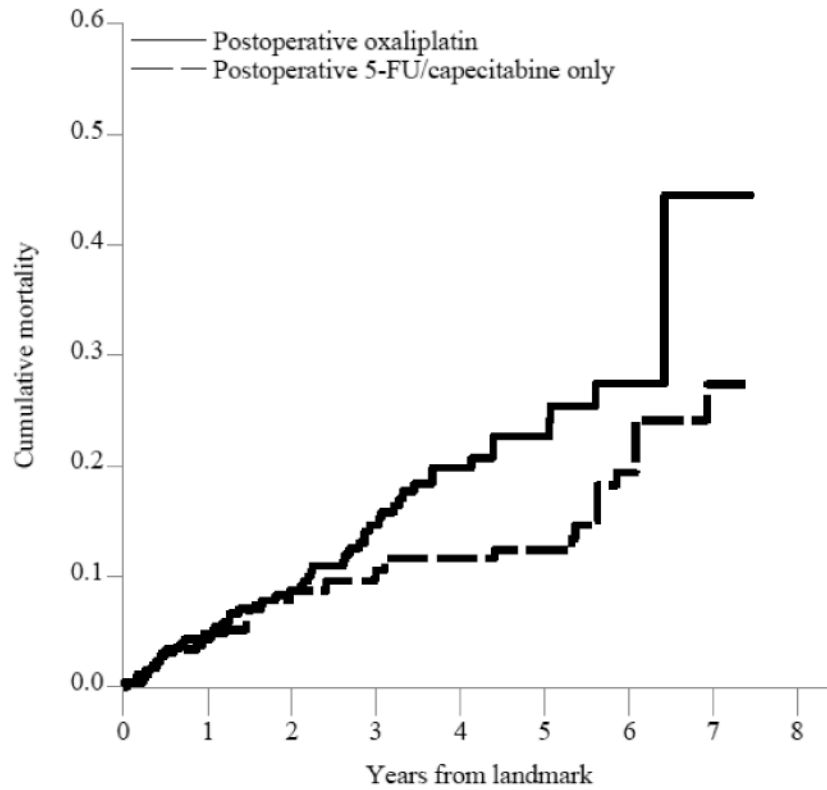
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e) All-cause mortality, Age 66-74 years, aHR=1.57 (0.93, 2.65)



f) Cancer-specific mortality, Age 66-74 years, aHR=2.14 (0.90, 5.06)

