Prognostic Relevance of Palliative Primary Tumor Removal in 37,793 Metastatic Colorectal Cancer Patients

A Population-based, Propensity Score–adjusted Trend Analysis

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Objective: To assess whether palliative primary tumor resection in colorectal cancer patients with incurable stage IV disease is associated with improved survival.

Background: There is a heated debate regarding whether or not an asymptomatic primary tumor should be removed in patients with incurable stage IV colorectal disease.

Methods: Stage IV colorectal cancer patients were identified in the Surveillance, Epidemiology, and End Results database between 1998 and 2009. Patients undergoing surgery to metastatic sites were excluded. Overall survival and cancer-specific survival were compared between patients with and without palliative primary tumor resection using risk-adjusted Cox proportional hazard regression models and stratified propensity score methods.

Results: Overall, 37,793 stage IV colorectal cancer patients were identified. Of those, 23,004 (60.9%) underwent palliative primary tumor resection. The rate of patients undergoing palliative primary cancer resection decreased from 68.4% in 1998 to 50.7% in 2009 ($P < 0.001$). In Cox regression analysis after propensity score matching primary cancer resection was associated with a significantly improved overall survival [hazard ratio (HR) of death = 0.40, 95% confidence interval (CI) = 0.39–0.42, $P < 0.001$] and cancer-specific survival (HR of death = 0.39, 95% CI = 0.38–0.40, $P < 0.001$). The benefit of palliative primary cancer resection persisted during the time period 1998 to 2009 with HRs equal to or less than 0.47 for both overall and cancer-specific survival.

Conclusions: On the basis of this population-based cohort of stage IV colorectal cancer patients, palliative primary tumor resection was associated with improved overall and cancer-specific survival. Therefore, the dogma that an asymptomatic primary tumor never should be resected in patients with unresectable colorectal cancer metastases must be questioned.

Keywords: incurable, metastases, metastatic colorectal cancer, palliative resection

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Of all patients with colorectal cancer, approximately 25% present with metastatic disease and another 25% are likely to develop metachronous metastases. Considering the prevalence of the disease—the third most common malignancy—metastatic colorectal cancer represents a tremendous public health problem with more than 140,000 new colorectal cancer patients and more than 50,000 cancer deaths estimated for 2012 in the United States.[1]

It is well known that removal of both primary tumor as well as all metastatic lesions is associated with the longest overall survival. However, in many stage IV patients, complete resection is not an option, for example, due to the extent of the disease or prohibitive comorbidities. In this context, it is a matter of great debate whether some of these patients benefit from a palliative primary tumor resection. The main arguments in favor of resection are a low operative morbidity and mortality for elective colorectal surgery compared with higher complication rates in the emergency situation. Indeed, by removing the primary tumor potential problems due to obstruction or bleeding can be avoided.[2–4] Conversely, a nonoperative management of asymptomatic patients is associated with a low incidence of primary tumor–related adverse events requiring a surgical intervention.[5–8] Furthermore, removing the primary tumor may be associated with postoperative complications in some patients precluding an early application of life-prolonging systemic therapy.[9]

With respect to overall and cancer-specific survival, the debate is even more controversial.[10,11] It is still unknown whether the removal of the primary tumor without resection of distant metastases leads to any survival benefit. Unfortunately, comparative data on outcomes of metastatic colorectal cancer patients who did and who did not undergo palliative primary tumor resection are scarce. Therefore, the objective of this population-based investigation of metastatic colorectal cancer patients in the United States was to assess whether palliative primary tumor removal—without resection of metastases—results in an improved overall and cancer-specific survival. We hypothesized that the difference in overall and cancer-specific survival between the subsets of patients who did and who did not undergo primary tumor resection would decrease over time because of improvement of systemic treatment.

METHODS

Cohort Definition: Surveillance, Epidemiology, and End Results

The recent ASCII text data version of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute in the United States, covering approximately 28% of cancer cases in the United States, was the source of present population-based analysis.[12] SEER data were collected and reported using data items and codes as documented by the North American Association of Central Cancer Registries (NAACCR).[13] Primary cancer site and histology were coded according to criteria in the third edition of the International Classification of Diseases for Oncology (ICD-O-3).[14] Colorectal cancer patients were identified by the ICD-O-3 site codes C180, C182 to C189, C199 and C209 and behavior code 3 (NAACCR items 400 and 523). Patients diagnosed at autopsy or by death

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certificate only as well as patients without histological confirmation were excluded (NAACCR items 490 and 2180). The analysis was restricted to patients with adenocarcinoma identified by the ICD-O-3 histology codes 8140, 8144, 8210, 8211, 8220, 8221, 8261, 8262, and 8263 (NAACCR item 522). The following patients were excluded: patients with other SEER reportable cancers if the colorectal malignancy was not the first diagnosed cancer (NAACCR Item 380); patients without distant metastases (NAACCR items 790 and 2980); patients who underwent surgical procedures of other sites than the primary tumor (NAACCR items 1294 and 1648), patients receiving only local tumor excision or local tumor destruction; and patients with lacking information regarding the operation of the primary tumor site (NAACCR items 1290 and 1646). The remaining patients were grouped in 2 subsets according to whether or not a primary tumor resection was performed (NAACCR items 1290 and 1646). Patients who died before the recommended surgery were accounted into the group of patients undergoing primary tumor resection (NAACCR Item 1340) according to the intention-to-treat principle.

Statistical Analysis

Statistical analyses were performed using the R statistical software (www.r-project.org). A 2-sided $P < 0.05$ was considered statistically significant. Continuous data are expressed as means ± standard deviation.

