**Table S1.** Definition of colorectal cancer and cognitive disorders by ICD-10 diagnostic codes.

|  |  |
| --- | --- |
| **ICD-10 codes** | **Diseases** |
| **Colorectal cancer** | |
| C18 | Malignant neoplasm of colon |
| C19 | Malignant neoplasm of rectosigmoid junction |
| C20 | Malignant neoplasm of rectum |
| **Cognitive disorders** |  |
| F00 | Dementia in Alzheimer disease |
| F01 | Vascular dementia |
| F02 | Dementia in other diseases classified elsewhere |
| F03 | Unspecified dementia |
| F06.7 | Mild cognitive impairment |
| G30 | Alzheimer disease |
| G31.00 | Behavioral variant frontotemporal dementia |
| G31.82 | Dementia with Lewy bodies |

**Table S2.** Insurance claim fee codes for colorectal cancer treatments.

|  |  |
| --- | --- |
| **Insurance claim fee codes** | **Medications or procedures** |
| **Primary resection: colon** | |
| QA671 | Right or left hemicolectomy, without lymph node dissection. |
| QA672 | Right or left hemicolectomy, with lymph node dissection. |
| Q1261 | Subtotal colectomy, without lymph node dissection. |
| Q1262 | Subtotal colectomy, with lymph node dissection. |
| QA671 | Total colectomy, without lymph node dissection. |
| QA672 | Subtotal colectomy, with lymph node dissection. |
| QA673 | Segmental colectomy, without lymph node dissection. |
| Q2673 | Segmental colectomy, with lymph node dissection. |
| QA679 | Colectomy with proximal colostomy and distal stump,  without lymph node dissection. |
| Q2679 | Colectomy with proximal colostomy and distal stump,  with lymph node dissection. |
| **Primary resection: rectum** |  |
| QA921 | Anterior resection, without lymph node dissection. |
| Q2921 | Anterior resection, with lymph node dissection. |
| QA922 | Low anterior resection, without lymph node dissection. |
| Q2922 | Low anterior resection, with lymph node dissection. |
| Q2927 | Low anterior resection, with colonic J pouch formation. |
| QA923 | Abdominoperineal/abdominosacral resection, without lymph node dissection. |
| Q2923 | Abdominoperineal/abdominosacral resection, with lymph node dissection. |
| **Chemotherapy** |  |
| 122701ATB | Capecitabine, 0.15g |
| 122702ATB | Capecitabine, 0.5g |
| 205830BIJ | Oxaliplatin, 0.05g |
| 205832BIJ | Oxaliplatin, 0.2g |
| 205834BIJ | Oxaliplatin, 0.1g |
| 205803BIJ | Oxaliplatin, 0.15g |
| 161430BIJ | 5-fluorouracil (5-FU), 0.25g |
| 161431BIJ | 5-FU, 0.5g |
| 161432BIJ | 5-FU, 1g |
| 177430BIJ | Irinotecan, 0.04g |
| 177431BIJ | Irinotecan, 0.1g |
| 177433BIJ | Irinotecan, 0.2g |
| 177435BIJ | Irinotecan, 0.3g |
| **Radiotherapy** |  |
| HD051 | Low energy teletherapy, single port. |
| HD052 | Middle energy teletherapy, single port. |
| HD053 | High energy teletherapy, single port. |
| HD054 | Low energy teletherapy, parallel opposed ports. |
| HD055 | Middle energy teletherapy, parallel opposed ports. |
| HD056 | High energy teletherapy, parallel opposed ports. |
| HD057 | Low energy rotational irradiation |
| HD058 | Middle energy rotational irradiation |
| HD059 | High energy rotational irradiation |
| HD061 | 3-Dimensional conformal therapy |
| HD080 | Brachytherapy |
| HD081 – HD082 | Intracavity therapy, high dose rate |
| HD083 – HD084 | Intracavity therapy, low dose rate |
| HD085 – HD086 | Interstitial/intraluminal therapy, high dose rate |
| HD087 – HD088 | Interstitial/intraluminal therapy, high dose rate |
| HD121 | Proton therapy |
| HZ271 | Intensity modulated radiation therapy |
| **Folate therapy** |  |
| 566132BIJ | Leucovorin, 0.2g |
| 566134BIJ | Leucovorin, 0.35g |
| 622630BIJ | Levoleucovorin, 0.05g |
| 622631BIJ | Levoleucovorin, 0.2g |
| 622632BIJ | Levoleucovorin, 0.45g |

