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Title: The Influence of Local Recurrence on Survival in Patients with Rectal Cancer.

Short Title: Rectal Cancer and Local Recurrence.

By

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ABSTRACT

Background Recent trials on rectal cancer have demonstrated significant improvements in local recurrence without improvements in overall survival. The aim of this paper was to define the influence of local recurrence on survival in a prospective series of patients who underwent R0 or R1 resections for rectal cancer.

Methods Patients presenting with rectal cancer from 1996 to 2012 were prospectively audited. The study included patients who underwent an R0 or R1 resection. Local recurrence was defined as cancer regrowth detected in the pelvis regardless of whether or not new metastases were found elsewhere. Kaplan-Meier curves, smoothed hazard functions and Cox models using both time since diagnosis and age as the time scale were used to define the influence of local recurrence on overall survival.

Results The study involved 483 patients, of mean age 66 years (SD=13) and a median follow-up of 5.2 years. The results at 5 years were: overall survival 71% (95%CI 66-75), local recurrence 7% (95%CI 5-10), and distant recurrence 18% (95% CI 14-22). Patients diagnosed with local recurrence died faster than patients diagnosed with either distant recurrence or no recurrence, and this was particularly obvious for younger patients (local HR 54, 95%CI 12-253 and distant HR19, 95%CI 4-80). Local recurrence that developed early following surgery also had worse survival outcomes.

Conclusions Within this cohort of rectal cancer patients, the early development of local recurrence was the single most important indicator of a reduced survival, and carried a worse prognosis than the development of distant metastases alone.

INTRODUCTION

A major emphasis over the last 20 years in the management of rectal cancer has been to reduce the rates of local recurrence. This is because it is considered to be both an important prognostic factor and a clinical indicator of the quality of treatment. During this period a number of reports have demonstrated a significant reduction in the rates of local recurrence[1-6]. Yet despite this, three recent clinical trials reporting mature long-term results, have highlighted significant improvements in local recurrence without an improvement in survival[5,6]. A pooled analysis of the EORTC trial 22921 and the FFCD 9203 trial (evaluating pre operative chemo-radiotherapy versus radiotherapy regimes) with a median follow-up of 6 years showed a significant decrease in local recurrence (11% vs 15%) but no difference in the 5 year overall survival (66% vs 66%)[6]. Similarly, the Dutch TME (Total Mesorectal Excision) and radiotherapy trial reported 12 year follow-up results that demonstrated a significant decrease in local recurrence (5% vs 11%) and no difference in overall survival (48% vs 49%)[5](Table I).

The aim of this study was to determine the rate and pattern of recurrence in patients undergoing R0 or R1 resections for rectal cancer and to quantify its influence on overall survival using Cox models and to demonstrate the findings graphically using smoothed hazard functions with age as the time scale.

METHODS

This study included all patients with biopsy proven adenocarcinoma of the rectum who were managed from 1996 to 2012 by a single colorectal surgeon. Patients were excluded if they did not undergo surgery or if the resection was R2 (i.e. leaving obvious macroscopic disease). Patients in this cohort diagnosed from 1996-2006 were treated predominantly in the public health care system whereas patients diagnosed after 2006 were treated in a private hospital. This meant that calendar year and hospital type were correlated. Surgical procedures included high anterior resections, low anterior resections (anastomosis within 10 cm of the anal verge), ultralow anterior resections (i.e. total mesorectal excision with an anastomosis within 6cm of the anal verge), and local excisions. The height of the cancer was measured from the inferior aspect of the internal anal sphincter to the lower tumour border. Tumour stage was classified according to the AJCC guidelines[9]. All patients were prospectively entered into a database (Filemaker Pro) that was maintained by a research nurse. Patients were followed up as per a defined plan that included six monthly visits for five years, a thoraco-abdominal CT scan every 12 months, a colonoscopy at 12 months, three years and five years.

Neoadjuvant therapy in the form of long course radiotherapy and chemotherapy (CMT) was offered to all patients presenting electively with distal rectal cancers (within 12 cm of the anal verge) and imaging evidence of either a T3/4 rectal tumour and/or involved mesorectal lymph nodes. The preoperative clinical and imaging stage was used for the purposes of the analysis if there was no residual tumour in the specimen after preoperative CMT. For patients in whom the tumour was down staged, the preoperative T staging was used. N staging relied upon the histological evaluation. Patients with residual mucin pools and no tumour within the nodes were classified as positive. Patients receiving CMT were offered postoperative chemotherapy to complete their treatment.

Recurrence was defined as the development of either biopsy proven or radiological evidence (including a positive PET scan) of tumour regrowth following the initial surgery. Local recurrence was defined as cancer regrowth detected in the pelvis regardless of whether or not new metastases were found elsewhere. All patients who developed recurrent disease were assessed for possible curative resection.

