**Appendix 1.** Ovid Medline Search Strategy.

1. ("time interval" or "time factor$" or "time to treatment" or timing or wait$ or time or interval or delay$).mp.
2. (cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$).mp. or exp Neoplasms/
3. treatment.mp. or exp Therapeutics/
4. (pneumonectomy or lobectomy or excision or resection or colectomy or hemicolectomy or mastectomy or lumpectomy or laryngectomy or $pharyngectomy or hysterectomy or surgery or resection or radiotherapy or radiation or chemotherapy or immunotherapy or endocrine therapy or hormone therapy or systemic therapy or adjuvant).mp. or exp Antineoplastic Agents/ or targeted therapy.mp. or exp Molecular Targeted Therapy/ or exp Antibodies, Monoclonal/ or exp Drug Therapy/ or exp Immunotherapy/
5. 1 and 2
6. 3 or 4
7. 5 and 6
8. (survival or recurrence or (loc$ adj2 control) or outcome$ or mortality or morbidity).mp.
9. 7 and 8
10. ("time interval" or "time factor$" or "time to treatment" or timing or wait$ or time or interval or delay$).ti.
11. 9 and 10
12. diagnostic delay.mp. or exp Delayed Diagnosis/
13. 11 not 12
14. prostate cancer.ti.
15. 13 not 14
16. limit 15 to (english language and humans and yr="2000 -Current")
17. colon cancer.mp. or exp Colonic Neoplasms/
18. lung cancer.mp. or exp Lung Neoplasms/
19. breast cancer.mp. or exp Breast Neoplasms/
20. larynx cancer.mp. or exp Laryngeal Neoplasms/
21. oropharynx cancer.mp. or exp Oropharyngeal Neoplasms/
22. oral cancer.mp. or exp Mouth Neoplasms/
23. nasopharyngeal cancer.mp. or exp Nasopharyngeal Neoplasms/
24. hypopharyngeal cancer.mp. or exp Hypopharyngeal Neoplasms/
25. rectal cancer.mp. or exp Rectal Neoplasms/
26. cervical cancer.mp. or exp Uterine Cervical Neoplasms/
27. "head and neck cancer".mp. or exp Head Neck Neoplasms/
28. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 16 and 28
30. limit 29 to (meta analysis or "review" or "systematic review")
31. (circadian or watch or reconstruction or prime).ti.
32. 29 not 31
33. 30 not 31
34. 32 not 33
35. bladder cancer.mp. or exp Urinary Bladder Neoplasms/
36. 16 and 35
37. limit 36 to (meta analysis or "review" or "systematic review")
38. 37 not 31
39. 38 not 33
40. 36 not 34
41. 40 not 37
42. 36 not 37

**Appendix 2. Technical Appendix**

### A. Converting Hazard Ratio (HR) to per four-week delay estimates

Waiting time (WT) effect size (HR) in each study was converted to a regression coefficient and standard error corresponding to a continuous representation per 4 weeks of WT. For studies which already had a continuous effect, the unit of HR was converted to per four-weeks and the SE was estimated from the confidence interval. For studies without a continuous effect measure that could be used, the most robust analysis was selected for meta-analysis according to WT categories. For studies with multiple WT categories, a central value of WT was assigned to each category. This took into account reported information on the distribution of WT in each study, and clinical knowledge of waiting times. On a log scale, a weighted linear regression of the log of the HR on exposure level was used to estimate the slope with weights equal to the inverse of the variance of the HR estimates (and corresponding standard error (SE)). The SE for the slope was calculated according to the approach described by Greenland and Longnecker (1).

### B. Converting HR per four-week delay to other units

The following formula is used, where X is the unit of time desired, expressed here in units of weeks:

HR per X-week delay= HR per 4 week delay$^{\text{X-weeks/4 weeks}}$

Example of an HR of 1.08 per 4 week delay converted into smaller units:

HR per 2-week delay= $1.08^{2\text{ weeks/4 weeks}} = 1.08^{0.5}=1.04$

Example of an HR of 1.08 per 4 week delay converted into larger units:

HR per 6-week delay= $1.08^{6\text{ weeks/4 weeks}}= 1.08^{1.5}= 1.12$

### C. Worked example comparing the log-linear assumption used in the paper with a linear HR model

To examine the impact of the log-linear assumption used in the paper versus the linear effect of HR over time, we compared HRs in the range of 4 to 20 weeks in an example. The table below compares incremental hazard ratios (HR) per 4 weeks and cumulative HR with 4 weeks as the reference in the two models. The models are set to have identical HR at 4 and 20 weeks. The example uses a log-linear HR of 1.06 per 4 weeks (i.e. the summary estimate for Head and Neck – Surgery from the Liao et al and Murphy et al pooled analysis).

| | **(log) Linear model** | | **Linear HR model** | |
|---|---|---|---|---|
| Week | Incremental HR | Cumulative HR | Incremental HR | Cumulative HR |
| 4 | 1.00 | **1.000** | 1.000 | **1.000** |
| 8 | 1.060 | 1.060 | 1.066 | 1.066 |
| 12 | 1.060 | 1.124 | 1.062 | 1.131 |
| 16 | 1.060 | 1.191 | 1.058 | 1.197 |
| 20 | 1.060 | **1.262** | 1.055 | **1.262** |

As can be seen in the table above, the incremental HR are similar in the two models – the difference being a very slightly stronger effect of wait early on in the linear HR model, and a slightly lesser effect for later wait times. These differences would be more pronounced outside of this range of wait times. However, within the range that is the target of this paper there is little difference in predicted HR from the two models.