**Table S3.** Definition of comorbidities by ICD-10 diagnostic codes.

|  |  |
| --- | --- |
| **ICD-10 codes** | **Diseases** |
| **Myocardial infarction** | |
| I21 | Acute myocardial infarction |
| I22 | Subsequent myocardial infarction |
| I25.2 | Old myocardial infarction |
| **Heart failure** |  |
| I50 | Heart failure |
| I11.0 | Hypertensive heart disease with (congestive) heart failure |
| I13.2 | Hypertensive heart and renal disease with both (congestive) heart failure and renal failure |
| I42.0 | Congestive cardiomyopathy |
| **Peripheral vascular disease** |  |
| I70 | Atherosclerosis |
| I71 | Aortic aneurysm and dissection |
| I73.1 | Thromboangiitis obliterans [Buerger] |
| I73.8 | Other specified peripheral vascular diseases |
| I73.9 | Peripheral vascular disease, unspecified |
| I77.1 | Stricture of artery |
| I79 | Disorders of arteries, arterioles and capillaries in diseases classified elsewhere |
| K55 | Vascular disorders of intestine |
| **Cerebrovascular disease** |  |
| G45 | Transient cerebral ischaemic attacks and related syndromes |
| G46 | Vascular syndromes of brain in cerebrovascular diseases |
| I60 | Subarachnoid haemorrhage |
| I61 | Intracerebral haemorrhage |
| I62 | Other nontraumatic intracranial haemorrhage |
| I63 | Cerebral infarction |
| I64 | Stroke, not specified as haemorrhage or infarction |
| I65 | Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction |
| I66 | Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction |
| I67 | Other cerebrovascular diseases |
| I68 | Cerebrovascular disorders in diseases classified elsewhere |
| I69 | Sequelae of cerebrovascular disease |
| **Dementia** |  |
| F00 | Dementia in Alzheimer’s disease |
| F01 | Vascular dementia |
| F02 | Dementia in other diseases classified elsewhere |
| F03 | Unspecified dementia |
| F05.1 | Delirium superimposed on dementia |
| G30 | Alzheimer’s disease |
| G31.00 | Behavioral variant frontotemporal dementia |
| G31.92 | Dementia with Lewy bodies |
| **Chronic obstructive pulmonary disease** | |
| J42 | Unspecified chronic bronchitis |
| J43 | Emphysema |
| J44 | Other chronic obstructive pulmonary disease |
| I27 | Other pulmonary heart diseases |
| J68.4 | Chronic respiratory conditions due to chemicals, gases, fumes and vapours |
| J70.1 | Chronic and other pulmonary manifestations due to radiation |
| J70.3 | Chronic drug-induced interstitial lung disorders |
| **Connective tissue disease** |  |
| M05 | Seropositive rheumatoid arthritis |
| M06 | Other rheumatoid arthritis |
| M30 | Polyarteritis nodosa and related conditions |
| M31 | Other necrotizing vasculopathies |
| M32 | Systemic lupus erythematosus |
| M33 | Dermatopolymyositis |
| M34 | Multiple sclerosis |
|  |  |
| M35 | Other systemic involvement of connective tissue |
| M36 | Systemic disorders of connective tissue in diseases classified elsewhere |
| **Mild iver disease: should not have ICD-10 diagnostic codes indicating ‘moderate to severe liver disease’.** | |
| B18 | Chronic viral hepatitis |
| K70 | Alcoholic liver disease |
| K71 | Toxic liver disease |
| K72 | Hepatic failure, NEC |
| K73 | Chronic hepatitis, NEC |
| K74 | Fibrosis and cirrhosis of liver |
| K76 | Other diseases of liver |
| **Moderate to severe liver disease** | |
| K70.4 | Alcoholic hepatic failure |
| K71.1 | Toxic liver diseas with hepatic necrosis |
| K76.6 | Portal hypertension |
| K76.7 | Hepatorenal syndrome |
| I85 | Oesophageal varices |
| I86.4 | Gastric varices |
| I98.2 | Oesophageal varices without bleeding in diseases classified elsewhere |
| **Diabetes mellitus without complication: should not have ICD-10 diagnostic codes indicating ‘diabetes mellitus with complication’.** | |
| E10 | Insulin-dependent diabetes mellitus |