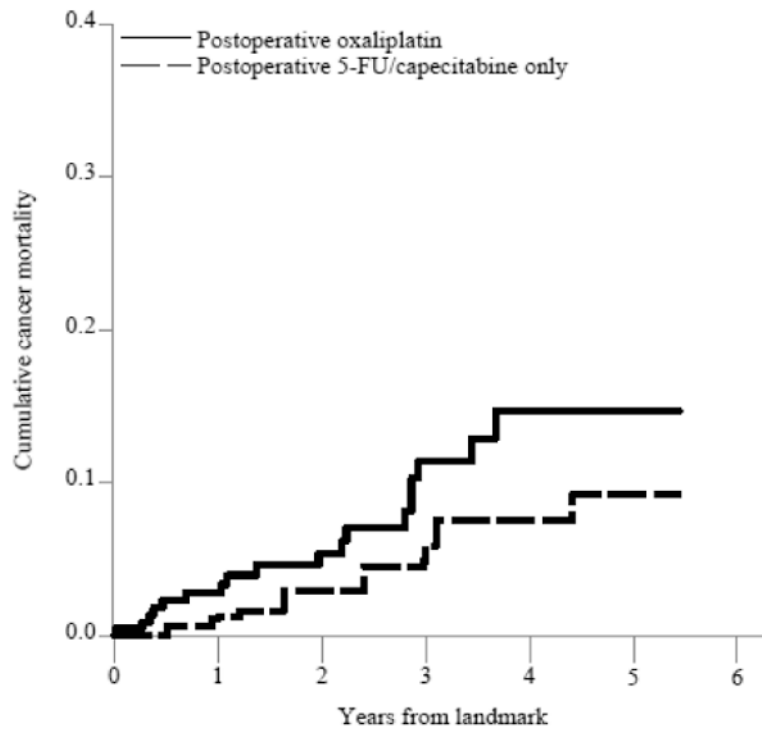


Figure 2. Figure 2a-f. Propensity score-weighted cumulative all-cause and cancer-specific mortality among patients with non-metastatic rectal cancer who received postoperative 5-FU or capecitabine alone vs. no postoperative chemotherapy by age group (panels a-d) and postoperative oxaliplatin vs. postoperative 5-FU/capecitabine alone among patients age 66-74 years (panels e-f)

In panels a-d, the blue (solid) line represents the cumulative incidence of the specific outcome (i.e., all-cause or cancer specific mortality) for individuals who received postoperative 5-FU/capecitabine alone while the red (dashed) line represents the cumulative incidence of the outcome for individuals who did not receive postoperative chemotherapy. In panels e-f, the blue (solid) line represents the cumulative incidence of the outcome for individuals who received postoperative oxaliplatin and the red (dashed) line represents the cumulative incidence of the outcome for individuals who received postoperative 5-FU/capecitabine alone.

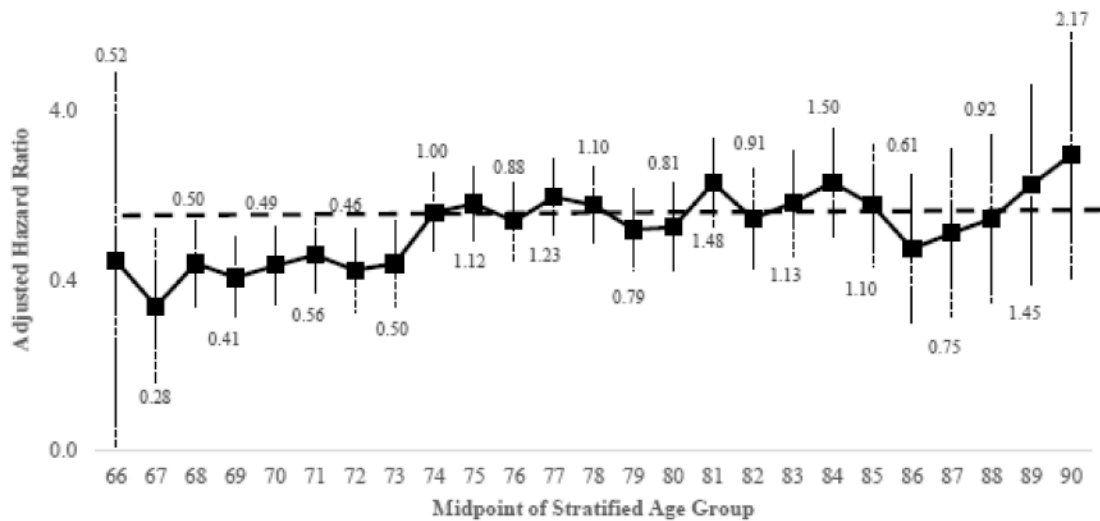


Figure 3. Exploratory analysis of treatment effect heterogeneity by age at diagnosis comparing postoperative 5-FU/capecitabine alone versus no postoperative chemotherapy and all-cause mortality

The solid black line denotes the adjusted hazard ratio estimated using age-stratified subgroups and a one-year moving window, resulting in 25 estimates. All estimates used 5-year age groupings (e.g., 71-75 years, age midpoint=73 years), when possible. The estimates for age 66 and 67 used one and three-year age groups, respectively. Estimates for ages beyond 90 years were not calculated, as data was sparse. The adjusted hazard ratios are plotted at the midpoint of each age group along with robust 95% confidence intervals (plotted on the log scale).