First, χ^2 statistics were used to compare dichotomous or categorical patient characteristics. To analyze the time trends in the prevalence of metastatic colorectal cancer and primary cancer removal, Spearman's rho was estimated. To assess putative bias of patient characteristics for primary cancer resection, a full logistic regression model was applied. Significance levels were estimated using likelihood ratio tests, and Wald type 95% confidence intervals (CIs) were computed. Second, resection of the primary cancer was assessed as a prognostic factor for survival in Kaplan-Meier analysis and in Cox regression analyses with and without risk adjustment for year of diagnosis, age, sex, race/ethnicity, marital status, place of birth, location of tumor, carcinoembryonic antigen level (CEA), and grading (risk set). Statistical testing was done by likelihood ratio tests and Wald type 95% CIs were provided. The variables T-stage and N-stage were purposefully not included in multivariable analyses as a large fraction of patients did not undergo primary tumor resection and thus data were not available as pathologic staging. The proportional hazard assumption was tested by scaled Schoenfeld residuals and by inspection of the hazard ratio (HR) plots.[15] Third, a propensity score analysis as a superior and more refined statistical method to adjust for potential baseline confounding variables was performed.[16–18] The "MatchIt" and the "optmatch" R packages were used to perform a bipartite weighting propensity score analysis.[19,20] The distance measure was estimated by logistic regression using the risk set described earlier with stratification for the year of diagnosis to predict primary cancer resection. Patients undergoing primary tumor resection without a counterpart were excluded from the analysis. Afterwards, the baseline risk profiles of the matched patients were compared to assure that no major difference in baseline patient characteristics persisted by χ^2 statistics. Fourth, the prognostic value of primary tumor

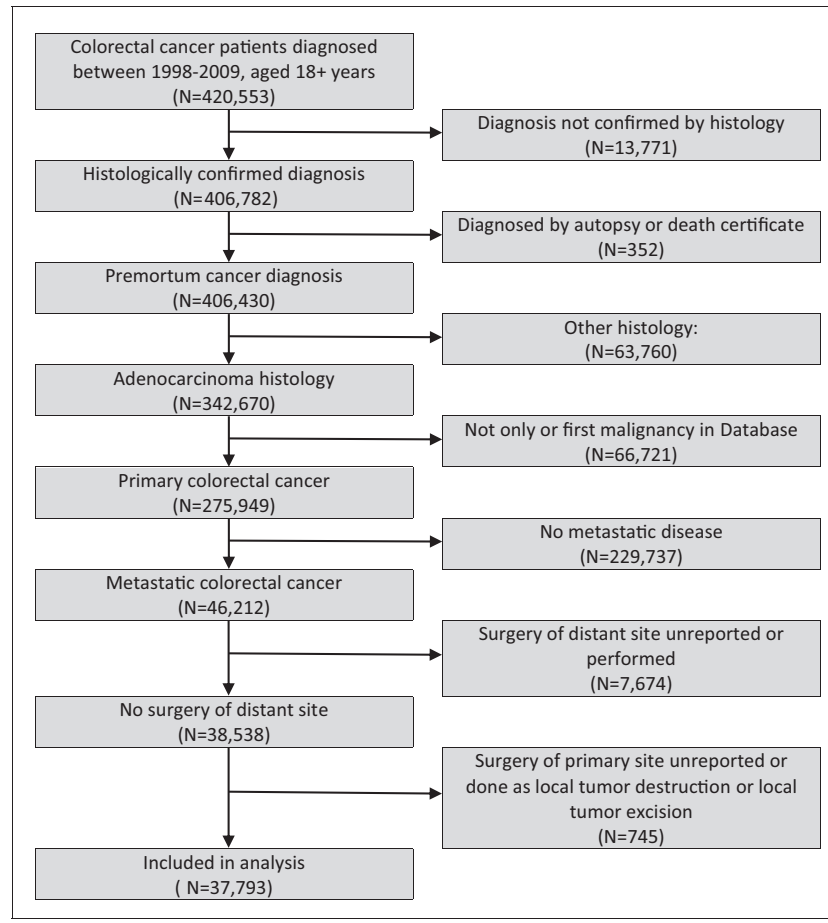

FIGURE 1. Flow chart of patients' cohort definition.

TABLE 1. Patient Characteristics for Subsets With and Without Primary Tumor Resection