**Appendix 3.** Study-Specific Waiting Time Categories, Hazard Ratios, and Sample Size

| Indication | Source | Overall Survival and Raw HR Data (95% CI) | WT Categories (days) | Sample Size |
|---|---|---|---|---|
| **SURGERY** | | | | |
| Bladder | Chu et al(2), 2019 | Referent: <85 days<br>HR = 1.34 (1.03 – 1.76) | Total | 991 |
| | | | <85 | NR |
| | | | ≥85 | NR |
| | Gore et al(3), 2009 | Referent: 28-56 days<br>57-84 days: HR = 1.01 (p-value 0.94);<br>85-168 days: HR = 1.59 (p-value 0.004) | Total | 441 |
| | | | 28-56 | NR |
| | | | 57-84 | NR |
| | | | 85-168 | NR |
| | Kulkarni et al(4), 2009 | Continuous HR = 1.001 (1.000 – 1.002) per day | Total | 2397 |
| | | | ≤ 90 | 1,916 |
| | | | > 90 | 481 |
| Breast | Bleicher et al(5), SEER 2016 | Continuous HR = 1.09 (1.06-1.13) per 30 day interval | Total | 94,544 |
| | | | ≤ 30 | 73,491 |
| | | | 31-60 | 17,345 |
| | | | 61-90 | 2586 |
| | | | 91-120 | 686 |
| | | | 121-180 | 436 |
| | Bleicher et al(5), NCDB 2016 | Continuous HR = 1.10 (1.07-1.13) per 30 day interval | Total | 115,790 |
| | | | ≤ 30 | 80,505 |
| | | | 31-60 | 28,832 |
| | | | 61-90 | 4,697 |
| | | | 91-120 | 1,152 |
| | | | 121-180 | 604 |
| | Eaglehouse et al(6), 2019 | Referent: 1-21 days<br>0 days: HR = 1.15 (0.93-1.43);<br>22-35 days: HR = 0.97 (0.78-1.21);<br>≥ 36 days: HR = 1.3 (1.04-1.61) | Total | 9,669 |
| | | | 0 | 2,083 |
| | | | 1-21 | 2,754 |
| | | | 22-35 | 2,571 |
| | | | ≥ 36 | 2,261 |
| | Polverini et al(7), 2016 | Referent: 0-27 days<br>28-55 days: HR = 0.98 (0.96-1.00);<br>56-84 days: HR = 1.03 (0.99-1.06);<br>85-182 days: HR = 1.14 (1.09-1.20) | Total | 420,792 |
| | | | 0-27 | 202,985 |
| | | | 28-55 | 163,771 |
| | | | 56-84 | 38,402 |
| | | | 85-182 | 15,634 |
| | | Referent: 8-28 days | Total | 2,045 |

| | | | | |
|---|---|---|---|---|
| | Shin et al(8), 2013 | 0-7 days: HR = 1.2 (0.77-1.87);<br>29-56 days: HR = 1.33 (0.77-2.31);<br>57-84 days: HR = 0.77 (0.30-1.97);<br>> 84 days: HR = 1.91 (1.06 – 3.49) | 0-7 | 639 |
| | | | 8-28 | 877 |
| | | | 29-56 | 277 |
| | | | 57-84 | 110 |
| | | | > 84 | 142 |
| | Mateo et al (9), 2020 | Continuous HR: 1.10 (1.08-1.13) per month | Total | 351,087 |
| Colon | Bagaria et al(10), 2019 | Referent: 1-7 days<br>8-14 days: HR = 1.02 (0.92-1.14);<br>15-21 days: HR 1.03 (0.90-1.17);<br>22-28 days: HR = 1.05 (0.89-1.23);<br>29-35 days: HR = 1.12 (0.92-1.36);<br>36-42 days: HR = 1.14 (0.89-1.46);<br>43-49 days: HR = 1.11 (0.79-1.56);<br>50-63 days: HR = 1.17 (0.86-1.60);<br>64-84 days: HR = 1.07 (0.73-1.57);<br>> 84 days: HR = 1.47 (1.02-2.11) | Total | 4,685 |
| | | | 1-7 | 1,762 |
| | | | 8-14 | 1,063 |
| | | | 15-21 | 704 |
| | | | 22-28 | 415 |
| | | | 29-35 | 266 |
| | | | 36-42 | 161 |
| | | | 43-49 | 90 |
| | | | 50-63 | 90 |
| | | | 64-84 | 73 |
| | | | > 84 | 61 |
| | Flemming et al(11), 2017 | Referent: ≤41 days<br>HR = 1.05 (0.93-1.18) | Total | 4,326 |
| | | | ≤41 | 3504 |
| | | | >41 | 822 |
| NSCLC | Kanarek et al(12), 2014 | Continuous HR 1.04 (1.00-1.09) per week | Total | 174 |
| | | | ≤ 42 | 52 |
| | | | > 42 | 122 |
| | Samson et al(13),2015 | Continuous HR = 1.004 (1.002-1.007) per week | Total | 55,653 |
| | | | < 56 | 39,995 |
| | | | ≥ 56 | 15,658 |
| Head and Neck | Murphy et al(14), 2016 | Referent: 0-30 days<br>31-60 days: HR = 1.06 (1.01-1.12);<br>61-90 days: HR = 1.25 (1.14-1.37);<br>> 90 days: HR = 1.24 (1.08-1.43) | Total | 9,669 |
| | | | ≤ 30 | 6,858 |
| | | | 31-60 | 2,125 |
| | | | 61-90 | 442 |
| | | | > 90 | 244 |
| | Liao et al(15), 2017 | Referent: ≤ 30 days<br>31-60 days: HR = 1.1 (1.03-1.18);<br>61-90 days: HR = 1.26 (1.08-1.46);<br>> 90 days: HR = 1.26 (1.12-1.41) | Total | 18,667 |
| | | | ≤ 30 | 15055 |
| | | | 31-60 | 2661 |
| | | | 61-90 | 403 |
| | | | > 90 | 558 |
| **SYSTEMIC THERAPY** | | | | |
| | | Referent: <78 days | Total | 271 |

