Appendix table 6. Characteristics and treatments of non-randomized clinical trials

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ID | (Trial) | Journal | Study design | Reviewed period | Sample size | Median  follow-up | Age | PS | Gender (Male%) | Surgery | TRT | Chemo | PCI or not |
| Retrospective studies | | | | | | | | | | | | | |
| 28 | Bang, 2018(1) | Int J Radiat Oncol Biol Phys | ED-SCLC, without baseline BM, at least PR to chemo:  PCI vs  no PCI | 01-01-2005 ~  31-12-2011 | 397 screened  155 eligible | NI | 66 (43-89); | 0: 13/155 (8.4%); 1: 86/155 (55.5%); 2: 31/155 (20%); 3: 23/155 (14.8%); 4: 2/155 (1.3%); | 57.4% | NI | PCI: 62%; No PCI: 55%; (P=0.40) | Yes | PCI: 68  No PCI: 87 |
| 34 | Bernhardt, 2017(2) | Clin Lung Cancer | ED-SCLC, PCI | 2007 ~ 2015 | 136 | NI | 62 (45-86); | KPS:  80 (50-100) | 85/136 (62.5%) | NI | NI | Yes | Yes |
| 52 | Brewster, 1995(3) | Radiother Oncol | LD-SCLC,  PCI 8Gy | 07.1986 - 03.1989. | 106; patients with CR:73. | ≥ 24 months | 58 | NI | 59/106 (55.7%) | NI | 12.5Gy, 1f | Yes | Yes |
| 80 | Chen, 2016(4) | Strahlenther Onkol | ED-SCLC, without baseline BM, at least PR to chemo:  PCI vs no PCI | 04.2005 - 05.2014 | 204 | 11.2 months (range 2.9–71.7 months). | 58 (IQR 52–63). | 0: 71/204 (34.8%); 1: 124/204 (60.8%); 2: 9/204 (4.4%); | 171/204 (83.8%) | NI | NI | Yes | Yes: 45/204 (22.1%) |
| 81 | Chen, 2018(5) | Strahlenther Onkol | ED-SCLC:  Early vs late PCI | 11.2011 - 07.2016 | 103 | 12 months (range: 3–36 months). | 59 (IQR: 53–65) | 0: 37/103 (35.9%); 1: 61/103 (59.2%); 2: 5/103 (4.9%); | 89/103 | NI | Yes | Yes | Yes: 59/103 (57.3%) |
| 82 | Choi, 2017(6) | Clin Lung Cancer | LD-SCLC with PET-CT or not:  PCI vs no PCI | 04.2001 ~ 04.2013 | 1423 screened,  280 eligible | NI | <60: 103/280 (36.8%); 60-70: 129/280 (46.1%); ≥70 years: 48/280 (17.1%). | 0: 54/280 (19.3%); 1: 213/280 (76.1%); 2: 13/280 (4.6%). | 247/280 (88.2%) | NI | Yes | Yes | PCI: 90/280 ( %); No PCI: 190/280( %) |
| 86 | Chu, 2019(7) | Radiat Oncol | risk factors for pre-PCI BM | 2011-2017 | 283 screened, 110 eligible | For OS: 22.7 months (range 6.4– 92.0months); For BM: 5.2 months (range 2.8–9.2 months). | 38-79 | NI | 95/110 (86.4%) | NI | Yes: CCRT: 93/110; SCRT: 17/110 | Yes | No |
| 108 | El Sharouni, 2009(8) | Anticancer Res | LD-SCLC: SCRT vs CCRT; | 1996-2005 | 151 eligible,  16 lost to follow-up:  SCRT: 95; CCRT:40.  SCRT+PCI: 67; CCRT+PCI: 23 | NI | 32-81.7 | NI | 94/151 (62.3%) | NI | Yes | Yes | Yes |
| 112 | Eze, 2017(9) | Clin Lung Cancer | LD-SCLC with MRI:  PCI vs no PCI | 1998 ~ 2012 | 184 eligible | NI | 63 (34-83). | median: 1 (range, 0-3). | 111/184 (60%) | NI | Yes | Yes | PCI: 71/184 (39%); No PCI: 113/184 (61%) |