Age and year at diagnosis were collapsed into grouped variables. A time-to-event analysis was performed on the rectal cancer patient cohort using non-parametric Kaplan-Meier, log-rank tests and smoothed hazard functions and semi-parametric Cox models. The *hazard function* or force of mortality can be interpreted as a measure of the tendency to die at a given point in time provided the patient has survived up to that time point. The main outcome measure was all-cause mortality with local and distant disease recurrence treated as time dependent covariates. A separate investigation of factors present at time of surgery that were associated with the rate of recurrence was also performed but using time since diagnosis as the time scale. It is traditional to use time since diagnosis as the origin for cancer survival studies. An alternative is to use age as the time scale. When age is used as the time scale, the age effect on survival is removed as it is absorbed into the unspecified baseline hazard. Using age as the time scale is useful when investigating all-cause mortality outcomes (i.e. overall survival) as these are strongly associated with age during follow-up or attained age[7,8].

Patients were followed up until date of death or study censor date (31st March 2012). Date of death was determined from linkage of patient identifiers to the state based death registry on a regular basis. Loss to follow-up for recurrence was expected to be minimal because few patients left the state (three patients identified). Likelihood ratio tests were used to include or exclude covariates from the adjusted (and most parsimonious) model and to identify any potential plausible interaction terms at the 5% level. Chi - square, Fisher's exact, and rank sum tests were also used to test equality in proportions and medians where appropriate. All statistical analyses were performed using Stata Version 12 (Stata Corp, College Station, Texas).

RESULTS

There were 483 patients with rectal cancer in the study cohort with more males than females (Table 2). Mean age at diagnosis was 66.1 (SD= 13.1) years with ages ranging from 28 to 93 years. Median length of follow-up was 5.2 years from time of diagnosis and ranged from 0.2 to 16 years. There were 179 deaths during follow-up, six patients died in the 30 day postoperative period (1.2%), and 25 patients developed local recurrence. Of the patients who developed local recurrence, 9 (36%) had isolated disease within the pelvis, the remainder had systemic disease as well. The five year outcome proportions were: overall survival 70.9% (95%CI 66.4-75), local recurrence 6.8% (95%CI 4.6-10), distant recurrence 17.6% (95%CI 14.1-21.9). When patients who had R1 resections or local excisions were excluded, the five year local recurrence rate for R0 resections was 3.1% (95%CI 1.7-5.7%).

A univariate analysis of equality of survivorship function by various individual demographic and clinical parameters is summarized in Table 2. Survival outcomes differed by patient age, stage at diagnosis, resection status, recurrence, and curative intent. Survival was also observed to differ by year of diagnosis, type of operation, and whether extramural venous invasion was documented. There was no difference in overall survival by sex, height of tumour, lymph node involvement, chemotherapy or radiotherapy when each variable was tested individually.

The univariate log rank tests indicated that patients had a different survival experience after a local or distant recurrence (Table 2). A Kaplan -Meir curve of the survivorship function by recurrence state and using time since diagnosis as the analysis time shows that after patients were diagnosed with local recurrence they appeared to die faster than patients diagnosed with distant recurrence or no recurrence (Fig 1A). A smoothed hazard function of the same data (Fig 1B) shows that the rate of dying following a local recurrence was highest when it occurred within a short time of diagnosis (less than two years) then falling to a stable but high rate. The rate of dying following a distant recurrence appeared to increase

with time since diagnosis, peaking at around four years post diagnosis and then falling to levels similar to patients without a recurrence recorded.

Age was used as the analysis time scale to investigate whether the rates of dying following a recurrence varied by age (Fig 2A). Of patients with a local recurrence, those who were aged 50 - 65 years showed a tendency to die faster than older patients. In contrast, patients with distant recurrence had an increasing mortality rate with age, similar to patients who did not have a recurrence recorded; albeit at a higher rate. Using attained age as the time scale, factors associated with all-cause mortality of the rectal cancer cohort were estimated using a Cox proportional hazards regression model (Table 3). After experiencing either a local or distant recurrence of disease, the relative rate of dying increased significantly although this depended on the age at diagnosis. Patients diagnosed when younger than 60 years of age or older than 70 years died more quickly after local and distant recurrence compared to similar aged patients who did not have a recurrence. Whereas in patients diagnosed when aged 60-79 years there was no difference in the rate of dying after a local recurrence and only a smaller increased risk of dying after distant recurrence. For patients who never experienced a recurrence, chemotherapy was associated with a 60% decreased rate of dying. However, once a recurrence had occurred, having had a history of chemotherapy was not associated with all-cause mortality outcome.

The rate of dying was dependent on age at diagnosis but the extent of this effect varied by tumour stage at diagnosis (Table 3). Amongst patients diagnosed with early stage tumours (A & B), there was no difference in survival outcomes for those diagnosed younger than 60 years and those diagnosed 60-69 years. There was evidence that younger patients had poorer survival outcomes from later stage cancers (C & D) compared to those diagnosed 60-69 years. Patients diagnosed over 70 years of age had poorer survival compared to 60-69 years olds for all four cancer stages.