| | | | | |
|---|---|---|---|---|
| Neoadjuvant CT, Bladder | Chu et al(2), 2019 | HR = 1.63 (1.06 – 2.52) | <78 | NR |
| | | | ≥78 | NR |
| Adjuvant CT, Bladder | Corbett et al(16), 2019 | 31-60: HR = 0.60 (0.52-0.69);<br>61-90: HR = 0.62 (0.53-0.74);<br>91-180: HR = 0.69 (0.55-0.87) | Total | 1,009 |
| | | | 31-60 | 538 |
| | | | 61-90 | 321 |
| | | | 91-180 | 150 |
| | Booth et al(17), 2014 | Continuous HR = 1.03 (1.00-1.07) per week | Total | 533 |
| | | | ≤ 84 | 413 |
| | | | 85-112 | 120 |
| Neoadjuvant CT, Breast | Sanford et al(18), 2016 | Referent: <57 days<br>HR ≥57 days 1.62 (1.07-2.36) | Total | 1101 |
| | | | ≥ 57 | NR |
| Adjuvant CT, Breast | Gagliato et al (19), 2014 | Referent: ≤ 30 days<br>31-60 HR: 1.05 (0.94-1.18)<br>≥61 HR: 1.19 (1.02-1.38) | Total | 6,827 |
| | | | ≤30 | 2,716 |
| | | | 31-60 | 2,994 |
| | | | ≥61 | 1,117 |
| | Mateo et al (9), 2020 | Continuous HR = 1.10 (1.08-1.12) per month | Total | 129,685 |
| | Hershman et al (20), 2006 | Referent: < 1month<br>1-2 month HR = 1.00 (0.88-1.14)<br>2-3 month HR = 1.08 (0.85-1.36)<br>>3 month HR = 1.46 (1.21-1.75) | Total | 5007 |
| | | | <1 month | 2361 |
| | | | 1-2 month | 1846 |
| | | | 2-3 month | 323 |
| | | | >3 month | 477 |
| Adjuvant CT, Colon Rectum | Hershman et al (21), 2006 | Referent < 1 month<br>1-2 month HR = 1.1 (0.9-1.3)<br>2-3 month HR = 1.4 (1.2-1.7)<br>>3 month HR = 1.6 (1.3-2.0) | Total | 4,382 |
| | | | <1 month | 1,122 |
| | | | 1-2 month | 2,391 |
| | | | 2-3 month | 454 |
| | | | >3 month | 415 |
| | Cheung et al (22), 2009 | Referent: <56 days<br>57-84 days: 1.07 (0.94-1.23)<br>>84 days: 1.65 (1.43-1.90) | Total | 6,059 |
| | | | <56 | 4,476 |
| | | | 57-84 | 873 |
| | | | >84 | 710 |
| | Bayraktar et al (23), 2011 | Referent: ≤ 60 days<br>>60 days HR: 2.07 (1.02-4.19) | Total | 186 |
| | | | ≤ 60 | 137 |
| | | | > 60 | 49 |
| | Lima et al (24), 2011 | Referent <56 days<br>56-84 HR: 1.03 (0.76-1.39)<br>85-112 HR: 1.43 (0.96-2.13) | Total | 648 |
| | | | <56 | 286 |
| | | | 56-84 | 284 |
| | | | 85-112 | 78 |
| | | | Total | 1133 |

