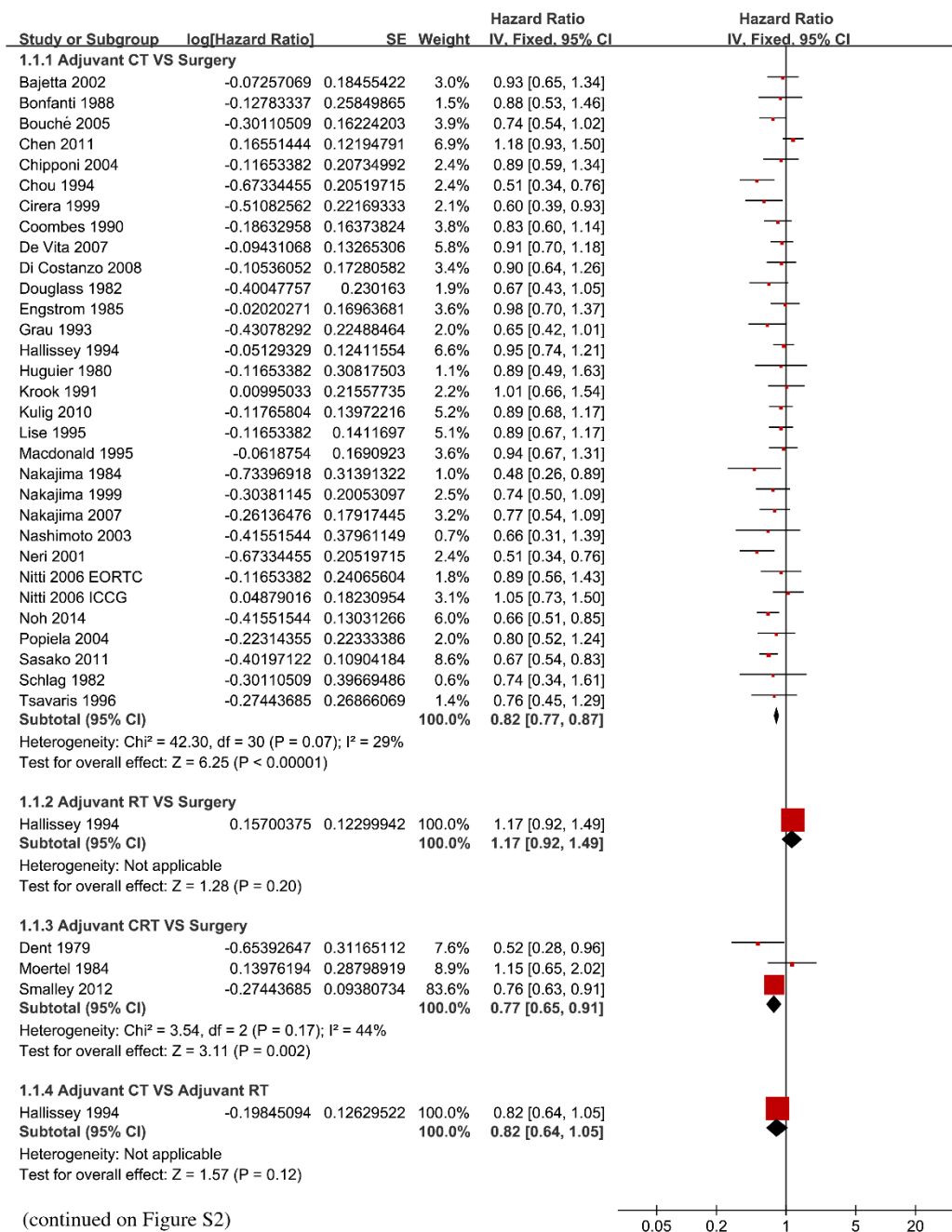
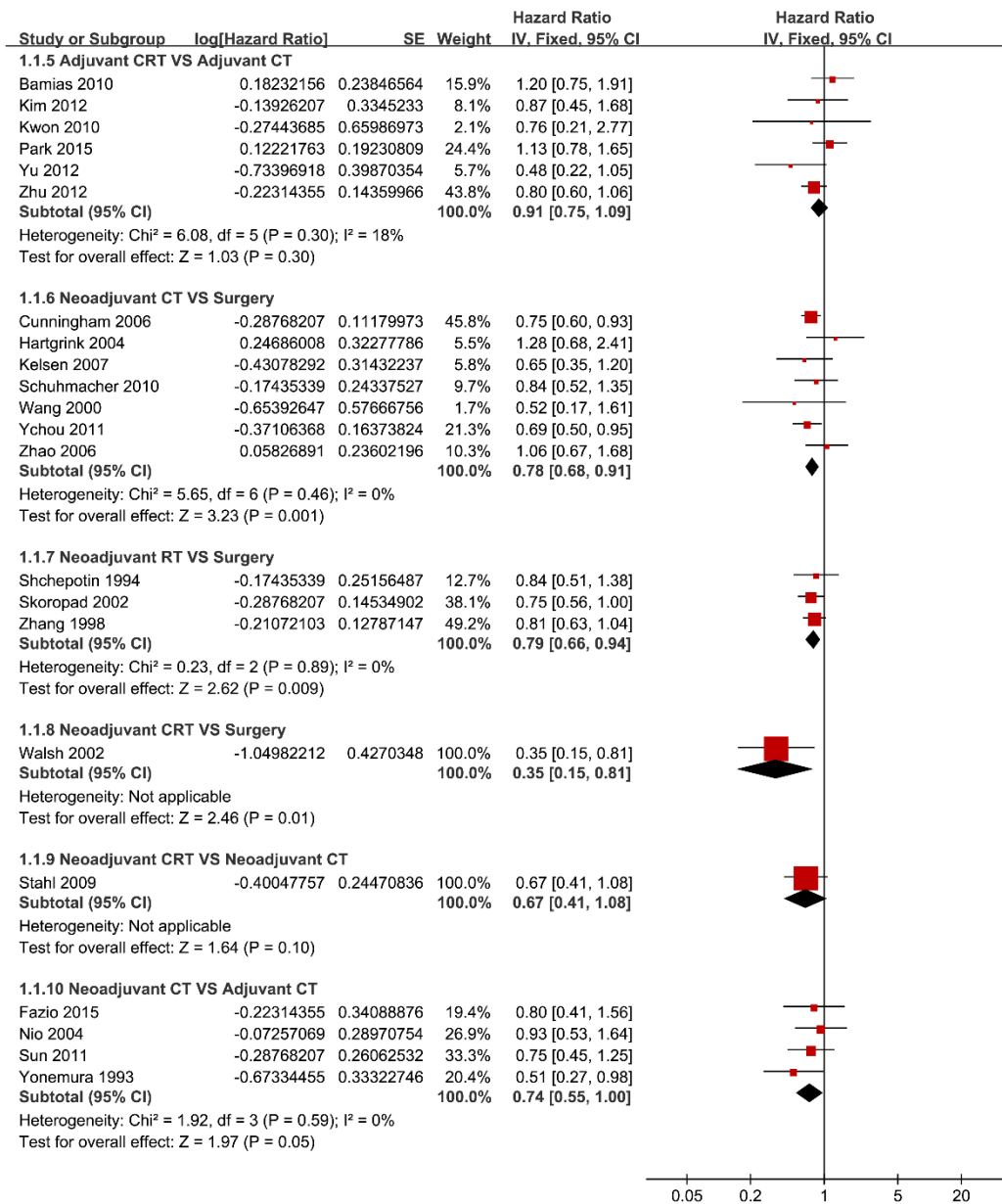