The type of surgery performed, year of diagnosis and ASA were also significantly associated with all-cause mortality after adjusting for cancer stage, age at diagnosis, CMT and recurrence (Table 3). Patients who underwent a low anterior resection died four times faster than patients who had ultralow anterior resections and those who had less common procedures, coded as "*other*" (including proctocolectomy and ileal J pouch), died three times faster. Local excision of the cancer was not associated with an increased mortality. Improved survival outcomes were observed over time in this cohort although this effect is a likely confounded by correlation with hospital, patient and surgeon characteristics (i.e. learning curve) that changed in a non-random way over the study period. For each increase of one in ASA score, the relative rate of dying increased by 42% in this study cohort after adjusting for the other included covariates.

The relative hazard of developing a recurrence, either local or distant, was estimated by a proportional hazards regression model (Table 4). Only the resection status (R1) and the use of chemotherapy were associated with a significant increase in recurrence. Therefore, sex, age at diagnosis, curative intent, type of operation, height of tumour, extramural venous invasion, radiotherapy, year of diagnosis, ASA, tumour stage and positive lymph nodes were not associated with the relative rate of recurrence in this rectal cancer cohort.

DISCUSSION

The results of this study have indicated that the development of local recurrence in patients with rectal cancer is associated with a worse survival than patients developing distant metastases alone. This observation was especially strong in patients under the age of 60 years and when the recurrence developed within two years of diagnosis. A multivariate analysis of survival demonstrated a number of recognized associations (i.e. age, stage, and ASA score). The study also found that recurrence is most closely predicted by the resection status and the use of chemotherapy. Of interest was the poor survival associated with performing a low versus ultra low anterior resection, a finding not previously noted in the literature. This study failed to demonstrate any survival advantage for patients receiving radiotherapy.

It could be argued that cancer survival is mainly dependent on the development of distant metastatic disease. Yet this study highlights the strong association between local recurrence and survival. Of those patients developing local recurrence, nearly two thirds also had systemic disease at the same time. This is a similar rate to that noted in the Dutch TME trial[5]. Untreated local recurrence of a rectal cancer is a fatal condition[10]. Table I details a series of clinical trials published over the last 15 years that have evaluated various treatment modalities such as surgical technique, chemotherapy and radiotherapy in the management of rectal cancer. Many of these trials have extended follow-up periods and their results are mature. Of interest is the fact that a majority have shown long-term improvements in local recurrence yet this has not translated into a benefit in overall survival[1-6]. Some trials such as the NSABP R03 have shown improved disease-free survival but not overall survival[4]. You can debate which is the more relevant survival analysis, however, overall survival is such a robust and unbiased outcome measure that the authors think it should be considered the more clinically relevant[11].

There are a number of possible explanations for the apparent lack of association between local recurrence and survival. Firstly, that the adjuvant treatments may have a negative effect on long term overall

survival and that this is reducing the benefits derived from decreasing the rate of local recurrence. Early trials of radiotherapy did show increased rates of morbidity from treatment[12], however, modern techniques are felt to have resolved these problems. An alternative explanation is that the local recurrence is not really prevented but rather suppressed, so that it exists in smaller volume and hence not as readily diagnosed. Perhaps the rates of recurrence are not reduced at all, only suppressing the disease to a subclinical volume. Recurrence can be difficult to diagnose, and small volume disease may contribute to systemic disease and a reduced survival.

A number of trials have evaluated predictors of local recurrence following treatment of rectal cancer. Perhaps the strongest associations have been found in relation to the tumour stage, the location of the tumour to the anal verge, and the resection margin[13-15]. The strongest predictors in this trial were the use of chemotherapy and the resection margin. The lack of association of survival on the location of the rectal cancer is in discord with a majority of other studies[13-15]. These studies have included multiple surgeons whereas this trial was drawn form a single surgeon experience. The advantage of this is that the complexity of rectal surgery is more standardized, however, these results are less transferable. The association of recurrence with chemotherapy probably relates to the use of such treatment on those patients with more advanced disease. Yet, in the era of CMT, it is difficult to accurately define rectal cancer staging, as approximately 23% of patients are complete responders to their treatment. The association of recurrence with resection margins is well recognized and again noted in this study. Achieving R0 resections in rectal cancer is just so critical to the outcome of these patients[16-18].