	Patient Characteristics in Raw Data				Logistic Regression for Resection of the Primary*		Patient Characteristics After Propensity Score Weighting†		
	Total (N = 37,793)	No Surgery (N = 14,789)	Surgery (N = 23,004)	*P*	Odds Ratio (95% CI)	*P*‡	No Surgery (N = 14,754)	Surgery (N = 22,858)	*P*
Year									
1998–2001	9694 (25.7%)	3279 (22.2%)	6415 (27.9%)	<0.001§	Reference	<0.001	3215.0 (22.1%)	6382 (27.9%)	<0.001§
2002–2005	13,807 (36.5%)	5167 (34.9%)	8640 (37.6%)		0.91 (0.85–0.97)		5092.0 (34.9%)	8561 (37.5%)	
2006–2009	14,292 (37.8%)	6343 (42.9%)	7949 (34.6%)		0.69 (0.64–0.75)		6268.0 (43.0%)	7915 (34.6%)	
Age, yr									
Up to 64	17,006 (45.0%)	6365 (43.0%)	10,641 (46.3%)	<0.001§	Reference	<0.001	6742.0 (46.3%)	10,541 (46.1%)	0.788§
>65	20,787 (55.0%)	8424 (57.0%)	12,363 (53.7%)		0.78 (0.75–0.83)		7833.0 (53.7%)	12,317 (53.9%)	
Sex									
Male	20,534 (54.3%)	8202 (55.5%)	12,332 (53.6%)	<0.001§	Reference	0.002	7780.5 (53.4%)	12,268 (53.7%)	0.586§
Female	17,259 (45.7%)	6587 (44.5%)	10,672 (46.4%)		1.08 (1.03–1.14)		6794.5 (46.6%)	10,590 (46.3%)	
Race/ethnicity									
Caucasian	29,139 (77.1%)	11,233 (76.0%)	17,906 (77.8%)	<0.001§	Reference	<0.001	11,123.0 (76.3%)	17,778 (77.8%)	<0.001§
African-American	5525 (14.6%)	2375 (16.1%)	3150 (13.7%)		0.82 (0.76–0.88)		2036.0 (14.0%)	3144 (13.8%)	
Other/Unknown	3129 (8.3%)	1181 (8.0%)	1948 (8.5%)		0.99 (0.90–1.09)		1416.1 (9.7%)	1936 (8.5%)	
Marital status									
Married	19,664 (52.0%)	6798 (46.0%)	12,866 (55.9%)	<0.001§	Reference	<0.001	8124.6 (55.7%)	12,741 (55.7%)	0.038§
Other	16,828 (44.5%)	7360 (49.8%)	9468 (41.2%)		0.70 (0.66–0.74)		5957.4 (40.9%)	9449 (41.3%)	
Unknown	1301 (3.4%)	631 (4.3%)	670 (2.9%)		0.63 (0.55–0.72)		493.0 (3.4%)	668 (2.9%)	
Place of birth									
US	23,990 (63.5%)	9665 (65.4%)	14,325 (62.3%)	<0.001§	Reference	<0.001	8289.9 (56.9%)	14,253 (62.4%)	<0.001§
Non-US	4319 (11.4%)	1668 (11.3%)	2651 (11.5%)		0.97 (0.89–1.06)		2073.4 (14.2%)	2634 (11.5%)	
Unknown	9484 (25.1%)	3456 (23.4%)	6028 (26.2%)		1.20 (1.13–1.28)		4211.7 (28.9%)	5971 (26.1%)	
Location of tumor									
Right colon	11,982 (31.7%)	3544 (24.0%)	8438 (36.7%)	<0.001§	Reference	<0.001	5274.0 (36.2%)	8371 (36.6%)	0.013§
Transverse colon	2107 (5.6%)	526 (3.6%)	1581 (6.9%)		1.21 (1.08–1.36)		886.2 (6.1%)	1525 (6.7%)	
Left colon	10,908 (28.9%)	3192 (21.6%)	7716 (33.5%)		0.99 (0.93–1.06)		5082.5 (34.9%)	7694 (33.7%)	
Colon Overlapping/NOS	2174 (5.8%)	1665 (11.3%)	509 (2.2%)		0.29 (0.26–0.33)		364.5 (2.5%)	509 (2.2%)	
Rectosigmoid	3565 (9.4%)	1322 (8.9%)	2243 (9.8%)		0.71 (0.65–0.77)		1353.9 (9.3%)	2242 (9.8%)	
Rectum	7057 (18.7%)	4540 (30.7%)	2517 (10.9%)		0.20 (0.19–0.22)		1613.8 (11.1%)	2517 (11.0%)	
CEA									
Positive/elevated	11,656 (30.8%)	5204 (35.2%)	6452 (28.0%)	<0.001§	Reference	<0.001	4601.8 (31.6%)	6432 (28.1%)	<0.001§
Negative/normal	2239 (5.9%)	609 (4.1%)	1630 (7.1%)		2.01 (1.79–2.25)		1256.3 (8.6%)	1578 (6.9%)	
Borderline/Unknown	23,898 (63.2%)	8976 (60.7%)	14,922 (64.9%)		1.22 (1.15–1.30)		8716.9 (59.8%)	14,848 (65.0%)	
Grading									
G1	1535 (4.1%)	731 (4.9%)	804 (3.5%)	<0.001§	Reference	<0.001	511.0 (3.5%)	804 (3.5%)	0.514§
G2	21,054 (55.7%)	6417 (43.4%)	14,637 (63.6%)		2.10 (1.87–2.34)		9343.4 (64.1%)	14,622 (64.0%)	
G3	8869 (23.5%)	2299 (15.5%)	6570 (28.6%)		2.44 (2.17–2.74)		4102.5 (28.1%)	6518 (28.5%)	
G4	419 (1.1%)	74 (0.5%)	345 (1.5%)		4.09 (3.10–5.46)		198.1 (1.4%)	266 (1.2%)	
GX	5916 (15.7%)	5268 (35.6%)	648 (2.8%)		0.12 (0.10–0.14)		420.0 (2.9%)	648 (2.8%)	
Outcome variables									
Cause of death									
Alive	4326 (11.4%)	971 (6.6%)	3355 (14.6%)	<0.001§					
Dead from cancer	30,996 (82.0%)	12,892 (87.2%)	18,104 (78.7%)						
Dead not from cancer	2471 (6.5%)	926 (6.3%)	1545 (6.7%)						

Values are expressed as n (%) unless otherwise indicated.
*Full model logistic regression.
†Patient characteristics after propensity score weighting.
‡Likelihood ratio test.
§χ^2 test.

resection for overall mortality was assessed in a Cox regression analysis using the weights and strata obtained by the bipartite matching propensity score analysis. Statistical testing was done by likelihood ratio tests, and Wald type 95% CIs were provided. The confirmatory analysis was based on an intention-to-treat analysis and further verified by a per-protocol analysis, which served as a sensitivity analysis. Finally, the computations were repeated as sensitivity analysis after substituting unknown/undocumented data (category "Unknown" for race/ethnicity, marital status, place of birth, and CEA and category "G_x" for grading) using a random survival forest method.[21]

RESULTS

Patient Characteristics and Treatment Trend

For present investigation, 37,793 of 445,603 patients diagnosed with colorectal cancer between 1998 and 2009 were included (Fig. 1). Of those, 23,004 (60.9%) patients underwent primary tumor resection, whereas 14,789 (39.1%) did not. Table 1 summarizes the patients' characteristics for both groups.

Figure 2 displays the trends for the prevalence of metastatic disease and the rate of primary cancer removal over time. The rate of metastatic colorectal cancer continuously increased from 15.4% in 1998 to 18.1% in 2009 ($P < 0.001$). The rate of patients undergoing a primary cancer resection decreased continuously from 68.4% in 1998 to 50.7% in 2009 ($P < 0.001$). The same trend was observed both for patients 65 years or younger (70.6% in 1998 to 50.8% in 2009, $P < 0.001$) and patients older than 65 years (67.1% in 1998 to 50.6% in 2009, $P < 0.001$).