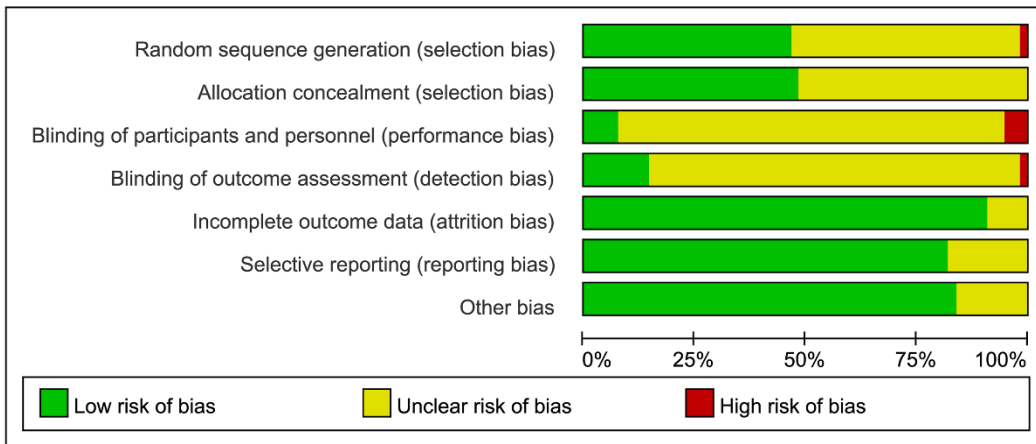
## Supplementary figures and figure legends:



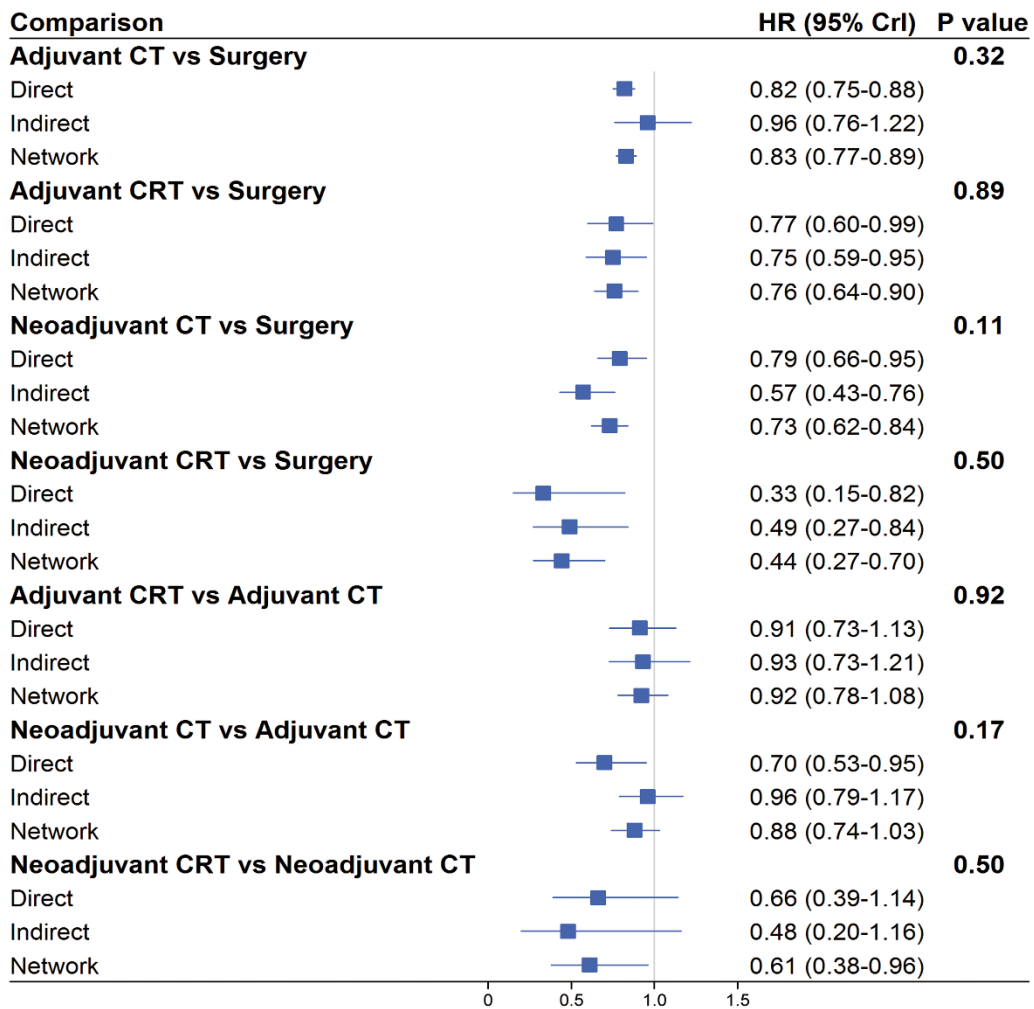
Supplementary Fig. S1 Pair-wise meta-analysis for overall survival.



Supplementary Fig. S2 Pair-wise meta-analysis for overall survival (continued).



Supplementary Fig. S3 Risk of bias graph for all studies included.



Supplementary Fig. S4 Consistency between direct and indirect comparisons with node-split models.