| E11 | Non-insulin dependent diabetes mellitus |
| E12 | Malnutrition-related diabetes mellitus |
| E13 | Other specified diabetes mellitus |
| E14 | Unspecified diabetes mellitus |
| **Diabetes mellitus with complication** |  |
| E10.0 | Insulin-dependent diabetes mellitus with coma |
| E10.1 | Insulin-dependent diabetes mellitus with acidosis |
| E10.2 | Insulin-dependent diabetes mellitus with renal complications |
| E10.3 | Insulin-dependent diabetes mellitus with retinopathy |
| E10.4 | Insulin-dependent diabetes mellitus with neurologic complications |
| E10.5 | Insulin-dependent diabetes mellitus with peripheral circulatory complications |
| E10.6 | Insulin-dependent diabetes mellitus with other specified complications |
| E11.0 | Non-insulin-dependent diabetes mellitus with coma |
| E11.1 | Non-insulin-dependent diabetes mellitus with acidosis |
| E11.2 | Non-insulin-dependent diabetes mellitus with renal complications |
| E11.3 | Non-insulin-dependent diabetes mellitus with retinopathy |
| E11.4 | Non-insulin-dependent diabetes mellitus with neurologic complications |
| E11.5 | Non-insulin-dependent diabetes mellitus with peripheral circulatory complications |
| E11.6 | Non-insulin-dependent diabetes mellitus with other specified complications |
| E12.0 | Malnutrition-related diabetes mellitus with coma |
| E12.1 | Malnutrition-related diabetes mellitus with acidosis |
| E12.2 | Malnutrition-related diabetes mellitus with renal complications |
| E12.3 | Malnutrition-related diabetes mellitus with retinopathy |
| E12.4 | Malnutrition-related diabetes mellitus with neurologic complications |
| E12.5 | Malnutrition-related diabetes mellitus with peripheral circulatory complications |
| E12.6 | Malnutrition-related diabetes mellitus with other specified complications |
| E13.0 | Other specified diabetes mellitus with coma |
| E13.1 | Other specified diabetes mellitus with acidosis |
| E13.2 | Other specified diabetes mellitus with renal complications |
| E13.3 | Other specified diabetes mellitus with retinopathy |
| E13.4 | Other specified diabetes mellitus with neurologic complications |
| E13.5 | Other specified diabetes mellitus with peripheral circulatory complications |
| E13.6 | Other specified diabetes mellitus with other specified complications |
| E14.0 | Unspecified diabetes mellitus with coma |
| E14.1 | Unspecified diabetes mellitus with acidosis |
| E14.2 | Unspecified diabetes mellitus with renal complications |
| E14.3 | Unspecified diabetes mellitus with retinopathy |
| E14.4 | Unspecified diabetes mellitus with neurologic complications |
| E14.5 | Unspecified diabetes mellitus with peripheral circulatory complications |
| E14.6 | Unspecified diabetes mellitus with other specified complications |
| **Moderate to severe chronic kidney disease** | |
| I12.0 | Hypertensive renal disease with renal failure |
| I13 | Hypertensive heart and renal disease |
| N18 | Chronic kidney disease |
| N19 | Unspecified kidney failure |
| **Neoplasms (both solid and hematologic): All ‘C’ codes** | |
| **Metastatic neoplasms** |  |
| C77 | Secondary and unspecified malignant neoplasm of lymph nodes |
| C78 | Secondary malignant neoplasm of respiratory and digestive organs |
| C79 | Secondary malignant neoplasm of other and unspecified sites |
| C80 | Malignant neoplasm without specification of site |
| **Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS)** | |
| B20 | Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases |
| B21 | Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms |
| B22 | Human immunodeficiency virus [HIV] disease resulting in other specified diseases |
| B23 | Human immunodeficiency virus [HIV] disease resulting in other conditions |
| B24 | Unspecified human immunodeficiency virus [HIV] disease |