Primary Cancer Resection as a Prognostic Factor for Survival

Figures 3A and 3B show Kaplan-Meier curves for overall and cancer-specific survival in patients with and without palliative primary tumor resection subdivided into 3 time intervals. Survival increased for both groups during later time periods but patients with palliative primary tumor resection consistently had a better overall and cancer-specific survival compared with those not undergoing surgery. Figure 3C and 3D display the trend in median overall and cancer-specific survival for patients who did and who did not undergo palliative primary tumor resection. Median overall and cancer-specific survival significantly improved over time for both subsets. In unadjusted Cox proportional hazards regression analysis, palliative primary tumor resection was a statistically significant protective factor for overall (HR of death = 0.49, 95% CI = 0.48–0.50, $P < 0.001$) and cancer-specific survival (HR of death = 0.49, 95% CI = 0.47–0.50, $P < 0.001$), respectively. After multivariable risk adjusting in Cox proportional hazard regression analysis, palliative primary tumor resection had a significantly protective effect on overall survival (HR of death = 0.45, 95% CI = 0.43–0.46, $P < 0.001$) and cancer-specific survival (HR of death = 0.44, 95% CI = 0.43–0.45, $P < 0.001$) (Table 2). Figures 3E and 3F display the HRs of death for overall and cancer-specific survival after stratification for the year of diagnosis. Palliative primary cancer resection was consistently protective for survival over time with HRs ranging between 0.37 (95% CI = 0.32–0.42) and 0.47 (95% CI = 0.42–0.52) for overall survival and 0.36 (95% CI = 0.32–0.42) and 0.47 (95% CI = 0.42–0.52) for cancer-specific survival.

Adjusting for Patients Characteristics With Propensity Score Matching

Patients undergoing palliative primary tumor resection were younger, more often female, more often Caucasians, to a higher percentage married, had less often rectal cancer, presented more often with negative/normal CEA values, and had a higher grading score (Table 1). To further corroborate the findings from univariate and multivariable Cox proportional hazard regression analyses, a propensity

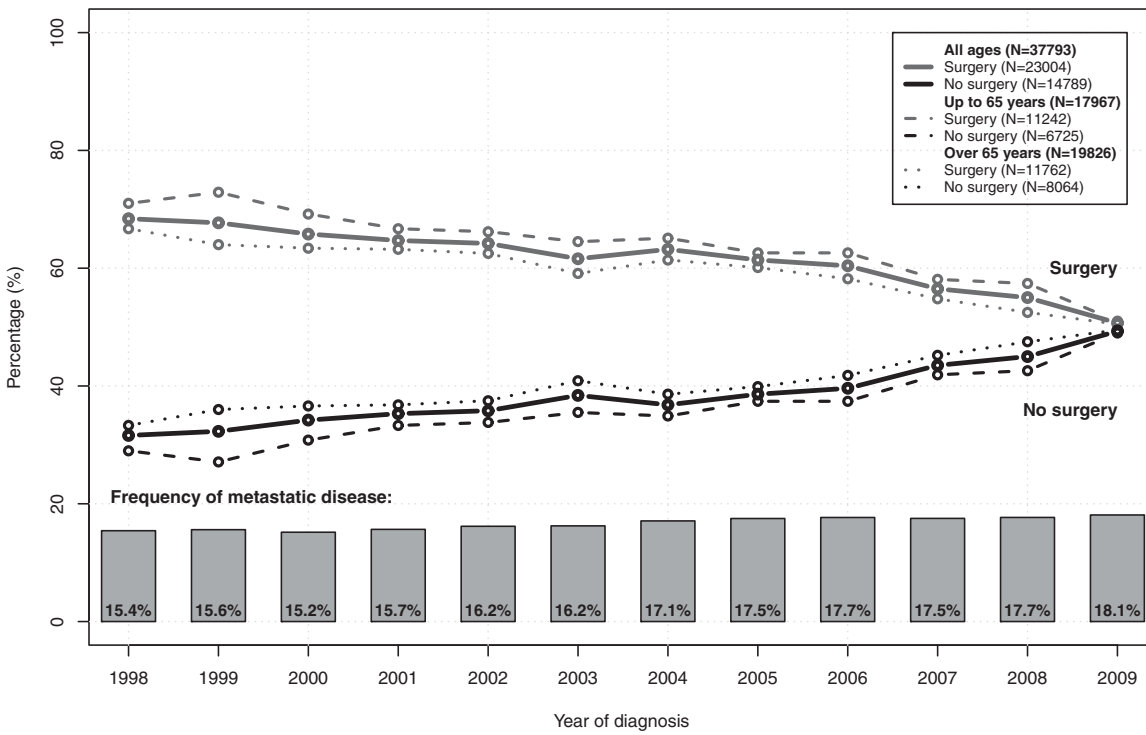

FIGURE 2. Trend for prevalence of metastatic disease and primary tumor resection.