There are a number of limitations with a study of this nature. Because this is a single surgeon series, its findings lack generalizability, and the relative small study size means that it may be underpowered to detect some important differences. For example, the extramural vascular invasion (EMV) data has only been accurately collected over the last 6 years. Yet in the multivariate analysis it always looked like it

was going to stay in the models, but it kept dropping out due to lack of sample size. With only 25 people developing local recurrence it meant that the analysis lacked power. Nonetheless, the advantage of this dataset is that it was prospectively collected and the patients were intensively followed up. Because of the geographical isolation of the study group, few patients were lost to follow-up (3 only). It would be of interest to validate these findings on a larger dataset.

In conclusion, over the last two decades the rates of local recurrence have significantly reduced in patients with rectal cancer. This has occurred through of a variety of different approaches including improved surgery, and the use of adjuvant chemotherapy and radiotherapy. What is difficult to know is which of these factors is playing the most dominant role in these reductions. This study has shown that local recurrence is one of the most important predictors for survival in patients with rectal cancer, yet this is in contrast to recent trials indicating improved local recurrence rates without improvements in survival. The results of this trial need to be validated, and if they are, then we should continue to focus attention on reducing local recurrence rates in relationship to the management of rectal cancer.

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REFERENCES

1. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336:980-987.
2. Wolmark N, Wieand HS, Hyams DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum. National Surgical Adjuvant Breast and Bowel Project Protocoal R-02. J Natl Cancer Inst. 2000;92:388-396.
3. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the german CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2011:29(suppl): abstract 3516.
4. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009;27:5124-5130.
5. Van Gijn W, Marijinen CAM, Nagtegaal ID, et al. Preopertive radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12 year follow-up of the multicentre, randomized controlled TME trial. Lancet Oncol. 2011;12:575-582.
6. Bonnetain F, Bosset J, Gerard J, et al. An analysis preoperative chemoradiotherapy with 5FU/leucovorin for T3-4 rectal cancer on survival in a pooled analysis of EORTC 22921 and FFCD 9203 trials: surrogacy in question? J Clin Oncol. 2011;29(suppl.): abstract 3506.
7. Commenges D, Letenneur L, Joly P, Alioum A, Dartigues JF. Modelling age-specific risk: application to dementia. Stat Med. Sep 15 1998;17(17):1973-1988.
8. Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med. Dec 30 2004;23(24):3803-3820.
9. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual 7th Ed. 2010. New York, NY: Springer.
10. Platell C. A community based hospital experience with colorectal cancer. Aust NZ J Surg 1997;67:420-423.

11. Platell C, Semmens J. A review of survival curves for colorectal cancer. Dis Colon Rectum 2004;47:2070-2075.
12. Holm T, Singnomklao T, Rutqvist LE, Cedermark B. Adjuvant preoperative radiotherapy in patients with rectal carcinoma. Adverse effects during long term follow-up of two randomized trials. Cancer 1996;78(5):968-976.
13. Kaiser AM, Klaristenfeld D, Beart RW. Preoperative versus Postoperative Radiotherapy for Rectal Cancer in a Decision Analysis and Outcome Prediction Model. Ann Surg Oncol. 2012 Jul 6. [Epub ahead of print]
14. Lim SB, Yu CS, Hong YS, Kim TW, Park JH, Kim JH, Kim JC. Failure patterns correlate with the tumor response after preoperative chemoradiotherapy for locally advanced rectal cancer. J Surg Oncol. 2012 Jun 11. [Epub ahead of print]
15. Bernstein TE, Endreseth BH, Romundstad P, Wibe A; on behalf of the Norwegian Colorectal Cancer Registry. Improved local control of rectal cancer reduces distant metastases. Colorectal Dis. 2012 May 31. [Epub ahead of print]
16. Fitzgerald TL, Brinkley J, Zervos EE. Pushing the envelope beyond a centimeter in rectal cancer: oncologic implications of close, but negative margins. J Am Coll Surg. 2011 Nov;213(5):589-595. Epub 2011 Aug 19.
17. Bernstein TE, Endreseth BH, Romundstad P, Wibe A; Norwegian Colorectal Cancer Registry. What is a safe distal resection margin in rectal cancer patients treated by low anterior resection without preoperative radiotherapy? Colorectal Dis. 2012 Feb;14(2):e48-55.
18. Kiran RP, Lian L, Lavery IC. Does a subcentimeter distal resection margin adversely influence oncologic outcomes in patients with rectal cancer undergoing restorative proctectomy? Dis Colon Rectum. 2011 Feb;54(2):157-163.

Table I. A Selection of Clinical Trials on Patients with Rectal Cancer that Evaluated Radiotherapy and/or Chemotherapy.