| | | | | |
|---|---|---|---|---|
| | Becerra et al(25), 2017 | *Propensity score 1:1 matching* (only unmatched sample size reported in manuscript)<br>Referent ≤ 56 days<br>>56 days HR 1.34 (1.22-1.52) | ≤ 56 | 730 |
| | | | > 56 | 403 |
| | Turner et al (26), 2018 | < 6 weeks HR: 0.441 (0.424-0.458)<br>6-8 weeks HR: 0.452 (0.433-0.472)<br>8-12 weeks HR 0.52 (0.496-0.545)<br>12-24 weeks HR: 0.612 (0.574-0.653)<br>>24 weeks HR: 0.675 (0.579-0.787) | Total | 72,057 |
| | | | <6 weeks | 22,705 |
| | | | 6-8 weeks | 15,412 |
| | | | 8-12 weeks | 9,049 |
| | | | 12-24 weeks | 3,595 |
| | | | >24 weeks | 489 |
| | | | No chemo | 20,807 |
| | Xu et al (27), 2014 | Propensity score matched analysis<br>Referent: < 60 days<br>≥ 60 days: HR: 1.68 (1.40-2.00) | Total | 1,996 |
| | | | <60 | 998 |
| | | | ≥60 | 998 |
| | Massarweh et al (28), 2015 | Continuous HR per 1 week = 1.03 (1.02-1.03) | Total | 51,331 |
| Adjuvant CT, NSCLC | Booth et al(29), 2013 | Continuous HR per 4 weeks = 0.98 (0.85-1.13) | Total | 1,032 |
| | Salazar et al(30), 2017 | Referent: 39-56 days<br>≤ 38 days: HR = 1.009 (0.944-1.080);<br>> 56 days: HR = 1.037 (0.972-1.105) | Total | 12,473 |
| | | | ≤ 38 | 3,359 |
| | | | 39-56 | 5,137 |
| | | | > 56 | 3,977 |
| **RADIOTHERAPY** | | | | |
| Adjuvant RT Breast | Hébert-Croteau et al (31), 2004 | Referent ≤ 56 days<br>57-84 days HR: 0.92 (0.65-1.30)<br>>84 days HR: 0.93 (0.62-1.39) | Total | 1,062 |
| | | | ≤56 | 452 |
| | | | 57-84 | 319 |
| | | | >84 | 291 |
| Adjuvant RT Cervix | Jhawar et al(32), 2017 | Referent: ≤ 56 days<br>HR = 1.20 (1.00-1.44) | Total | 3,051 |
| | | | ≤ 56 | 2,287 |
| | | | > 56 | 764 |
| Radical Head and Neck | Sharma et al (33), 2016 | Referent: ≤ 30 days<br>> 30 days: HR: 1.12 (1.03-1.20)<br>Continuous measured in weeks: HR: 1.022 (1.011-1.033) | Total | 6,606 |
| | | | ≤ 30 | 3,020 |
| | | | > 30 | 3,586 |
| Adjuvant Head and Neck | Harris et al (34)2018 | Referent: 21-42 days<br>43-49 days: HR: 0.98 (0.93-1.04)<br>50-90 days: HR: 1.07 (1.02-1.12) | Total | 25,216 |
| | | | 21-42 | 9,765 |
| | | | 43-49 | 4,735 |

| | | | | |
|---|---|---|---|---|
| | | | 50-90 | 10,716 |
| Naso-pharyngeal cancer | Chen et al(35) 2016 | Referent ≤ 28 days<br>> 28 days HR: 2.23 (1.03-4.82)<br>(Patients without neoadjuvant chemotherapy) | Total | 578 |
| | | | ≤ 28 | 289 |
| | | | > 28 | 289 |

**CI** Confidence Interval **CT** Chemotherapy **HR** Hazard Ratio **RT** Radiotherapy **WT** Wait Time

**Appendix 4. Factors considered in primary literature adjusted analysis. X:** Adjusted, stratified, restricted or balanced **SES:** neighbourhood or individual income, education and/or deprivation groups. **Year:** Year of diagnosis or treatment **Geography:** Region of residence or registry, distance to cancer centre, and/or urban/rural