TABLE 2. Prognostic Factors for Overall and Cancer-specific Mortality

	Overall Survival						Cancer-specific Survival					
	Unadjusted*		Cox Regression, Full Model†		Propensity Score Cox Regression‡		Unadjusted*		Cox Regression, Full Model†		Propensity Score Cox Regression‡	
	HR (95% CI)	*P*§	HR (95% CI)	*P*§	HR (95% CI)	*P*§	HR (95% CI)	*P*§	HR (95% CI)	*P*§	HR (95% CI)	*P*§
Surgery of primary												
No	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Yes	0.49 (0.48–0.50)		0.45 (0.43–0.46)		0.38 (0.37–0.39)		0.49 (0.47–0.50)		0.44 (0.43–0.45)		0.37 (0.36–0.38)	
Year												
1998–2001	Reference	<0.001	Reference	<0.001	—¶		Reference	<0.001	Reference	<0.001	—¶	
2002–2005	0.86 (0.84–0.88)		0.87 (0.85–0.90)		—¶		0.86 (0.84–0.89)		0.87 (0.85–0.90)		—¶	
2006–2009	0.76 (0.74–0.79)		0.75 (0.73–0.78)		—¶		0.76 (0.73–0.78)		0.74 (0.72–0.77)		—¶	
Age, yr												
Up to 64	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
>65	1.64 (1.61–1.68)		1.57 (1.53–1.60)		1.67 (1.59–1.75)		1.57 (1.54–1.61)		1.50 (1.46–1.53)		1.60 (1.52–1.68)	
Sex												
Male	Reference	<0.001	Reference	0.389	Reference	0.158	Reference	<0.001	Reference	0.832	Reference	0.453
Female	1.08 (1.06–1.11)		0.99 (0.97–1.01)		0.97 (0.93–1.01)		1.09 (1.06–1.11)		1.00 (0.98–1.03)		0.98 (0.94–1.03)	
Race/ethnicity												
Caucasian	Reference	<0.001	Reference	<0.001	Reference	0.035	Reference	<0.001	Reference	<0.001	Reference	0.038
African-American	1.12 (1.08–1.15)		1.08 (1.05–1.11)		1.07 (1.01–1.13)		1.11 (1.08–1.15)		1.07 (1.03–1.10)		1.06 (1.00–1.12)	
Other/Unknown	0.87 (0.84–0.91)		1.01 (0.96–1.05)		0.97 (0.91–1.03)		0.86 (0.82–0.89)		1.00 (0.95–1.04)		0.95 (0.89–1.01)	
Marital status												
Married	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Other	1.29 (1.26–1.32)		1.19 (1.17–1.22)		1.22 (1.15–1.29)		1.27 (1.25–1.30)		1.18 (1.15–1.20)		1.21 (1.14–1.28)	
Unknown	1.31 (1.23–1.39)		1.19 (1.12–1.26)		1.26 (1.13–1.41)		1.29 (1.21–1.37)		1.16 (1.09–1.24)		1.22 (1.09–1.38)	
Place of birth												
US	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Non-US	0.78 (0.75–0.80)		0.82 (0.79–0.85)		0.84 (0.79–0.89)		0.75 (0.72–0.78)		0.79 (0.76–0.82)		0.82 (0.77–0.87)	
Unknown	0.72 (0.70–0.73)		0.75 (0.73–0.77)		0.82 (0.78–0.86)		0.70 (0.68–0.72)		0.74 (0.72–0.76)		0.80 (0.76–0.84)	
Location of tumor												
Right colon	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Transverse colon	0.94 (0.90–0.99)		1.01 (0.96–1.06)		0.98 (0.91–1.05)		0.94 (0.90–0.99)		1.01 (0.96–1.06)		1.00 (0.93–1.08)	
Left colon	0.74 (0.71–0.76)		0.79 (0.77–0.81)		0.77 (0.73–0.80)		0.73 (0.71–0.76)		0.78 (0.76–0.81)		0.76 (0.72–0.79)	
Colon	1.59 (1.52–1.67)		1.12 (1.07–1.18)		0.89 (0.71–1.11)		1.59 (1.51–1.67)		1.11 (1.06–1.17)		0.91 (0.72–1.15)	
Overlapping/NOS												
Rectosigmoid	0.73 (0.70–0.76)		0.74 (0.71–0.77)		0.67 (0.62–0.73)		0.73 (0.70–0.76)		0.74 (0.71–0.77)		0.67 (0.61–0.72)	
Rectum	0.75 (0.73–0.78)		0.62 (0.60–0.64)		0.38 (0.30–0.48)		0.76 (0.73–0.78)		0.61 (0.59–0.63)		0.38 (0.30–0.48)	
CEA												
Positive/elevated	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Negative/normal	0.63 (0.60–0.66)		0.68 (0.64–0.71)		1.07 (1.01–1.13)		0.62 (0.59–0.65)		0.67 (0.63–0.71)		1.09 (1.02–1.15)	
Borderline/Unknown	1.10 (1.08–1.13)		0.99 (0.96–1.02)		0.83 (0.75–0.92)		1.10 (1.08–1.13)		0.99 (0.96–1.02)		0.80 (0.72–0.89)	
Grading												
G1	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
G2	0.95 (0.90–1.01)		1.09 (1.03–1.15)		1.25 (1.08–1.44)		0.96 (0.90–1.02)		1.10 (1.04–1.16)		1.21 (1.04–1.40)	
G3	1.31 (1.24–1.39)		1.54 (1.46–1.64)		1.80 (1.54–2.10)		1.34 (1.26–1.43)		1.59 (1.49–1.69)		1.78 (1.51–2.10)	
G4	1.35 (1.20–1.52)		1.69 (1.50–1.89)		2.82 (2.25–3.54)		1.39 (1.23–1.56)		1.74 (1.54–1.96)		2.75 (2.17–3.48)	
GX	1.78 (1.67–1.89)		1.26 (1.18–1.34)		0.78 (0.49–1.23)		1.82 (1.71–1.94)		1.28 (1.20–1.37)		0.73 (0.45–1.19)	

Values are expressed as HRs with 95% *Wald type* CIs unless otherwise indicated.

*univariate Cox regression analysis.

†*Full model* Cox regression analysis.

‡*Full model* Cox regression analysis after propensity score matching and weighting with stratification for year of diagnosis.

§*Likelihood* ratio tests.

¶Propensity score estimation was stratified for year of diagnosis.