**Table S4.** Estimated hazard ratios of chemotherapy and radiotherapy on cognitive impairment under landmark analyses.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Lag time = 6 months** | | | | |
|  | **Colon cancer, HR (95% CI)** | | **Rectal cancer, HR (95% CI)** | |
|  | **Fully adjusted model** | **Interaction model** | **Fully adjusted model** | **Interaction model** |
| Capecitabine | **1.45 (1.23 - 1.70)** | 1.52 (0.37 - 6.21) | 1.06 (0.82 - 1.37) | 0.69 (0.10 - 4.80) |
| Oxaliplatin | *0.77 (0.65 - 0.92)* | 0.34 (0.07 - 1.62) | 0.89 (0.68 - 1.16) | 0.32 (0.03 - 2.95) |
| 5-FU | *0.59 (0.43 - 0.81)* | 0.34 (0.02 - 6.47) | *0.63 (0.45 - 0.87)* | 1.09 (0.08 - 15.33) |
| Irinotecan | **2.10 (1.39 - 3.18)** | 0.59 (0.01 - 27.97) | 1.54 (0.93 - 2.53) | 0.38 (0.01 - 16.77) |
| Radiotherapy |  |  | 0.94 (0.86 - 1.02) | 0.62 (0.31 - 1.20) |
| Interaction terms |  |  |  |  |
| Capecitabine\*Age |  | 1.00 (0.98 - 1.02) |  | 1.01 (0.98 - 1.03) |
| Oxaliplatin\*Age |  | 1.01 (0.99 - 1.03) |  | 1.02 (0.98 - 1.05) |
| 5-FU\*Age |  | 1.01 (0.97 - 1.05) |  | 0.99 (0.96 - 1.03) |
| Irinotecan\*Age |  | 1.02 (0.97 - 1.07) |  | 1.02 (0.97 - 1.08) |
| Radiotherapy\*Age |  |  |  | 1.01 (1.00 - 1.02) |
| **Lag time = 12 months** | | | | |
|  | **Colon cancer, HR (95% CI)** | | **Rectal cancer, HR (95% CI)** | |
|  | **Model 1** | **Model 2** | **Model 1** | **Model 2** |
| Capecitabine | **1.39 (1.17 - 1.66)** | 1.99 (0.46 - 8.59) | 1.02 (0.77 - 1.33) | 0.74 (0.10 - 5.58) |
| Oxaliplatin | *0.76 (0.63 - 0.91)* | 0.25 (0.05 - 1.31) | 0.82 (0.61 - 1.09) | 0.59 (0.06 - 6.08) |
| 5-FU | *0.45 (0.32 - 0.65)* | 0.45 (0.02 - 12.41) | *0.50 (0.35 - 0.73)* | 1.52 (0.09 - 26.42) |
| Irinotecan | **2.77 (1.76 - 4.36)** | 0.39 (0.91 - 24.86) | **1.99 (1.17 - 3.38)** | 0.33 (0.01 - 17.74) |
| Radiotherapy |  |  | 0.94 (0.86 - 1.03) | 0.66 (0.33 - 1.31) |
| Interaction terms |  |  |  |  |
| Capecitabine\*Age |  | 0.99 (0.97 - 1.02) |  | 1.00 (0.98 - 1.03) |
| Oxaliplatin\*Age |  | 1.02 (0.99 - 1.04) |  | 1.00 (0.97 - 1.04) |
| 5-FU\*Age |  | 1.00 (0.95 - 1.05) |  | 0.98 (0.94 - 1.03) |
| Irinotecan\*Age |  | 1.03 (0.97 - 1.09) |  | 1.03 (0.97 - 1.09) |
| Radiotherapy\*Age |  |  |  | 1.01 (1.00 - 1.02) |
| **Lag time = 18 months** | | | | |
|  | **Colon cancer, HR (95% CI)** | | **Rectal cancer, HR (95% CI)** | |
|  | **Model 1** | **Model 2** | **Model 1** | **Model 2** |
| Capecitabine | **1.44 (1.23 - 1.68)** | 1.81 (0.47 - 7.01) | 1.04 (0.81 - 1.34) | 0.59 (0.08 - 4.05) |
| Oxaliplatin | *0.76 (0.64 - 0.89)* | 0.56 (0.12 - 2.50) | 0.87 (0.67 - 1.13) | 0.31 (0.03 - 2.71) |
| 5-FU | *0.69 (0.52 - 0.92)* | 0.24 (0.02 - 3.78) | 0.75 (0.55 - 1.01) | 1.44 (0.12 - 17.07) |
| Irinotecan | **1.90 (1.29 - 2.80)** | 0.63 (0.02 - 25.09) | 1.32 (0.82 - 2.13) | 0.28 (0.01 - 12.33) |
| Radiotherapy |  |  | ***0.91 (0.83 - 0.99)*** | 0.71 (0.36 - 1.37) |
| Interaction terms |  |  |  |  |
| Capecitabine\*Age |  | 1.00 (0.98 - 1.02) |  | 1.01 (0.98 - 1.04) |
| Oxaliplatin\*Age |  | 1.00 (0.98 - 1.03) |  | 1.02 (0.98 - 1.05) |
| 5-FU\*Age |  | 1.01 (0.98 - 1.05) |  | 0.99 (0.96 - 1.03) |
| Irinotecan\*Age |  | 1.02 (0.97 - 1.07) |  | 1.02 (0.97 - 1.08) |
| Radiotherapy\*Age |  |  |  | 1.00 (0.99 - 1.01) |

Fully adjusted model: Adjusted for age, sex, Charlson Comorbidity Index, and monthly insurance premium;

Interaction model: Interaction between cancer treatment and age was estimated by each treatment modality.

HR, hazard ratio; CI, confidence interval.