**Supplementary Table S1.** Characteristics of the included studies

| Study                             | Year | Region        | Chemotherapy  | Radiotherapy | Concurrent<br>Sequential | Lymph<br>node<br>resection | Intervention<br>Group Size | Control<br>Group Size | Median<br>follow-up<br>(Range), m |
|-----------------------------------|------|---------------|---|--------------|--------------------------|----------------------------|----------------------------|-----------------------|-----------------------------------|
| <b>Adjuvant CT versus Surgery</b> |      |               |   |              |                          |                            |                            |                       |                                   |
| Noh et al. [1]                    | 2014 | International | Capecitabine, oxaliplatin   | N/A          | N/A                      | D2                         | 520                        | 515                   | 62.4<br>(54–70)                   |
| Sasako et al. [2]                 | 2011 | Japan         | S-1   | N/A          | N/A                      | D2                         | 529                        | 530                   | 36                                |
| Chen et al. [3]                   | 2011 | China         | FAM group: fluorouracil,<br>doxorubicin, mitomycin;<br>FOLFOX group: oxaliplatin,<br>leucovorin, fluorouracil | N/A          | N/A                      | D2                         | 115                        | 153                   | 87<br>(25–216)                    |
| Kulig et al. [4]                  | 2010 | Poland        | Doxorubicin, cisplatin,<br>etoposide  | N/A          | N/A                      | D1–D3                      | 141                        | 154                   | 37<br>(31–51)                     |
| Di Costanzo et al. [5]            | 2008 | Italy         | Cisplatin, epirubicin,<br>leucovorin, fluorouracil  | N/A          | N/A                      | D1–D4                      | 130                        | 128                   | 73<br>(46.8–81.6)                 |
| Nakajima et al. [6]               | 2007 | Japan         | Uracil–tegafur  | N/A          | N/A                      | D2                         | 95                         | 95                    | 74.4                              |

|                             |      |        |  |     |     |             |     |     |                 |
|-----------------------------|------|--------|--|-----|-----|-------------|-----|-----|-----------------|
| De Vita et al. [7]          | 2007 | Italy  | Epirubicin, leucovorin,<br>fluorouracil, etoposide               | N/A | N/A | D1 at least | 112 | 113 | 60              |
| Nitti et al. (EORTC)<br>[8] | 2006 | Italy  | Methotrexate, fluorouracil,<br>leucovorin, adriamycin            | N/A | N/A | D2          | 103 | 103 | 79.2            |
| Nitti et al. (ICCG) [8]     | 2006 | Italy  | Fluorouracil, methotrexate,<br>leucovorin, epirubicin            | N/A | N/A | N/A         | 91  | 100 | 76.8            |
| Bouche et al. [9]           | 2005 | France | Fluorouracil, cisplatin  | N/A | N/A | D0–D2       | 127 | 133 | 97.8            |
| Chipponi et al. [10]        | 2004 | France | Leucovorin, fluorouracil,<br>cisplatin                           | N/A | N/A | D1, D2      | 101 | 104 | 101<br>(43–140) |
| Nashimoto et al. [11]       | 2003 | Japan  | Mitomycin, fluorouracil,<br>cytarabine                           | N/A | N/A | D2 mostly   | 127 | 123 | 69              |
| Bajetta et al. [12]         | 2002 | Italy  | Etoposide, adriamycin,<br>cisplatin, leucovorin,<br>fluorouracil | N/A | N/A | D2          | 137 | 137 | 66<br>(2–83)    |
| Neri et al. [13]            | 2001 | Italy  | Epidoxorubicin, leucovorin,<br>fluorouracil                      | N/A | N/A | N/A         | 69  | 68  | 31<br>(7–60)    |
| Cirera et al. [14]          | 1999 | Spain  | Mitomycin, tegafur   | N/A | N/A | N/A         | 76  | 72  | 37              |

|                       |      |               |   |     |     |     |     |     |              |
|-----------------------|------|---------------|---|-----|-----|-----|-----|-----|--------------|
|                       |      |               |   |     |     |     |     |     | (3–122)      |
| Nakajima et al. [15]  | 1999 | Japan         | Mitomycin, fluorouracil, uracil<br>plus tegafur | N/A | N/A | N/A | 288 | 285 | 72           |
| Macdonald et al. [16] | 1995 | USA           | Fluorouracil, doxorubicin,<br>mitomycin         | N/A | N/A | N/A | 93  | 100 | 114          |
| Lise et al. [17]      | 1995 | International | Fluorouracil, doxorubicin,<br>mitomycin         | N/A | N/A | N/A | 155 | 159 | 78           |
| Chou et al. [18]      | 1994 | Taiwan        | Ftorafur  | N/A | N/A | N/A | 59  | 56  | 27<br>(8–57) |
| Grau et al. [19]      | 1993 | Japan         | Mitomycin                                       | N/A | N/A | N/A | 68  | 66  | 105          |
| Krook et al. [20]     | 1991 | USA           | Fluorouracil, doxorubicin                       | N/A | N/A | N/A | 61  | 64  | 84           |
| Tsavaris et al. [21]  | 1996 | Greece        | Fluorouracil, epirubicin,<br>mitomycin          | N/A | N/A | N/A | 42  | 42  | 60           |
| Bonfanti et al. [22]  | 1988 | Italy         | Semustine, fluorouracil                         | N/A | N/A | N/A | 75  | 69  | 81           |
| Douglass et al. [23]  | 1982 | USA           | Semustine, fluorouracil                         | N/A | N/A | N/A | 71  | 71  | N/A          |
| Engstrom et al. [24]  | 1985 | International | Fluorouracil, semustine                         | N/A | N/A | N/A | 91  | 89  | 64           |
| Popiela et al. [25]   | 2004 | Poland        | Fluorouracil, adriamycin,                       | N/A | N/A | D2  | 53  | 52  | N/A          |