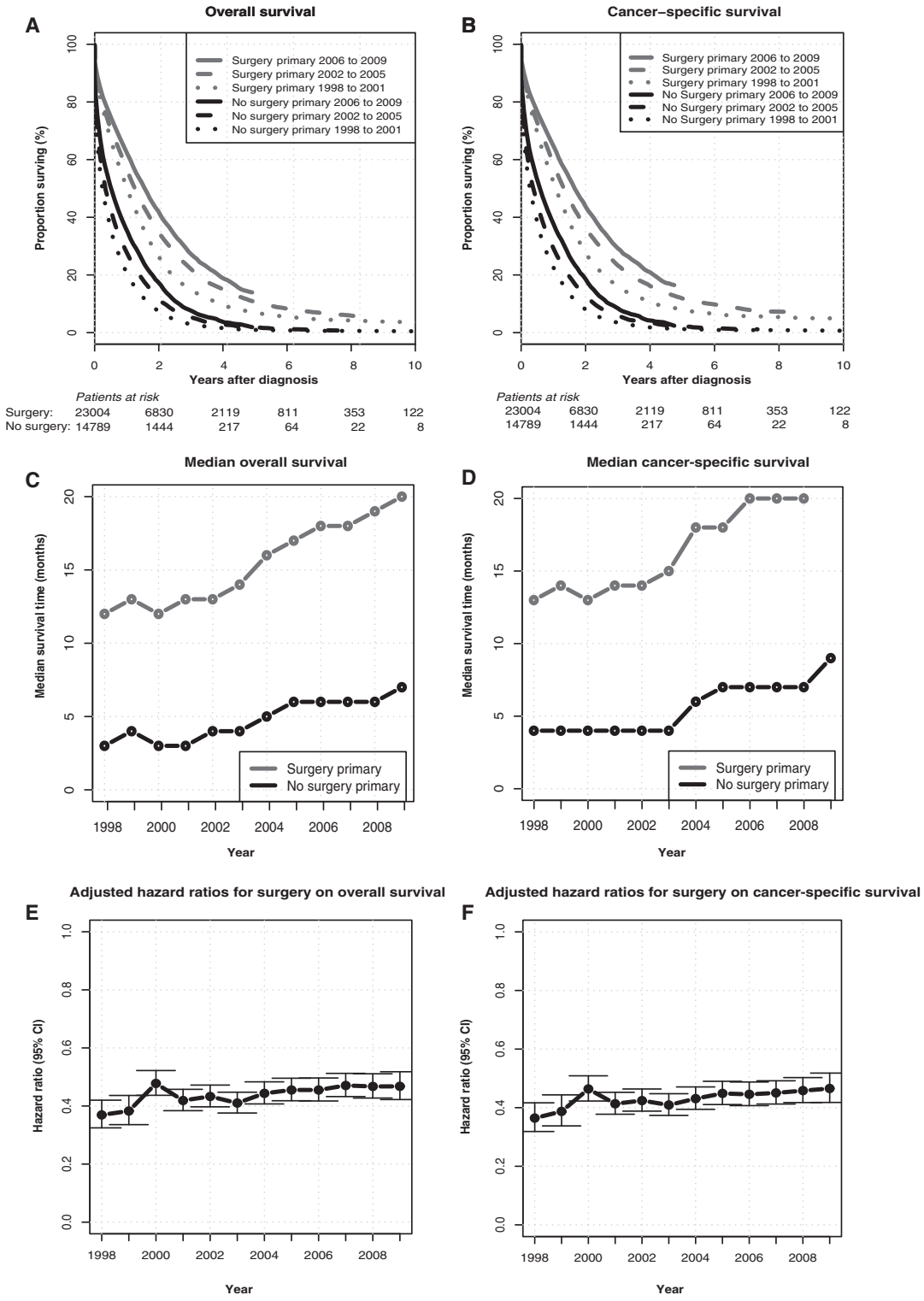

FIGURE 3. Survival trend for patients with metastatic colorectal cancer with and without primary tumor removal. A and B, Kaplan-Meier-curves for overall and cancer-specific survival in patients with and without primary cancer resection subdivided in 3 time intervals. Life tables for patients at risk are given below each plot. C and D, trend in median overall and cancer-specific survival for patients who did and who did not undergo primary tumor resection. E and F, HRs of death for primary tumor resection for overall and cancer-specific survival after stratification for the year of diagnosis. An HR of less than 1 indicates a beneficial effect of primary tumor removal.

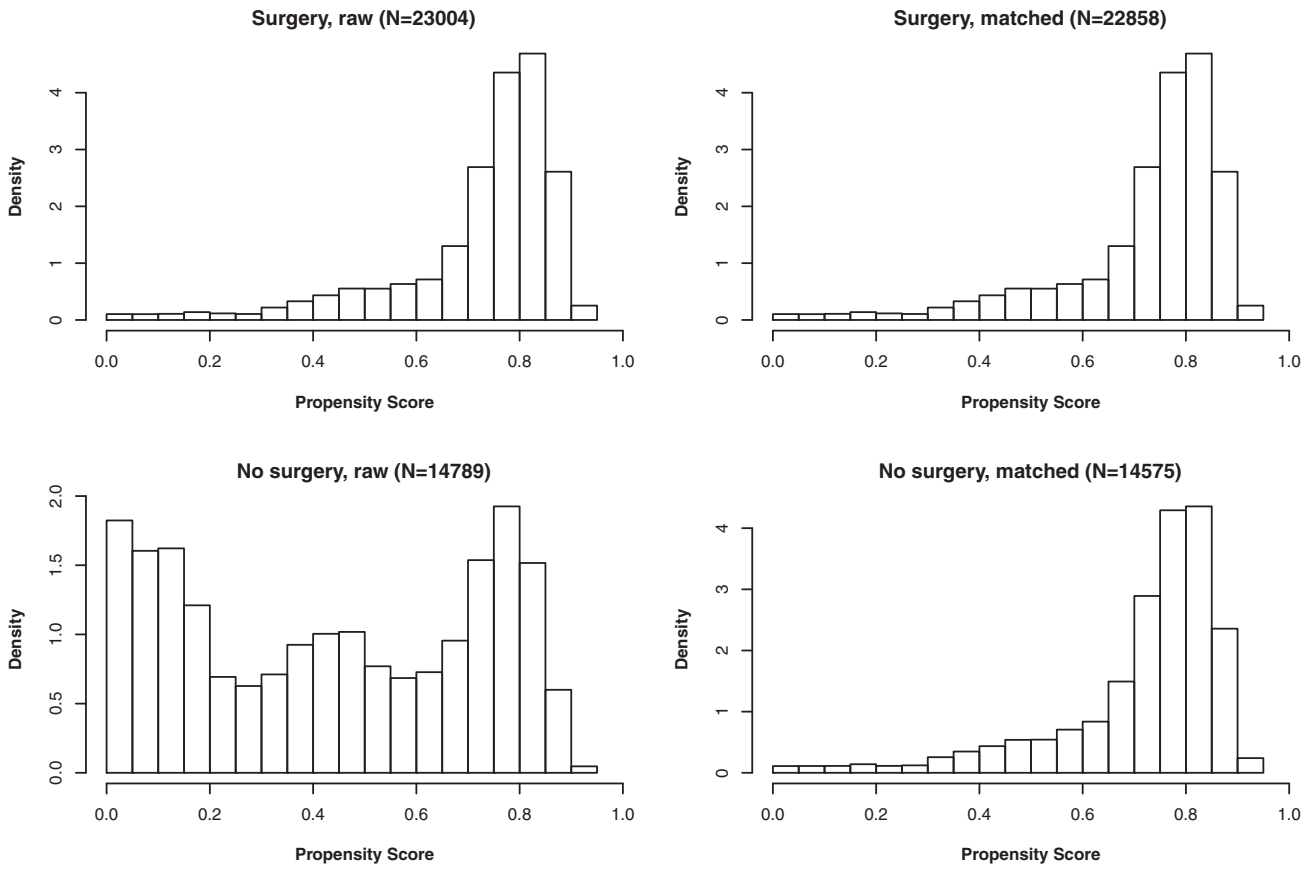

FIGURE 4. Distribution of propensity score before and after propensity matching procedure. Left upper and left lower panel show the propensity score distribution for patients with and without primary tumor resection before the matching procedure. Right upper and right lower panel display the propensity score distribution after full propensity score matching.