| 115 | Farooqi, 2017(10) | Radiother Oncol | LS-SCLC:  PCI vs no PCI | 1986 ~ 2012 | 658  (PCI: 364; No PCI: 294) | 21.2 months (range 1.2–240.8 months) | 62 (27–95); ≥70 years: 151/668 (22.9%). | KPS: ≥ 80: 550/658 (83.6%); < 80: 108/658 (16.4%) | 342/658 (52.0%) | No | Yes | Yes | PCI: 364 (55.3%);  No PCI: 294 (44.7%) |
| 134 | Giuliani, 2010(11) | Cancer | LD-SCLC:  PCI vs no PCI | 1997 ~ 2007 | 796 screened, 207 analyzed | 18.8 months (range, 2.2-130.1 months). | 65.7  (38.6- 88.1). | NI | 111/207 (53.6%) | NI | 4005 cGy / 15 fractions | Yes | PCI: 127/207(61.4%) No PCI: 80/207(38.6%) |
| 139 | Gong, 2013(12) | Int J Radiat Oncol Biol Phys | SCLC with surgery | 01.1998 - 12.2009 | 126 eligible | NI | 59 (28–79). | NI | 91/126 (72.2%) | Yes | Yes: 50/126 (39.7%) | Induction: 51/126 (40.5%); adjuvant: 112/126 (88.9%) | No |
| 145 | Greenspoon, 2011(13) | J Thorac Oncol | risk factors for BM in ED-SCLC | 01.01.2004 - 31.12.2006 | 130,  101 without baseline BM | NI | NI | 0: 3/130 (2.3%);  1: 49/130 (37.7%); 2: 48/130 (36.9%);  3: 21/130 (16.2%);  4: 9/130 (6.9%). | 66/130 (50.8%) | Yes: 111/130 (85.4%) | NI | NI | No |
| 203 | Kim, 2019(14) | J Radiat Res | LD-SCLC:  PCI vs no PCI | 11.1994 ~ 06.2010 | 320 screened,  235 analyzed | 22 months (range 1–150 months). | 61 (34–77). | 0: 29; 1-2: 205 | 204/234 (87%) | NI | Yes | Yes | PCI: 139/234 (59.4%); No PCI: 95/234 (40.6%) |
| 263 (264) | Manapov, 2012(15)  (Manapov, 2012(16)) | Strahlenther Onkol  ( J Neurooncol) | LD-SCLC, PS 2-3 | 1997-2008 | 149, 125 completed CRT: SCRT: 51/125 (41%); CCRT:74/125(59%) | NI | Median: 63.2 | 2 (2-3) | 78/125(62%) | NI | Yes | Yes | CCRT: 16 (31%);  SCRT: 20 (27%). |
| 265 | Manapov, 2013(17) | Tumori | LD-SCLC | 1998-2007 | 125: SCRT: 51/125 (41%); CCRT:74/125(59%) | 448 days (range, 35-3432). | Median: 63 | 2 (1-3) | 78/125(62%) | NI | Yes | Yes | 36/125 (29%) patients who achieved a CR. |
| 303 | Nakamura, 2018(18) | J Radiat Res | LD-SCLC:  PCI vs no PCI | 01.2006~ 12.2014 | 162 analyzed | 38 months (range, 6–105 months). | 67.5 (23–85) | 0: 71 (44%); 1-2: 91 (56%) | 130 (80%) | NI | Yes (45Gy/bid, or 50Gy/qd) | Yes | PCI: 93/162 (57%); No PCI: 69/162 (43%) |
| 312 | Nicholls, 2016(19) | Asia Pac J Clin Oncol | SCLC:  PCI vs no PCI | 01.2008 - 12.2013 | 203 | 7.6 months (range 0.5–76.5) | 65.4 (±10.7) | 0: 50/203 (24.6%); 1: 91/203 (44.8%); 2: 34/203(16.7%); 3: 19/203 (9.4%); 4: 3/203(1.5%); | 160/203 (79%) | NI | LD: Yes: 55/74;  ED: Yes: 63/129; | LD: Yes: 55/74;  ED: Yes: 101/129; | LD: 32/74 (43.2%); ED: 17/129 (13.1%) |