|                      |      |               |  |     |     |     |     |     |     |
|----------------------|------|---------------|--|-----|-----|-----|-----|-----|-----|
|                      |      |               | mitomycin  |     |     |     |     |     |     |
| Huguier et al. [26]  | 1980 | France        | Fluorouracil, vinblastine,<br>cyclophosphamide   | N/A | N/A | N/A | 27  | 26  | 60  |
| Coombes et al. [27]  | 1990 | International | Fluorouracil, adriamycin,<br>mitomycin           | N/A | N/A | N/A | 133 | 148 | 68  |
| Nakajima et al. [28] | 1984 | Japan         | Mitomycin, fluorouracil,<br>cytosine arabinoside | N/A | N/A | N/A | 149 | 74  | N/A |
| Schlag et al. [29]   | 1982 | Germany       | Fluorouracil, carmustine                         | N/A | N/A | N/A | 49  | 54  | N/A |
| Hallssey et al. [30] | 1994 | UK            | Mitomycin, doxorubicin,<br>fluorouracil          | N/A | N/A | N/A | 138 | 145 | 60  |

#### Adjuvant CRT versus Surgery

|                     |      |              |                          |  |            |       |     |     |       |
|---------------------|------|--------------|--------------------------|--|------------|-------|-----|-----|-------|
| Smalley et al. [31] | 2012 | USA          | Fluorouracil, leucovorin | 45 Gy in 25 fractions<br>for 5 weeks   | Concurrent | D0–D2 | 282 | 277 | 123.6 |
| Moertel et al. [32] | 1984 | USA          | Fluorouracil             | 37.5 Gy delivered over<br>4 to 5 weeks | Concurrent | N/A   | 39  | 23  | N/A   |
| Dent et al. [33]    | 1979 | South Africa | Fluorouracil             | 20 Gy in 8 fractions<br>over 10 days   | Concurrent | N/A   | 35  | 31  | N/A   |

| <b>Adjuvant RT versus Surgery</b>      |      |             |                          |                                       |            |        |     |     |                          |
|--|------|-------------|--------------------------|---------------------------------------|------------|--------|-----|-----|--------------------------|
| Hallissey et al. [30]                  | 1994 | UK          | N/A                      | 45 Gy in 25 fractions<br>over 35 days | N/A        | N/A    | 153 | 145 | 60                       |
| <b>Adjuvant CRT versus Adjuvant CT</b> |      |             |                          |                                       |            |        |     |     |                          |
| Park et al. [34]                       | 2015 | South Korea | Capecitabine, cisplatin  | 45 Gy in 25 fractions<br>over 5 weeks | Concurrent | D2     | 230 | 228 | 84                       |
| Zhu et al. [35]                        | 2012 | China       | Fluorouracil, leucovorin | 45 Gy in 25 fractions<br>for 5 weeks  | Concurrent | D2     | 186 | 165 | 42.5                     |
| Kim et al. [36]                        | 2012 | South Korea | Fluorouracil, leucovorin | 45 Gy in 25 fractions<br>for 5 weeks  | Concurrent | D2     | 46  | 44  | 86.7<br>(60.3–<br>116.5) |
| Yu et al. [37]                         | 2012 | China       | Fluorouracil, leucovorin | 45 Gy in 25 fractions<br>for 5 weeks  | Concurrent | D1, D2 | 34  | 34  | 36                       |
| Kwon et al. [38]                       | 2010 | South Korea | Fluorouracil, cisplatin  | 45 Gy in 25 fractions<br>over 5 weeks | Concurrent | D2     | 31  | 30  | 77.2<br>(24–92.8)        |
| Bamias et al. [39]                     | 2010 | Greece      | Docetaxel, cisplatin     | 45 Gy in 25 fractions<br>for 5 weeks  | Sequential | D0–D2  | 72  | 71  | 53.7<br>(1–77.8)         |