score with stratification for the year of diagnosis was performed to optimally adjust for the aforementioned listed bias between the 2 groups. The propensity score for patients with primary tumor resection was 0.72 ± 0.16 compared with 0.44 ± 0.28 for patients without resection ($P < 0.001$). After propensity score matching, the score was 0.72 ± 0.16 for patients with and 0.71 ± 0.17 for those without primary tumor resection. During the propensity score analysis, 360 patients (146 patients with and 214 patients without palliative primary cancer resection) were excluded from the analysis because no counterpart propensity score was identified. Figure 4 displays the distribution of the propensity scores of the 2 groups prior and after propensity score matching and weighting. Table 1 summarizes patient characteristics after propensity score weighting.

Propensity Score Matched Prognostic Factors for Long-term Survival

When performing a univariable Cox regression analysis after propensity score matching palliative primary tumor resection persisted to be a significant protective predictor for overall survival (HR of death = 0.40, 95% CI = 0.39–0.42, $P < 0.001$) and cancer-specific survival (HR of death = 0.39, 95% CI = 0.38–0.40, $P < 0.001$). Table 2 displays the results of the multivariable full Cox regression model after propensity score matching and weighting.

Sensitivity Analyses

Missing data were replaced by a random survival forest procedure and confirmed the results stated earlier. In this sensitivity analysis, the resection of the primary tumor was associated with a significantly decreased risk for overall survival (HR of death = 0.42, 95% CI = 0.41–0.44, $P < 0.001$) and cancer-specific survival (HR of death = 0.42, 95% CI = 0.41–0.43, $P < 0.001$) in multivariable Cox regression. The protective effect of palliative primary tumor resection was confirmed after propensity score matching and weighting for overall (HR of death = 0.40, 95% CI = 0.39–0.41, $P < 0.001$) and cancer-specific mortality (HR of death = 0.39, 95% CI = 0.38–0.40, $P < 0.001$).

DISCUSSION

To our knowledge, this is the first population-based analysis comparing overall and cancer-specific survival trends from 1998 through 2009 in a large cohort of stage IV colorectal cancer patients who did and who did not undergo palliative primary cancer removal. The present investigation yields 3 key results: First, the rate of metastatic colorectal patients undergoing primary tumor removal diminished relevantly over the past decade. Second, overall and cancer-specific survival improved over time both for patients who did and who did not undergo palliative primary cancer removal. Third and most importantly, overall and cancer-specific survival remain significantly higher in patients undergoing palliative primary cancer removal, even after adjusting in multivariable or propensity score analyses. Indeed, the 2 patient subsets who did and who did not undergo palliative primary tumor removal were similar after the propensity score weighting, thus substantially decreasing putative

confounding (Fig. 4). Nonetheless, some selection bias is likely to persist despite thorough statistical adjustment in multivariable and propensity score analyses. However, the dogma that an asymptomatic primary tumor never should be resected in patients with unresectable colorectal cancer metastases must be questioned.

The mechanism, through which cancer-specific and overall survival might be prolonged in patients with metastatic colorectal cancer undergoing palliative primary tumor removal, remains to be clarified. Interestingly, a clear survival benefit of primary tumor resection was demonstrated in 2 randomized controlled trials in metastatic renal-cell cancer patients.[22,23] Two recent attempts of performing a randomized controlled trial in patients with unresectable metastatic colorectal disease have prematurely closed due to poor recruiting. The first was sponsored by University College London Hospitals (NCT01086618) and the second trial by Colorectal Surgical Society of Australia and New Zealand (ACTRN12609000680268). A third trial initiated in Germany (SYNCHRONOUS trial) is still recruiting and the results are anticipated with great interest.[24] Nonetheless, these trials emphasize the cardinal importance of the research question of the present investigation.

In contrast to previous SEER database analyses, the rate of metastatic colorectal cancer patients undergoing palliative primary tumor resection further diminished in this study.[25,26] This behavior might reflect previous studies demonstrating that leaving the primary tumor in situ does seldom result into life threatening complications such as bleeding or complete obstruction.[8] On the basis of these findings, the National Comprehensive Cancer Network's Guidelines recommend surgery in patients with asymptomatic metastatic colorectal disease only if performed in a curative attempt.[27,28] On the basis of our findings, however, this recommendation must be questioned as some selected stage IV colorectal cancer patients may benefit form primary tumor removal.

Major advances have been made in systemic treatment of metastatic colorectal cancer. Indeed, 10 years ago, only 2 chemotherapeutic drugs (5-fluoropyrimidine and irinotecan) were widely available, whereas the number of agents in the armamentarium has significantly increased over the past decade. In addition to other chemotherapeutic drugs such as Oxaliplatin,[29] there are anti-VEGF[30] and anti-EGFR antibodies[31] that nowadays play an important role in the treatment of metastatic colorectal cancer. Because of the improvement in systemic treatment, we anticipated that the difference in overall and cancer-specific survival between the subsets of patients who did and who did not undergo palliative primary tumor resection would decrease over time. However—against our a priori hypothesis—our analysis demonstrates the contrary. Indeed, the HR for overall survival is 0.44 in patients undergoing cancer-directed surgery in univariate analyses. This very low HR persisted after adjusting for putative confounders available in the SEER data set using multivariable and propensity score analyses and did not relevantly change over time. There is a heated debate in the medical and surgical oncology community regarding whether or not an asymptomatic primary tumor should be removed in patients with unresectable, synchronous colorectal cancer metastases.[10] Other studies have shown a benefit of removing the primary tumor first; however, these have been nonrandomized and thus a relevant selection bias cannot be excluded.[11] It is obvious that patients who are younger, less comorbid, and with less metastases are more likely to be operated, whereas the older, sicker patients with many metastatic sites will not undergo surgery. The same issue is of course true for this study, for which a selection bias must be anticipated. Although we did risk-adjust using both multivariable and propensity score analyses, this adjustment was only possible for known confounders present in the SEER data set. Some remaining confounding is therefore well possible. However, it seems unlikely that the large difference in overall and cancer-specific survival found in our investigation is solely due to unadjusted confounding.