| Indication | Source | Country | Age | Stage | Comorbidity or Functional status | Sex | Year | SES | Race | Insurance | Geo-graphy | Provider volume or type | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Surgery, Bladder | Chu et al (2), 2019 | US | X | X | X | X | - | - | X | X (All medicare beneficaries) | - | - | Marital status |
| | Gore et al (3), 2009 | US | X | X | X | X | - | - | X | X (All medicare beneficaries) | X | - | Cancer grade, marital status |
| | Kulkarni et al (4), 2009 | Canada | X | X | X | X | X | X | - | X (All OHIP) | X | X | Admission status, tumour grade, lymphadenectomy, adjuvant chemotherapy, surgeon experience, pre-operative consultation, pre-operative imaging, lymphovascular invasion, perineural invasion, margins |
| Surgery, Breast | Bleicher et al (5), SEER 2016 | US | X | X | X | X | X | X | X | X (All medicare beneficiaries) | X | - | Size of metropolitan area, marital status, sequence of breast cancer with other cancer diagnoses, histology, grade, tumor size, number of lymph nodes examined, surgery type, chemotherapy, radiotherapy |
| | Bleicher et al (5), NCDB 2016 | US | X | X | X | X | X | X | X | X | X | X | Histology, grade, tumor size, surgical margins, nodes examined, surgery type, chemotherapy use, radiotherapy use, endocrine therapy use, analytic case type, size of metropolitan area |
| | Eaglehouse et al (6), 2019 | US | X | X | X | X | X | - | X | X | X | X | Military service branch, active duty status, marital status, tumor grade, hormone receptor status, surveillance mammography, surgery type, chemotherapy, radiotherapy, endocrine therapy, benefit type |
| | Polverini et al (7), 2016 | US | X | X | X | X | - | - | X | X | - | X | Surgery type, grade, chemotherapy, radiotherapy, endocrine therapy |
| | Shin et al (8), 2013 | Korea | X | X | X | X | X | X | X | X (Korean National Health Insurance Program) | X | - | - |
| | Mateo et al (9), 2020 | US | X | X | X | X | X | X | X | X | X | X | Subtype (triple-negative, hormone receptor positive, her2 positive), transition, histology, grade, surgery type, radiation, endocrine therapy, nodes examined, chemotherapy |
| Surgery, Colon | Bagaria et al (10), 2019 | US | X | X | X | X | X | - | X | - | X | X | Hospital, marital status, colon cancer site, grade, number of lymph nodes examined |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Flemming et al (11), 2017 | Canada | X | X | X | X | - | X | - | X (Ontario Health Insurance Plan) | X | X | - |
| Surgery, NSCLC | Kanarek et al (12), 2014 | US | X | X | X | X | X | - | X | X | X | X | Smoking, tumor size, marital status |
| | Samson et al (13),2015 | US | X | X | X | X | - | X | X | - | - | X | Tumor size, surgical margins, type of operation |
| Surgery, Head & Neck | Murphy et al (14), 2016 | US | X | X | X | X | X | X | X | X | X | X | Transition to academic facility, cancer primary site |
| | Liao et al (15), 2017 | Taiwan | X | X | X | X | X | - | - | X (Taiwanese National Health Insurance Program) | - | - | Cancer subsite, treatment modality |
| Neoadjuvant CT, Bladder | Chu et al (2), 2019 | US | X | X | X | X | - | - | X | X (All medicare beneficaries) | - | - | Time from transurethral resection of bladder tumor to neo-adjuvant chemotherapy, marital status |
| Adjuvant CT, Bladder | Corbett et al (16), 2019 | US | X | X | X | X | - | X | X | X | X | X | Margins |
| | Booth et al (17), 2014 | Canada | X | X | X | X | X | X | - | X (Ontario Health Insurance Plan) | X | X | Margins, lymphovascular invasion, length of hospital stay |
| Neoadjuvant CT, Breast | Sanford et al (18), 2016 | US | X | X | X | X | - | - | X | - | - | X | Nuclear grade, histology, lymphovascular invasion, breast cancer subtype, pathologic complete response, surgery type |
| Adjuvant CT, Breast. | Gagliato et al (19) 2014. | US | X | X | X | X | - | - | X | - | - | X | HER 2 status, hormone receptor status, lymphovascular invasion, grade, surgery type, systemic therapy |
| | Mateo et al (9), 2020 | US | X | X | X | X | X | X | X | X | X | X | Subtype (triple-negative, hormone receptor positive, her2 positive), transition, histology, grade, surgery type, radiation, endocrine therapy, nodes examined |
| | Hershman et al (20), 2006 | US | X | X | X | X | - | X | X | X (All medicare beneficaries) | X | X | Marital status, hormone receptor status, grade, surgery type, radiation use |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adjuvant CT, Colon, Rectum | Hershman et al (21), 2006 | US | X | X | X | X | - | X | X | X (All medicare beneficaries) | X | X | Marital status, grade of tumour |
| | Cheung et al (22), 2009 | US | X | X | X | X | X | X | X | X (All medicare beneficiaries) | X | X | Marital status, tumor grade, post-operative length of stay, hospital re-admissions, use of neoadjuvant chemotherapy |
| | Bayraktar et al (23), 2010 | US | X | X | X | X | X | - | X | - | - | X | Marital status, tumor dimension |
| | Lima et al (24), 2011 | Canada | X | X | X | X | X | X | - | X (Alberta Health Care Insurance Plan) | X | - | Employment, marital status |
| | Becerra et al (25), 2017 | US | X | X | X | X | X | - | X | X ( All medicare beneficaries) | X | X | Surgeon, colectomy type, medical oncologist, hospital, unscheduled admission, readmission, complication, sepsis, length of stay |
| | Turner et al (26), 2018 | US | X | X | X | X | X | X | X | X | - | X | Primary tumor site, extent of resection, number of lymph nodes harvested, post-operative complication surrogates: length of stay, readmission |
| | Xu et al (27), 2014 | US | X | X | X | X | X | X | X | X (All medicare beneficaries) | X | - | Marital status, percentage of non-English speakers, grade, presence of perforation or obstruction at presentation, number of lymph nodes sampled, hospitalization, oxygen use, and wheelchair use, length of hospital stay, and postsurgical readmission |
| | Massarweh et al (28), 2015 | US | X | X | X | X | - | X | X | X | X | - | Extent of operation, surgical margins, pathologic grade, length of stay, hospital readmission |
| Adjuvant CT, NSCLC | Booth et al(29), 2013 | Canada | X | X | X | X | X | X | - | X (Ontario Health Insurance Plan) | - | - | Histology, surgery type |
| | Salazar et al (30), 2017 | US | X | X | X | X | X | X | X | X | - | X | Histology, primary site, tumour size, surgery type |
| Adjuvant RT, Breast | Hébert-Croteau et al (31), 2004 | Canada | X | X | X | X | - | - | - | X (Quebec Universal Health System) | - | - | Chemotherapy use, tamoxifen, nodal dissection, radiation dose, grade, hormone receptor status, lymphovascular invasion, margin status |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adjuvant RT, Cervix | Jhawar et al (32), 2017 | US | X | X | X | X | X | X | X | X | X | X | Parametrial invasion, lymph node status, surgical margins, number of pathologic risk factors, tumor size, histology, grade, radiotherapy overall treatment time, package time, chemotherapy time, hysterectomy type |
| Radical RT, Head & Neck | Sharma et al (33), 2016 | US | X | X | X | X | X | - | X | X | X | X | Primary tumor site, radiation technique |
| Adjuvant RT, Head & Neck | Harris et al (34), 2018 | US | X | X | X | X | X | X | X | X | X | X | Disease site, extracapsular extension, margin status, lymphovascular invasion, time from diagnosis to surgery, hospital length of stay, 30-day unplanned readmission, radiation dose, radiation modality, chemotherapy |
| Radical RT, Non-keratinizing NPC | Chen et al (35), 2016 | China | X | X | X | X | X | - | - | - | - | X | Chemotherapy regimen |

**NCDB** National Cancer Database (US) **NSCLC** Non-small cell lung cancer **SEER** Surveillance, Epidemiology, and End Results.