Trial	*Treatment*	*Number*	*Follow-up (years)*	*Overall Survival*	*Local Recurrence*
• ***Swedish Rectal Cancer Trial***[1]	*Pre RadioRx*	*866*	*5*	*58% vs 48%* *p=0.004*	*11% vs 27%* *p<0.001*
• ***NSABP R-02***[2]	*Post CMT vs RadioRx*	*694*	*8*	*53% vs 51%* *ns*	*13% vs 8%* *p=0.02*
• ***German CAO/ARO/AIO -94***[3]	*Pre vs Post CMT*	*823*	*11*	*60% vs 60%* *ns*	*7% vs 10%* *p=0.048*
• ***NSABP R-03***[4]	*Pre vs Post CMT*	*267*	*8*	*74% vs 66%* *ns*	*11% vs 11%* *ns*
• ***Dutch TME Trial***[5]	*Pre RadioRx vs TME*	*1861*	*12*	*48% vs 49%* *ns*	*5% vs 11%* *p=0.0001*
• ***EORTC 22921 & FFCD 9203***[6]	*Pre CMT vs Post ChemoRx*	*1753*	*6*	*66% vs 66%* *ns*	*11% vs 15%* *p=0.0001*

(CMT chemo-radiotherapy, RadioRx radiotherapy, ChemoRx chemotherapy, Pre preoperative, Post postoperative).

Table 2. Summary characteristics of the study cohort (N=483) and log rank test p values of equality of survival function.

Variable	Cases N	Cases %	Died N	p - value	Variable	Cases N	Cases %	Died N	p - value
Sex					**Surgery status**				
Male	281	58.2	110	0.163	Emergency	18	3.7	11	0.015
Female	202	41.8	69		Elective	465	96.3	168	
Age group					**Resection status**				
<55	103	21.3	22	0.010	R0	439	90.9	147	<0.001
55 - 64	112	23.2	24		R1	44	9.1	32	
65 - 74	155	32.1	58						
75+	113	23.4	75		**Height of tumour**				
					2 - 5 cm	106	21.9	40	0.399
Year diagnosed					6 – 10 cm	208	43.1	65	
1996 - 2001	185	38.3	102	0.006	11 – 18 cm	123	25.5	47	
2002 - 2006	184	38.1	72		Not recorded	46	9.5	27	
2007 - 2012	114	23.6	5						
					Lymph nodes				
Stage					No/unknown	434	89.9	167	0.422
A	168	34.8	44	<0.001	Yes	49	10.1	12	
B	119	24.6	45						
C	126	26.1	34		**Extramural veins**				
D	70	14.5	56		No	116	24.0	6	0.004
					Yes	11	2.3	3	
ASA					Not recorded	356	73.7	170	
1	90	18.6	12	<0.001					
2	242	50.1	79		**Curative intent**				
3	131	27.1	74		No	70	14.5	56	<0.001
4	20	4.1	14		Yes	413	85.5	123	
Operation type					**Radiotherapy**				
Ultralow AR	267	55.3	73	<0.001	No	293	60.7	117	0.175
Low AR	21	4.3	12		Yes	190	39.3	62	
High AR	33	6.8	14						
Abdominoperineal	62	12.8	27		**Chemotherapy**				
Hartmann's	20	4.1	16		No	260	53.8	111	0.593
Other	20	4.1	8		Yes	223	46.2	68	
Primary local excision	60	12.4	29						
					Recurrence type				
Hospital					None	412	85.3	133	<0.001
Private (06-12)	127	26.3	7	0.001	Local	25	5.2	17	
Public(96-06)	356	73.7	172		Distant	46	9.5	29	

Table 3. Relative hazard of dying following a diagnosis of rectal cancer by factors present at time of surgery and recurrence status (as a time-varying state) as estimated by a proportional hazards regression model and using age as the time scale.

Variable	Within variable[a]	HR	95%CI	p-value
Recurrence state	**Age at diagnosis**			
Local *vs* none	<60 years	54.2	11.6 - 253.1	**0.000**
	60-69 years	0.8	0.1 - 6.8	0.800
	70+ years	28.3	9.8 - 82.1	**0.000**
Distant *vs* none	<60 years	18.6	4.3 - 80.1	**0.000**
	60-69 years	4.0	1.4 - 10.9	**0.007**
	70+ years	8.0	2.3 - 28.0	**0.001**
Chemotherapy	**Recurrence state**			
Yes *vs* No	None	0.5	0.3 - 0.9	**0.013**
	Local	1.0	0.2 - 4.9	0.994
	Distant	0.5	0.1 - 2.9	0.479
Age at diagnosis	**Stage**			
<60 years *vs* 60-69 years	A	2.9	0.3 - 27.8	0.359
	B	6.5	1.0 - 42.0	**0.048**
	C	11.6	2.3 - 59.6	**0.003**
	D	7.1	1.1 - 44.8	**0.038**
70+ years *vs* 60-69 years	A	11.4	2.7 - 49.4	**0.001**
	B	8.9	2.5 - 32.0	**0.001**
	C	15.2	4.3 - 53.4	**0.000**
	D	3.9	1.3 - 11.6	**0.015**
Operation type				
Ultralow AR		1.0	referent	
Low AR		4.1	2.2 - 7.5	**0.000**
High AR		1.1	0.5 - 2.4	0.778
Abdominoperineal		0.9	0.5 - 1.6	0.642
Hartmann's		1.5	0.7 - 3.3	0.268
Other		2.9	1.6 - 5.4	**0.001**
Primary local excision		1.2	0.7 - 2.2	0.458
Year of diagnosis		0.9	0.9-1.0	0.002
ASA		1.4	1.1-1.9	0.018