| <b>Neoadjuvant RT versus Surgery</b>         |      |         |  |                                       |            |        |     |     |                 |
|--|------|---------|--|---------------------------------------|------------|--------|-----|-----|-----------------|
| Skoropad et al. [40]                         | 2002 | Russia  | N/A                                    | 20 Gy in 5 fractions<br>for 5 days    | N/A        | N/A    | 51  | 51  | N/A             |
| Zhang et al. [41]                            | 1998 | China   | N/A                                    | 40 Gy in 20 fractions<br>for 4 weeks  | N/A        | N/A    | 153 | 158 | 128<br>(89–192) |
| Shchepotin et al. [42]                       | 1994 | Ukrain  | N/A                                    | 20 Gy in 4 fractions<br>for 4 days    | N/A        | N/A    | 98  | 100 | N/A             |
| <b>Neoadjuvant CRT versus Surgery</b>        |      |         |  |                                       |            |        |     |     |                 |
| Walsh et al. [43]                            | 2002 | Ireland | Fluorouracil, cisplatin                | 40 Gy in 15 fractions<br>over 2 weeks | Concurrent | N/A    | 16  | 23  | 60              |
| <b>Neoadjuvant CRT versus Neoadjuvant CT</b> |      |         |  |                                       |            |        |     |     |                 |
| Stahl et al. [44]                            | 2009 | Germany | Fluorouracil, leucovorin,<br>cisplatin | 30 Gy in 15 fractions<br>for 3 weeks  | Concurrent | D2     | 60  | 59  | 46              |
| <b>Neoadjuvant CT versus Surgery</b>         |      |         |  |                                       |            |        |     |     |                 |
| Ychou et al. [45]                            | 2011 | France  | Fluorouracil, cisplatin                | N/A                                   | N/A        | D2     | 113 | 111 | 25              |
| Cunningham et al.<br>[46]                    | 2006 | UK      | Epirubicin, cisplatin,<br>fluorouracil | N/A                                   | N/A        | D1, D2 | 250 | 253 | 49              |

|                         |      |               |   |     |     |           |    |    |                |
|-------------------------|------|---------------|---|-----|-----|-----------|----|----|----------------|
| Schuhmacher et al. [47] | 2010 | International | Cisplatin, folinic acid, fluorouracil                       | N/A | N/A | D2 mostly | 72 | 72 | 52.8           |
| Hartgrink et al. [48]   | 2004 | Netherlands   | Methotrexate, leucovorin, doxorubicin                       | N/A | N/A | D1        | 29 | 30 | 83<br>(51–102) |
| Wang et al. [49]        | 2000 | China         | FPLC, fluorouracil  | N/A | N/A | N/A       | 30 | 30 | 60             |
| Zhao et al. [50]        | 2006 | China         | Group 1: 5'-DFUR<br>Group 2: fluorouracil, calcium folinate | N/A | N/A | N/A       | 34 | 20 | N/A            |
| Kelsen et al. [51]      | 2007 | International | Cisplatin, fluorouracil                                     | N/A | N/A | N/A       | 47 | 46 | (93.6–156)     |

#### Neoadjuvant CT versus Adjuvant CT

|                      |      |               |   |     |     |       |     |     |                |
|----------------------|------|---------------|---|-----|-----|-------|-----|-----|----------------|
| Yonemura et al. [52] | 1993 | Japan         | Cisplatin, mitomycin, etoposide, uracil | N/A | N/A | N/A   | 23  | 23  | 24<br>(6–42)   |
| Nio et al. [53]      | 2004 | Japan         | Uracil                                  | N/A | N/A | D0–D3 | 102 | 193 | 83<br>(37–140) |
| Sun et al. [54]      | 2011 | China         | Docetaxel, fluorouracil, leucovorin     | N/A | N/A | N/A   | 29  | 26  | N/A            |
| Fazio et al. [55]    | 2015 | International | Docetaxel, cisplatin,                   | N/A | N/A | D2    | 34  | 35  | N/A            |

|  |  |  |              |  |  |  |  |  |  |
|--|--|--|--------------|--|--|--|--|--|--|
|  |  |  | fluorouracil |  |  |  |  |  |  |
|--|--|--|--------------|--|--|--|--|--|--|

*CT* chemotherapy, *RT* radiotherapy, *CRT* chemoradiotherapy, *N/A* not available