**Appendix 5**. Sensitivity analysis, including studies that did not report or adjust for comorbidity or functional status but met other validity criteria. Summary results of the hazard ratio of treatment delay per four weeks on mortality for surgical, systemic therapy and radiotherapy indications.

| **Treatment modality** | **Treatment indication** | **Studies reporting and adjusting for comorbidity or functional status** | **Studies not reporting or adjusting for comorbidity or functional status** | **PRIMARY ANALYSIS Hazard ratio of mortality per 4 weeks delay excluding studies not reporting or adjusting for comorbidity or functional status (95% confidence interval)** | **SENSITIVITY ANALYSIS Hazard ratio of mortality per 4 weeks delay including studies not reporting or adjusting for comorbidity or functional status (95% confidence interval)** |
|---|---|---|---|---|---|
| Surgery | Breast partial or complete mastectomy | Bleicher et al,<br>Eaglehouse et al,<br>Polverini et al,<br>Shin et al<br>Mateo et al | Mujar et al (36) | 1.08 (1.03,1.13) | 1.08 (1.03,1.12) |
| | Colon colectomy | Bagaria et al,<br>Flemming et al | Wanis et al (37) | 1.06 (1.01,1.12) | 1.06 (1.01,1.11) |
| Systemic therapy | Breast neoadjuvant systemic therapy | Sanford et al | Omarini et al (38) | 1.28 (1.05,1.56) | 2.30 (0.50,10.70) |
| | Breast adjuvant chemotherapy | Gagliato et al<br>Mateo et al<br>Hershman et al | Cold et al (39)<br>Lohrisch et al (40)<br>Chavez-MacGregor et al (41)<br>Yu et al (42) | 1.09 (1.07,1.11) | 1.08 (1.05,1.11) |
| | Colon and rectum adjuvant chemotherapy | Hershman et al<br>Cheung et al<br>Bayraktar et al<br>Lima et al<br>Becerra et al<br>Turner et al | Ahmed et al (43)<br>Czaykowski et al (44)<br>Zeig-Owens et al (45)<br>Bos et al (46) | 1.13 (1.09,1.17) | 1.12 (1.09,1.16) |

| | | | | | |
|---|---|---|---|---|---|
| | | Xu et al<br>Massarweh et al | | | |
| Radiotherapy | Breast adjuvant radiation following breast conserving surgery | Hébert-Croteau et al | van Maaren et al (47) | 0.98 (0.88,1.09) | 1.04 (0.93,1.16) |

**References**


1. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. American journal of epidemiology. 1992 Jun 1;135(11):1301-9. PubMed PMID: 1626547.
2. Chu AT, Holt SK, Wright JL, Ramos JD, Grivas P, Yu EY, et al. Delays in radical cystectomy for muscle-invasive bladder cancer. Cancer. 2019 2019/06/15/;125(12):2011-7. en.
3. Gore JL, Lai J, Setodji CM, Litwin MS, Saigal CS, the Urologic Diseases in America P. Mortality increases when radical cystectomy is delayed more than 12 weeks: Results From a Surveillance, Epidemiology, and End Results-Medicare Analysis. Cancer. 2009 2009/03/01/;115(5):988-96. en.
4. Kulkarni GS, Urbach DR, Austin PC, Fleshner NE, Laupacis A. Longer Wait Times Increase Overall Mortality in Patients With Bladder Cancer. Journal of Urology. 2009 2009/10//;182(4):1318-24. en.
5. Bleicher RJ, Ruth K, Sigurdson ER, Beck JR, Ross E, Wong Y-N, et al. Time to Surgery and Breast Cancer Survival in the United States. JAMA oncology. 2016;2(3):330-9.
6. Eaglehouse YL, Georg MW, Shriver CD, Zhu K. Time-to-surgery and overall survival after breast cancer diagnosis in a universal health system. Breast cancer research and treatment. 2019;178(2):441-50.
7. Polverini AC, Nelson RA, Marcinkowski E, Jones VC, Lai L, Mortimer JE, et al. Time to Treatment: Measuring Quality Breast Cancer Care. Annals of surgical oncology. 2016;23(10):3392-402.
8. Shin DW, Cho J, Kim SY, Guallar E, Hwang SS, Cho B, et al. Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer. Annals of surgical oncology. 2013;20(8):2468-76.
9. Mateo AM, Mazor AM, Obeid E, Daly JM, Sigurdson ER, Handorf EA, et al. Time to Surgery and the Impact of Delay in the Non-Neoadjuvant Setting on Triple-Negative Breast Cancers and Other Phenotypes. Ann Surg Oncol. 2020 May;27(5):1679-92. PubMed PMID: 31712923. Pubmed Central PMCID: PMC7145740.
10. Bagaria SP, Heckman MG, Diehl NN, Parker A, Wasif N. Delay to Colectomy and Survival for Patients Diagnosed with Colon Cancer. Journal of Investigative Surgery. 2019 2019/05/19/;32(4):350-7. en.
11. Flemming JA, Nanji S, Wei X, Webber C, Groome P, Booth CM. Association between the time to surgery and survival among patients with colon cancer: A population-based study. European Journal of Surgical Oncology (EJSO). 2017 2017/08//;43(8):1447-55. en.
12. Kanarek NF, Hooker CM, Mathieu L, Tsai H-L, Rudin CM, Herman JG, et al. Survival After Community Diagnosis of Early-stage Non-small Cell Lung Cancer. The American Journal of Medicine. 2014 2014/05/01/;127(5):443-9. en.
13. Samson P, Patel A, Garrett T, Crabtree T, Kreisel D, Krupnick AS, et al. Effects of Delayed Surgical Resection on Short-Term and Long-Term Outcomes in Clinical Stage I Non-Small Cell Lung Cancer. Ann Thorac Surg. 2015 Jun;99(6):1906-12; discussion 13. PubMed PMID: 25890663. Pubmed Central PMCID: 4458152.
14. Murphy CT, Galloway TJ, Handorf EA, Egleston BL, Wang LS, Mehra R, et al. Survival Impact of Increasing Time to Treatment Initiation for Patients With Head and Neck Cancer in the United States. JCO. 2016 2016/01/10/;34(2):169-78. en.
15. Liao C-T, Chen H-N, Wen Y-W, Lee SR, Ng S-H, Liu T-W, et al. Association between the diagnosis-to-treatment interval and overall survival in Taiwanese patients with oral cavity squamous cell carcinoma. European journal of cancer. 2017 2017/02//;72:226-34. en.
16. Corbett CJ, Xia L, Mamtani R, Malkowicz SB, Guzzo TJ. Survival Benefit Persists With Delayed Initiation of Adjuvant Chemotherapy Following Radical Cystectomy for Locally Advanced Bladder Cancer. Urology. 2019 2019/10//;132:143-9. en.