[a] The relative rate all-cause mortality for some variables was modified by others, that is, a significant interaction was present. Interaction terms were present between age at diagnosis and recurrence state, recurrence state and preop chemotherapy and age diagnosis and tumour stage. Hazard ratios are presented within strata of the modifying variables.
Only variables significant at the 5% level were included in the final models.

Table 4. Relative hazard of developing a recurrence of tumour, either local or distant by factors present at time of surgery as estimated by a proportional hazards regression model and using time since diagnosis the time scale.

Variable	HR	95%CI	p-value
Chemotherapy			
No	1.0	ref	
Yes	3.8	2.2-6.7	**<0.001**
Resection margin			
R0	1.0	ref	
R1	3.1	1.7-5.6	**<0.001**

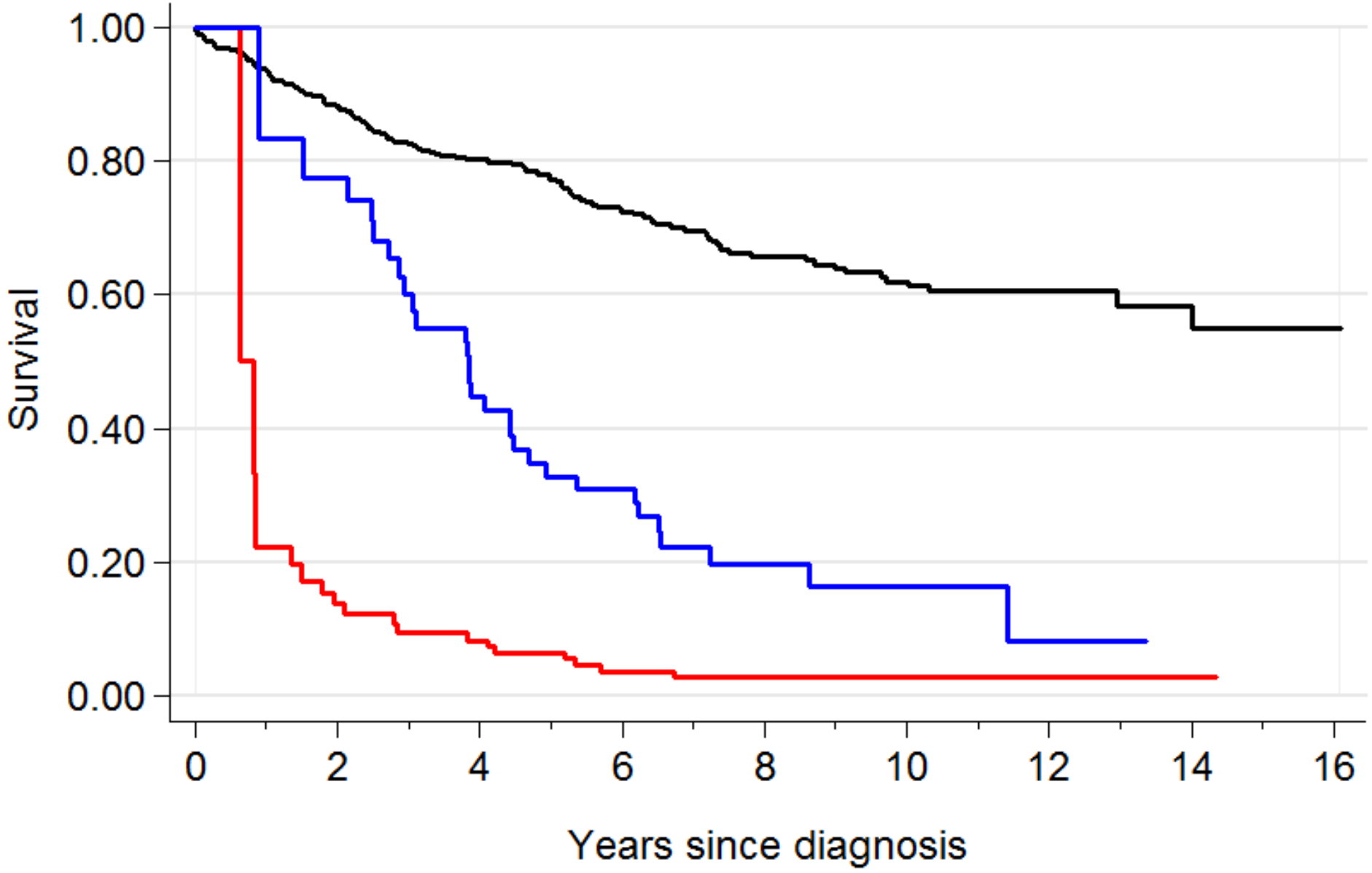
Only variables significant at the 5% level were included in the final models, thus sex, age at diagnosis, curative intent, type of operation, height of tumour, extramural venous invasion, radiotherapy, year of diagnosis, ASA, tumour stage and positive lymph nodes were not associated with the relative rate of recurrence in this rectal cancer cohort. Ref = referent category.