Table 1
Characteristics of 1,316 older patients with non-metastatic rectal cancer receiving preoperative treatment and surgical resection by postoperative treatment type, 2004-2009

Characteristics	No postoperative chemotherapy n=666		Postoperative 5-FU/ capecitabine alone n=309		Postoperative oxaliplatin n=341	
	n	%	n	%	n	%
Age at diagnosis						
	66-69 years	129	19	85	141	41
	70-74 years	213	32	98	113	33
	75-79 years	177	27	73	74	22
	80+ years	147	22	53	13	4
Male		381	57	178	214	63
Race/ethnicity						
	White, Non-Hispanic	526	79	244	287	84
	Black, Non-Hispanic	43	6	16	14	4
	Other, Non-Hispanic	46	7	23	23	7
	Hispanic	51	8	26	17	5
Marital status						
	Married	385	58	196	220	65
	Widowed	173	26	62	61	18
	Single	58	9	23	30	9
	Separated or Divorced	50	8	28	30	9
Metropolitan residence		598	90	257	309	91
% living below poverty line (census tract)						
	Quartile 1 (low)	151	23	65	107	31
	Quartile 2	168	25	71	90	26
	Quartile 3	173	26	82	76	22
	Quartile 4 (high)	174	26	91	68	20
AJCC pathologic stage						
	0 and I	204	31	75	54	16
	II	298	45	121	120	35
	III	164	25	113	167	49
Diagnosis year						

Characteristics	No postoperative chemotherapy		Postoperative 5-FU/ capecitabine alone		Postoperative oxaliplatin	
	n=666	%	n=309	%	n=341	%
2004	112	17	62	20	26	8
2005	125	19	61	20	62	18
2006	110	17	46	15	60	18
2007	118	18	46	15	64	19
2008	91	14	43	14	77	23
2009	110	17	51	17	52	15
Rectum vs. Rectosigmoid	597	90	278	90	309	91
Preoperative chemoradiation vs. radiation therapy only	527	79	290	94	312	91
Selected comorbidities						
Congestive heart failure	43	6	14	5	NR	NR
COPD	65	10	23	7	26	8
Diabetes without sequelae	141	21	72	23	60	18
Diabetes with sequelae	19	3	11	4	13	4
30-day post-operative hospitalization	245	37	69	22	58	17
Predicted probability of ADL-D (median, IQR)	0.034 (0.023, 0.054)		0.031 (0.021, 0.046)		0.026 (0.020, 0.038)	

Abbreviations: 5-FU=5-fluorouracil; NR=not reportable due to cell size less than 11; AJCC=American Joint Commission on Cancer; COPD=chronic obstructive pulmonary disease; ADL-D=activities of daily living dependence.

Table 2
Crude and weighted 3- and 5-year risk differences and risk ratios comparing postoperative 5-FU/capecitabine alo vs. no postoperative chemotherapy and all-cause and cancer-specific mortality