We would like to acknowledge the limitations of this study. The main drawback of this analysis is the lack of information on chemotherapeutic drugs or antibodies used, data that cannot be ascertained in the SEER registry. Similarly, information about comorbidities, performance status, and site and number of metastases are not available in the SEER database. Finally, it is not deducible from the SEER database whether the primary tumor was truly asymptomatic. To which extent these parameters might have influenced the selection of patients undergoing surgery remains unclear. However, the subset of stage IV colorectal cancer patients benefitting most from a primary tumor removal cannot be determined on the basis of the SEER database. In addition, there is a relevant number of missing values for certain parameters (eg, nodal status, T-stage), as many patients did not undergo surgery at all. However, such data are less relevant in patients with stage IV disease. Despite these limitations, this study has a variety of strengths. First, the population-based nature of the registry mirrors the real-world outcomes for patients with metastatic colorectal cancer and is associated with a high degree of generalizability. It is key to evaluate to which extend advances in often highly selected patients in randomized controlled trials have translated into the overall patient population. Second, our study reports data on a 12-year time period. Third, the large sample size is associated with a high degree of power.

CONCLUSIONS

This is the first population-based study reporting multivariable and propensity score–adjusted trends of cancer-specific and overall survival over 12 years in patients with metastatic colorectal cancer who did and who did not undergo palliative primary tumor resection. A statistically significant and clinically relevant survival benefit was found in patients who underwent primary cancer removal, which persisted from 1998 to 2009. Therefore, the dogma that an asymptomatic primary tumor never should be resected in patients with unresectable colorectal cancer metastases must be questioned.

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin.* 2012;62:10–29.
2. Longo WE, Virgo KS, Johnson FE, et al. Risk factors for morbidity and mortality after colectomy for colon cancer. *Dis Colon Rectum.* 2000;43:83–91.
3. Makela J, Haukipuro K, Laitinen S, et al. Palliative operations for colorectal cancer. *Dis Colon Rectum.* 1990;33:846–850.
4. Legendre H, Vanhuyse F, Caroli-Bosc FX, et al. Survival and quality of life after palliative surgery for neoplastic gastrointestinal obstruction. *Eur J Surg Oncol.* 2001;27:364–367.
5. Sarela AI, Guthrie JA, Seymour MT, et al. Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer. *Br J Surg.* 2001;88:1352–1356.
6. Tebbutt NC, Norman AR, Cunningham D, et al. Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases. *Gut.* 2003;52:568–573.
7. Scoggins CR, Meszoely IM, Blanke CD, et al. Nonoperative management of primary colorectal cancer in patients with stage IV disease. *Ann Surg Oncol.* 1999;6:651–657.
8. Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol.* 2009;27:3379–3384.

9. Group NGTAT. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol.* 1992;10:904–911.
10. Cirocchi R, Trastulli S, Abraha I, et al. Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable stage IV colorectal cancer. *Cochrane Database Syst Rev.* 2012;8:CD008997.
11. Eisenberger A, Whelan RL, Neugut AI. Survival and symptomatic benefit from palliative primary tumor resection in patients with metastatic colorectal cancer: a review. *Int J Colorectal Dis.* 2008;23:559–568.
12. National Cancer Institute. Surveillance epidemiology and end results. Available at http://seer.cancer.gov. Accessed May 31, 2013.
13. Wingo PA, Jamison PM, Hiatt RA, et al. Building the infrastructure for nationwide cancer surveillance and control: a comparison between the National Program of Cancer Registries (NPCR) and the Surveillance, Epidemiology, and End Results (SEER) Program (United States). *Cancer Causes Control.* 2003;14:175–193.
14. Fritz A, Percy C, Jack A, et al. *International Classification of Disease for Oncology*. 3rd ed. Geneva, Switzerland: World Health Organization; 2000.
15. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81:515–516.
16. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med.* 1997;127:757–763.
17. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. *Am J Epidemiol.* 1999;150:327–333.
18. Rosenbaum PR. Model-based direct adjustment. *J Am Stat Assoc.* 1987;82:387–394.
19. Hansen BB, Klopfer SO. Optimal full matching and related designs via network flows. *J Comput Graph Statist.* 2006;15:609–627.
20. Ho DE, Imai K, King G, et al. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Softw.* 2011;42:1–28.
21. Ishwaran H, Kogalur UB, Blackstone EH, et al. Random survival forests. *Ann App Statist.* 2008;2:841–860.
22. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med.* 2001;345:1655–1659.
23. Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet.* 2001;358:966–970.
24. Rahbari NN, Lordick F, Fink C, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS: a randomised controlled multicentre trial (ISRCTN30964555). *BMC Cancer.* 2012;12:142.
25. Cook AD, Single R, McCahill LE. Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. *Ann Surg Oncol.* 2005;12:637–645.
26. Temple LK, Hsieh L, Wong WD, et al. Use of surgery among elderly patients with stage IV colorectal cancer. *J Clin Oncol.* 2004;22:3475–3484.
27. Engstrom PF, Arnoletti JP, Benson AB, III, et al. NCCN Clinical Practice Guidelines in Oncology: rectal cancer. *J Natl Compr Canc Netw.* 2009;7:838–881.
28. Engstrom PF, Arnoletti JP, Benson AB, III, et al. NCCN Clinical Practice Guidelines in Oncology: colon cancer. *J Natl Compr Canc Netw.* 2009;7:778–831.
29. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet.* 2008;371:1007–1016.
30. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350:2335–2342.
31. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med.* 2009;360:1408–1417.