Figure 1. The survival experience of the rectal cancer cohort by whether patients have remained recurrence free (solid line), after recording a distant recurrence (dashed line) and after recording a local recurrence (dotted line) represented graphically from time since diagnosis using A) Kaplan-Meier estimates of the survival proportions and B) a smoothed hazard function (rate of dying). 95% confidence intervals of the estimated survival proportions are indicated by shading.

A

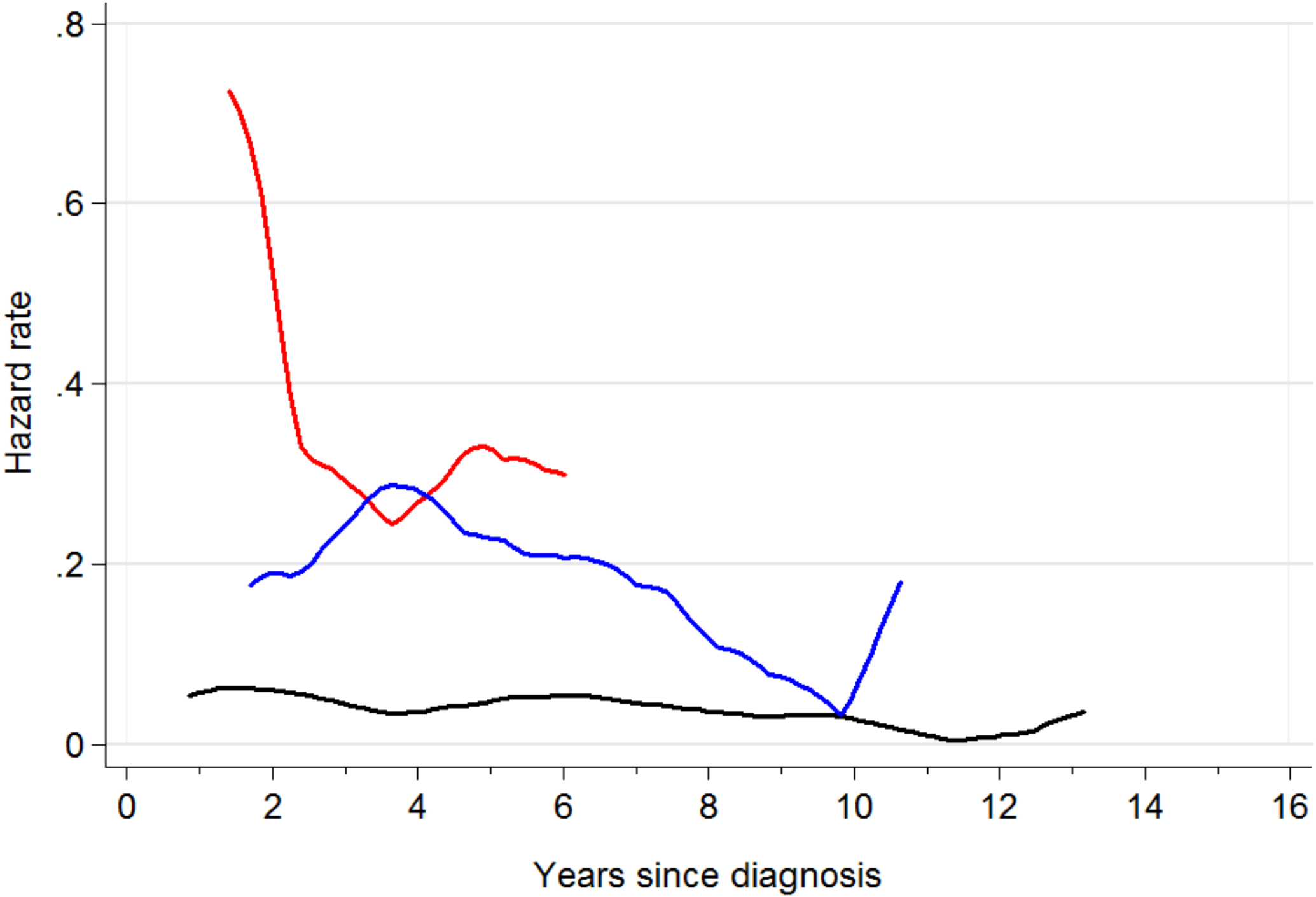
B

Figure 2. The estimated age-specific mortality rate (hazard rate) for the rectal cancer cohort using age as the time scale by whether patients have remained recurrence free (solid line), after recording a distant recurrence (dashed line) and after recording a local recurrence (dotted line).