17. Booth CM, Siemens DR, Peng Y, Tannock IF, Mackillop WJ. Delivery of perioperative chemotherapy for bladder cancer in routine clinical practice. Annals of oncology : official journal of the European Society for Medical Oncology. 2014 Sep;25(9):1783-8. PubMed PMID: 24915872.
18. Sanford RA, Lei X, Barcenas CH, Mittendorf EA, Caudle AS, Valero V, et al. Impact of Time from Completion of Neoadjuvant Chemotherapy to Surgery on Survival Outcomes in Breast Cancer Patients. Annals of surgical oncology. 2016;23(5):1515-21.
19. Gagliato Dde M, Gonzalez-Angulo AM, Lei X, Theriault RL, Giordano SH, Valero V, et al. Clinical impact of delaying initiation of adjuvant chemotherapy in patients with breast cancer. J Clin Oncol. 2014 Mar 10;32(8):735-44. PubMed PMID: 24470007. Pubmed Central PMCID: PMC3940536.
20. Hershman DL, Wang X, McBride R, Jacobson JS, Grann VR, Neugut AI. Delay of adjuvant chemotherapy initiation following breast cancer surgery among elderly women. Breast cancer research and treatment. 2006;99(3):313-21.
21. Hershman D, Hall MJ, Wang X, Jacobson JS, McBride R, Grann VR, et al. Timing of adjuvant chemotherapy initiation after surgery for stage III colon cancer. Cancer. 2006 Dec 1;107(11):2581-8. PubMed PMID: 17078055.
22. Cheung WY, Neville BA, Earle CC. Etiology of delays in the initiation of adjuvant chemotherapy and their impact on outcomes for Stage II and III rectal cancer. Dis Colon Rectum. 2009 Jun;52(6):1054-63; discussion 64. PubMed PMID: 19581846.
23. Bayraktar UD, Chen E, Bayraktar S, Sands LR, Marchetti F, Montero AJ, et al. Does delay of adjuvant chemotherapy impact survival in patients with resected stage II and III colon adenocarcinoma? Cancer. 2011 Jun 1;117(11):2364-70. PubMed PMID: 24048783.
24. Lima IS, Yasui Y, Scarfe A, Winget M. Association between receipt and timing of adjuvant chemotherapy and survival for patients with stage III colon cancer in Alberta, Canada. Cancer. 2011 Aug 15;117(16):3833-40. PubMed PMID: 21319156.
25. Becerra AZ, Aquina CT, Mohile SG, Tejani MA, Schymura MJ, Boscoe FP, et al. Variation in Delayed Time to Adjuvant Chemotherapy and Disease-Specific Survival in Stage III Colon Cancer Patients. Annals of surgical oncology. 2017 Jun;24(6):1610-7. PubMed PMID: 27738848.
26. Turner MC, Farrow NE, Rhodin KE, Sun Z, Adam MA, Mantyh CR, et al. Delay in Adjuvant Chemotherapy and Survival Advantage in Stage III Colon Cancer. J Am Coll Surg. 2018 Apr;226(4):670-8. PubMed PMID: 29378259.
27. Xu F, Rimm AA, Fu P, Krishnamurthi SS, Cooper GS. The impact of delayed chemotherapy on its completion and survival outcomes in stage II colon cancer patients. PLoS ONE. 2014;9(9):e107993. PubMed PMID: 25238395. Pubmed Central PMCID: PMC4169603.
28. Massarweh NN, Haynes AB, Chiang YJ, Chang GJ, You YN, Feig BW, et al. Adequacy of the National Quality Forum's Colon Cancer Adjuvant Chemotherapy Quality Metric: Is 4 Months Soon Enough? Ann Surg. 2015 Aug;262(2):312-20. PubMed PMID: 25185467. Pubmed Central PMCID: PMC4345158.
29. Booth CM, Shepherd FA, Peng Y, Darling G, Li G, Kong W, et al. Time to adjuvant chemotherapy and survival in non-small cell lung cancer: a population-based study. Cancer. 2013 Mar 15;119(6):1243-50. PubMed PMID: 23131995.
30. Salazar MC, Rosen JE, Wang Z, Arnold BN, Thomas DC, Herbst RS, et al. Association of Delayed Adjuvant Chemotherapy With Survival After Lung Cancer Surgery. JAMA oncology. 2017;3(5):610-9.
31. Hébert-Croteau N, Freeman CR, Latreille J, Rivard M, Brisson J. A population-based study of the impact of delaying radiotherapy after conservative surgery for breast cancer. Breast Cancer Res Treat. 2004 Nov;88(2):187-96. PubMed PMID: 15564801.
32. Jhawar S, Hathout L, Elshaikh MA, Beriwal S, Small W, Mahmoud O. Adjuvant Chemoradiation Therapy for Cervical Cancer and Effect of Timing and Duration on Treatment Outcome. International Journal of Radiation Oncology*Biology*Physics. 2017 2017/08//;98(5):1132-41. en.