Outcome	Subgroup	Crude/ Weighted and time period	Outcome risk						
			No postoperative chemotherapy	Postoperative 5-FU/capecitabine alone	Risk difference	95% CI	Risk ratio	95% CI	
<i>All-cause mortality</i>									
	Age 66-74 years	Crude							
		3-year	0.23	0.12	-0.11	(-0.18, -0.05)	0.51	(0.32, 0.80)	
		5-year	0.34	0.13	-0.21	(-0.29, -0.13)	0.39	(0.25, 0.61)	
	Age 75+ years	Crude							
		3-year	0.25	0.28	0.03	(-0.06, 0.12)	1.12	(0.79, 1.58)	
		5-year	0.41	0.42	0.01	(-0.10, 0.12)	1.02	(0.78, 1.34)	
	Age 66-74 years	Weighted ^b							
		3-year	0.25	0.12	-0.14	(-0.23, -0.04)	0.46	(0.28, 0.76)	
		5-year	0.36	0.13	-0.23	(-0.33, -0.12)	0.37	(0.23, 0.60)	
	Age 75+ years	Weighted ^b							
		3-year	0.22	0.28	0.05	(-0.05, 0.16)	1.24	(0.81, 1.91)	
		5-year	0.39	0.42	0.03	(-0.10, 0.16)	1.07	(0.77, 1.49)	
<i>Cancer-specific mortality</i>									
	Age 66-74 years	Crude							
		3-year	0.12	0.07	-0.05	(-0.11, 0.01)	0.59	(0.30, 1.16)	
		5-year	0.19	0.11	-0.08	(-0.17, 0.01)	0.58	(0.25, 1.33)	
	Age 75+ years	Crude							
		3-year	0.15	0.20	0.05	(-0.05, 0.15)	1.34	(0.75, 2.39)	
		5-year	0.22	0.23	0.01	(-0.12, 0.14)	1.05	(0.56, 1.97)	
	Age 66-74 years	Weighted ^b							
		3-year	0.18	0.07	-0.11	(-0.29, 0.06)	0.39	(0.13, 1.16)	
		5-year	0.24	0.11	-0.13	(-0.29, 0.04)	0.46	(0.17, 1.28)	
	Age 75+ years	Weighted ^b							
		3-year	0.16	0.20	0.03	(-0.09, 0.15)	1.20	(0.59, 2.43)	
		5-year	0.25	0.23	-0.02	(-0.17, 0.14)	0.93	(0.46, 1.88)	

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Abbreviations: CI=confidence interval

^aStandard error based on standard deviation of 200 nonparametric bootstrap resamples.

^bWeighted for age, sex, race/ethnicity, AJCC pathologic stage, cancer site, marital status, metropolitan residence, census tract poverty level (%), congestive heart failure, peripheral vascular disease, cerebrovascular disease, COPD, diabetes without sequelae, diabetes with sequelae, renal disease, 30-days post-operative hospitalization, preoperative therapy (chemoradiation or radiation therapy alone), predicted probability of ADL-D.

Table 3
Crude and weighted 3- and 5-year risk differences and risk ratios comparing postoperative oxaliplatin vs. postoperative 5-FU/capecitabine alone, patients age 66-74 years old

Outcome	Crude/Adjusted and time period	Outcome risk					
		Postoperative 5-FU/capecitabine alone	Postoperative oxaliplatin	Risk difference	95% CI ^a	Risk ratio	95% CI ^b
<i>All-cause mortality</i>	Crude						
	3-year	0.12	0.15	0.03	(-0.03, 0.10)	1.28	(0.76, 2.13)
	5-year	0.13	0.23	0.09	(0.02, 0.17)	1.71	(1.03, 2.82)
<i>Cancer-specific mortality</i>	Crude						
	3-year	0.11	0.15	0.04	(-0.03, 0.11)	1.38	(0.81, 2.36)
	5-year	0.12	0.23	0.10	(0.03, 0.18)	1.83	(1.11, 3.03)
	Crude						
	3-year	0.07	0.11	0.04	(-0.03, 0.11)	1.58	(0.67, 3.69)
	5-year	0.11	0.15	0.04	(-0.06, 0.13)	1.34	(0.57, 3.15)
	Crude						
	3-year	0.06	0.11	0.06	(-0.02, 0.13)	1.95	(0.74, 5.15)
	5-year	0.09	0.15	0.05	(-0.04, 0.15)	1.59	(0.62, 4.09)

Abbreviations: CI=confidence interval

^aStandard error based on standard deviation of 200 nonparametric bootstrap resamples.

^bWeighted for age (66-69, 70-74 years), sex, race/ethnicity, AJCC pathologic stage, married, metropolitan residence, census tract poverty level (%), COPD, diabetes, 30-day post-operative hospitalization, pre-operative therapy (chemoradiation or radiation therapy alone), predicted probability of ADL-D.