Number at risk (failures)

No recurrence	483	(53)	359	(31)	265	(23)	196	(16)	131	(6)	89	(2)	49	(1)	17	(1)	2
Local recurrence	0	(7)	9	(4)	9	(5)	4	(1)	3	(0)	3	(0)	2	(0)	1	(0)	0
Distant recurrence	0	(2)	19	(13)	23	(7)	15	(5)	8	(1)	2	(1)	1	(0)	0	(0)	0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Hazard rate
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2
4
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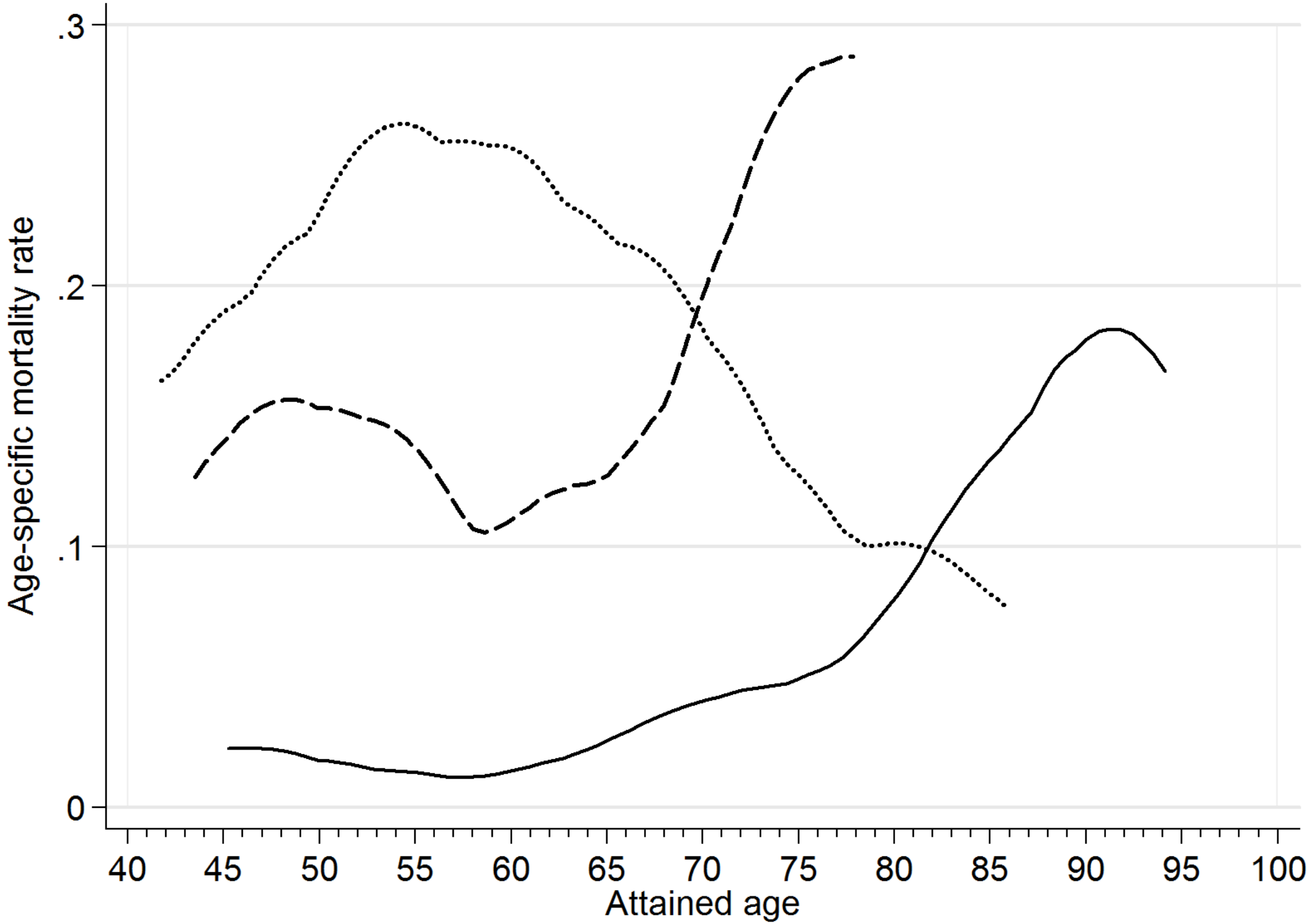
Years since diagnosis


.3
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Age-specific mortality rate
40
45
50
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60
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Attained age