33. Sharma S, Bekelman J, Lin A, Lukens JN, Roman BR, Mitra N, et al. Clinical impact of prolonged diagnosis to treatment interval (DTI) among patients with oropharyngeal squamous cell carcinoma. Oral Oncol. 2016 May;56:17-24. PubMed PMID: 27086482. Pubmed Central PMCID: PMC4968047.
34. Harris JP, Chen MM, Orosco RK, Sirjani D, Divi V, Hara W. Association of Survival With Shorter Time to Radiation Therapy After Surgery for US Patients With Head and Neck Cancer. JAMA Otolaryngol Head Neck Surg. 2018 Apr 1;144(4):349-59. PubMed PMID: 29522072. Pubmed Central PMCID: PMC5876822.
35. Chen YP, Mao YP, Zhang WN, Chen L, Tang LL, Li WF, et al. Prognostic value of wait time in nasopharyngeal carcinoma treated with intensity modulated radiotherapy: a propensity matched analysis. Oncotarget. 2016 Mar 22;7(12):14973-82. PubMed PMID: 26942870. Pubmed Central PMCID: PMC4924766.
36. Mujar M, Dahlui M, Yip CH, Taib NA. Delays in time to primary treatment after a diagnosis of breast cancer: does it impact survival? Preventive medicine. 2013;56(3-4):222-4.
37. Wanis KN, Patel SVB, Brackstone M. Do Moderate Surgical Treatment Delays Influence Survival in Colon Cancer? Diseases of the colon and rectum. 2017;60(12):1241-9.
38. Omarini C, Guaitoli G, Noventa S, Andreotti A, Gambini A, Palma E, et al. Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2017;43(4):613-8.
39. Cold S, During M, Ewertz M, Knoop A, Moller S. Does timing of adjuvant chemotherapy influence the prognosis after early breast cancer? Results of the Danish Breast Cancer Cooperative Group (DBCG). British journal of cancer. 2005;93(6):627-32.
40. Lohrisch C, Paltiel C, Gelmon K, Speers C, Taylor S, Barnett J, et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(30):4888-94.
41. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, Giordano SH. Delayed Initiation of Adjuvant Chemotherapy Among Patients With Breast Cancer. JAMA oncology. 2016;2(3):322-9.
42. Yu K-D, Fan L, Qiu L-X, Ling H, Jiang Y-Z, Shao Z-M. Influence of delayed initiation of adjuvant chemotherapy on breast cancer survival is subtype-dependent. Oncotarget. 2017;8(28):46549-56.
43. Ahmed S, Ahmad I, Zhu T, Arnold FP, Faiz Anan G, Sami A, et al. Early discontinuation but not the timing of adjuvant therapy affects survival of patients with high-risk colorectal cancer: a population-based study. Diseases of the colon and rectum. 2010;53(10):1432-8.
44. Czaykowski PM, Gill S, Kennecke HF, Gordon VL, Turner D. Adjuvant chemotherapy for stage III colon cancer: does timing matter? Diseases of the colon and rectum. 2011;54(9):1082-9.
45. Zeig-Owens R, Gershman ST, Knowlton R, Jacobson JS. Survival and time interval from surgery to start of chemotherapy among colon cancer patients. Journal of registry management. 2009;36(2):30-2.
46. Bos ACRK, van Erning FN, van Gestel YRBM, Creemers GJM, Punt CJA, van Oijen MGH, et al. Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer. European journal of cancer (Oxford, England : 1990). 2015;51(17):2553-61.
47. van Maaren MC, Bretveld RW, Jobsen JJ, Veenstra RK, Groothuis-Oudshoorn CG, Struikmans H, et al. The influence of timing of radiation therapy following breast-conserving surgery on 10-year disease-free survival. British journal of cancer. 2017;117(2):179-88.