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**Supplementary Table S2.** Main clinicopathologic characteristics of the enrolled patients in the included studies

| Study                    | Mean age<br>(years) | Sex  |        | Tumor stage |     |     |    | Nodal status |     |     |    | UICC/AJCC<br>stage |
|--------------------------|---------------------|------|--------|-------------|-----|-----|----|--------------|-----|-----|----|--------------------|
|                          |                     | Male | Female | T1          | T2  | T3  | T4 | N0           | N1  | N2  | N3 |                    |
| Noh et al. [1]           | 56                  | 731  | 304    | 11          | 564 | 456 | 4  | 103          | 621 | 311 | 0  | IB-IV              |
| Sasako et al. [2]        | 63                  | 736  | 323    | 1           | 575 | 457 | 26 | 115          | 577 | 367 | 0  | IB-IV              |
| Chen et al. [3]          | 56                  | 183  | 85     | 0           | 80  | 198 | 0  | 198          | 80  | 0   | 0  | IIA                |
| Kulig et al. [4]         | 61                  | 211  | 84     | 6           | 67  | 140 | 82 | 91           | 80  | 85  | 39 | IB-IV              |
| Di Costanzo et al. [5]   | 59                  | 157  | 101    | NA          | NA  | 124 | 14 | 42           | 213 |     |    | I-IV               |
| Nakajima et al. [6]      | 63                  | 143  | 45     | 0           | 188 | 0   | 0  | 0            | 141 | 47  | 0  | II                 |
| De Vita et al. [7]       | 63                  | 131  | 94     | 8           | 37  | 142 | 38 | 62           | 77  | 86  | 0  | IB-III B           |
| Nitti et al. (EORTC) [8] | 56                  | 127  | 79     | 17          | 68  | 114 | 7  | 39           | 83  | 84  | 0  | IB-III B           |

|                         |    |     |     |     |     |     |    |     |     |    |    |        |
|-------------------------|----|-----|-----|-----|-----|-----|----|-----|-----|----|----|--------|
| Nitti et al. (ICCG) [8] | 54 | 125 | 66  | 6   | 61  | 107 | 17 | 34  | 82  | 75 | 0  | IB-IV  |
| Bouche et al. [9]       | 61 | 186 | 74  | 59  |     | 288 | 10 | 43  | 138 | 48 | 21 | II-IV  |
| Chipponi et al. [10]    | 61 | 129 | 67  | NA  | NA  | NA  | NA | 33  | 163 |    |    | NA     |
| Nashimoto et al. [11]   | 58 | 169 | 81  | 74  | 155 | 21  | 0  | 139 | 80  | 31 | NA | I-III  |
| Bajetta et al. [12]     | 57 | 174 | 97  | 128 |     | 143 |    | 27  | 244 |    |    | I-III  |
| Neri et al. [13]        | 69 | 98  | 39  | 3   | 15  | 64  | 65 | 0   | 65  | 72 | 0  | NA     |
| Cirera et al. [14]      | 61 | 94  | 54  | 3   | 11  | 39  | 95 | 20  | 57  | 71 | 0  | III    |
| Nakajima et al. [15]    | NA | 363 | 210 | 188 | 323 | 62  | 0  | 237 | 286 | 46 | 4  | NA     |
| Macdonald et al. [16]   | 59 | 123 | 70  | NA  | NA  | NA  | NA | NA  | NA  | NA | NA | I-III  |
| Lise et al. [17]        | NA | 202 | 112 | 12  | 126 | 144 | 29 | NA  | NA  | NA | NA | II-III |
| Chou et al. [18]        | NA | 67  | 48  | NA  | NA  | NA  | NA | NA  | NA  | NA | NA | II-III |
| Grau et al. [19]        | 56 | 88  | 46  | 4   | 21  | 109 | 0  | 51  | 54  | 29 | 0  | NA     |
| Krook et al. [20]       | 63 | 98  | 27  | NA  | NA  | NA  | NA | NA  | NA  | NA | NA | NA     |
| Tsavaris et al. [21]    | 53 | 57  | 27  | NA  | NA  | NA  | NA | NA  | NA  | NA | NA | III    |
| Bonfanti et al. [22]    | NA | 138 | 75  | 40  | 70  | 103 |    | 89  | 124 |    |    | NA     |
| Douglass et al. [23]    | NA | 100 | 42  | NA  | NA  | NA  | NA | 54  | 88  |    |    | NA     |
| Engstrom et al. [24]    | NA | 120 | 60  | NA  | NA  | NA  | NA | NA  | NA  | NA | NA | NA     |

|                       |    |     |     |     |    |     |    |    |     |     |    |        |
|-----------------------|----|-----|-----|-----|----|-----|----|----|-----|-----|----|--------|
| Popiela et al. [25]   | 58 | 74  | 31  | 0   | 80 |     | 25 | 0  | 62  | 43  | 0  | III-IV |
| Huguier et al. [26]   | 60 | 38  | 15  | NA  | NA | NA  | NA | NA | NA  | NA  | NA | NA     |
| Coombes et al. [27]   | NA | NA  | NA  | 13  | 97 | 124 | 45 | 89 | 119 | 62  | 8  | II-III |
| Nakajima et al. [28]  | NA | 141 | 82  | NA  | NA | NA  | NA | 91 | 108 | 86  | 15 | I-IV   |
| Schlag et al. [29]    | 59 | 63  | 40  | NA  | NA | NA  | NA | NA | NA  | NA  | NA | II-III |
| Hallissey et al. [30] | 64 | 303 | 133 | NA  | NA | NA  | NA | NA | NA  | NA  | NA | II-III |
| Smalley et al. [31]   | 60 | 397 | 159 | 172 |    | 342 | 42 | 83 | 231 | 242 | 0  | IB-IV  |
| Moertel et al. [32]   | 58 | 46  | 16  | NA  | NA | NA  | NA | NA | NA  | NA  | NA | NA     |
| Dent et al. [33]      | NA | NA  | NA  | 4   | 8  | 46  | 0  | 22 | 9   | 27  | 0  | NA     |
| Park et al. [34]      | 56 | 296 | 162 | NA  | NA | NA  | NA | 62 | 253 | 101 | 42 | IB-IV  |
| Zhu et al. [35]       | 56 | 261 | 90  | 0   | 0  | 351 |    | 50 | 104 | 123 | 74 | IB-IV  |
| Kim et al. [36]       | NA | 59  | 31  | 0   | 33 | 51  | 6  | 2  | 25  | 43  | 20 | III-IV |
| Yu et al. [37]        | 56 | 43  | 25  | 0   | 7  | 42  | 19 | 0  | 40  | 28  | 0  | II-III |
| Kwon et al. [38]      | 56 | 44  | 17  | NA  | NA | NA  | NA | NA | NA  | NA  | NA | III-IV |
| Bamias et al. [39]    | NA | 100 | 43  | 4   | 26 | 107 | 6  | 17 | 74  | 40  | 11 | IB-IV  |
| Skoropad et al. [40]  | 55 | 74  | 28  | 11  | 27 | 58  | 6  | 48 | 37  | 15  | 2  | I-IV   |
| Zhang et al. [41]     | 56 | NA  | NA  | NA  | NA | NA  | NA | NA | NA  | NA  | NA | I-IV   |

|                         |    |     |     |    |    |     |    |    |     |    |    |        |
|-------------------------|----|-----|-----|----|----|-----|----|----|-----|----|----|--------|
| Shchepotin et al. [42]  | 55 | NA  | NA  | 0  | 6  | 127 | 65 | 71 | 121 |    | 0  | NA     |
| Walsh et al. [43]       | NA | NA  | NA  | NA | NA | NA  | NA | NA | NA  | NA | NA | NA     |
| Stahl et al. [44]       | 60 | 108 | 11  | 0  | 0  | 109 | 10 | NA | NA  | NA | NA | NA     |
| Ychou et al. [45]       | 63 | 187 | 37  | NA | NA | NA  | NA | NA | NA  | NA | NA | NA     |
| Cunningham et al. [46]  | 62 | 396 | 107 | NA | NA | NA  | NA | NA | NA  | NA | NA | NA     |
| Schuhmacher et al. [47] | 57 | 100 | 44  | 0  | 0  | 135 | 9  | 10 | 92  | 11 | 2  | III-IV |
| Hartgrink et al. [48]   | 60 | NA  | NA  | NA | NA | NA  | NA | NA | NA  | NA | NA | II-III |
| Wang et al. [49]        | 54 | 50  | 10  | NA | NA | NA  | NA | NA | NA  | NA | NA | NA     |
| Zhao et al. [50]        | NA | NA  | NA  | NA | NA | NA  | NA | NA | NA  | NA | NA | NA     |
| Kelsen et al. [51]      | 62 | NA  | NA  | NA | NA | NA  | NA | NA | NA  | NA | NA | NA     |
| Yonemura et al. [52]    | 64 | 41  | 14  | NA | NA | NA  | NA | NA | NA  | NA | NA | IV     |
| Nio et al. [53]         | 64 | 211 | 84  | NA | NA | NA  | NA | NA | NA  | NA | NA | I-IV   |
| Sun et al. [54]         | 52 | 37  | 18  | NA | NA | NA  | NA | NA | NA  | NA | NA | NA     |
| Fazio et al. [55]       | 57 | 47  | 22  | NA | NA | NA  | NA | NA | NA  | NA | NA | IB-IV  |

NA, not available