| 342 | Pezzi, 2020(20) | JAMA Netw Open | LD-SCLC with MRI:  PCI vs no PCI | 1992 ~ 2012 | 297 eligible,  168 matched | PCI: 83.64 months;  no-PCI group: 83.97 months | Before matching:  PCI: 62.2 years (range, 27.0-85.0 years); No PCI: 68.6 years (range, 40.0-86.0 years).  After matching:  PCI: 65.0 (44.0-85.0) No PCI: 67.5 (40.0-86.0) | before matching:  0: 72/297 (24.2%); 1: 189 /297 (63.6%); 2: 30/297 (10.1%); 3: 6/ 297 (2.0%).  after matching:  0: 38/168 (22.6%); 1: 105 /168 (62.5%); 2: 21/168 (12.5%); 3: 4/ 168 (2.4%). | before matching: 162/297 (54.5%); after matching: 96/168 (57.1%) | NI | Yes | Yes | before matching: PCI: 205/297(69%); No PCI: 92/297(31%);  after matching: PCI: 84/168 (50%) No PCI: 84/168 (50%) |
| 356 | Ramlov, 2012(21) | Lung Cancer | SCLC with PCI | 01.2007 ~ 08.2010 | 118 | All patients: 16.6 months (range 3–54 months); alive patients: 33 months (20–54 months) | 65 (46–80). | NI | 51/118 (43.2%) | Yes: 7/118 (6%) | Yes: 65/118 (53.4%) | Yes: 111/118 | Yes |
| 368 | Roengvoraphoj, 2017(22) | Strahlenther Onkol | LD-SCLC with CRT:  Male vs female | 1998 - 2012 | 179 | NI | 63 (range, 35–83) | 1 (range, 0–3) | 110/179 (61.5 %) | NI | Yes | Yes | Yes: 70/179 (39%) |
| 371 | Rubenstein, 1995(23) | Int J Radiat Oncol Biol Phys | LD-SCLC:  PCI vs no PCI | 06.1986 ~  12.1992 | 197 analyzed | mean:19 months, median:11.5 months (range, 1.1 - 89.8 months) | mean: 66 (range, 33 - 86) | Baseline KPS:  ≤80: 79 (41.8%); >80: 110 (58.2%). Pre-RT KPS: ≤80: 70 (37.0%); >80: 119 (63.0%). | NI | 10 (5.1%) | Yes: 195/197 (99%) | Yes | PCI: 112/197 (56.9%); No PCI: 69/197 (43.1%) |
| 376 | Sahmoun, 2004(24) | Anticancer Res | SCLC without PCI: Risk factors for BM in SCLC:  HT vs no HT | 06.1986 - 06.2003 | 232 screened, 185 eligible | NI | 67 (44-89); | NI | 130/185 (70%) | NI | NI | NI | No |
| 377 | Sahmoun, 2005(25) | Anticancer Res | Risk factors for BM and OS in SCLC:  Site, gender | 01.1989 - 12.2002 | 230 eligible, 209 without baseline BM | NI | 67 (41-89); | NI | 148/230 (64%) | NI | Yes: 134/230 | Yes: 182/230 | Yes: 12/209 (5.7%) |
| 384 | Sas-Korczyńska, 2010(26) | Strahlenther Onkol | LD-SCLC:  Early PCI vs Late PCI | 1995 - 2004 | 129 | 19 months (range: 4-135 months) | 57 (33-73) (Mean: 56.02) | 80 (60-90) | 83/129 (64.3%) | NI | Yes, CCRT | Yes | Yes: 86/129, 66.7%; (Early: 41/86. 47.7%; late: 45/86, 52.3%) |
| 393 | Scotti, 2014(27) | Tumori | TRT timing in LD-SCLC | 06.2000 - 05.2010 | 124:  CCRT: 53/124 (42.8%); SCRT: 71/124 (57.2%) | 2.2 years (range, 0.2-12.4) | ≤ 55: 34/124 (27.4%); 56-65: 42/124 (33.9%); ≥ 66: 48/124 (38.7%) | 0: 95/124 (76.6%); 1: 29/124 (23.4%) | 101/124 (81.5%) | NI | Yes | Yes | Yes: 38/124 (25.9%) |
| 439 | Suzuki, 2018(28) | Radiother Oncol | Risk factors for BM in SCLC:  Hematologic variables | 2001–2015 | 293 | 14.3 months  (IQR: 9.3–22.8 months) | 64 years (IQR, 58–71 years) | 0–1: 239/293 (82%) | 48% | No | ≥ 45 Gy: 200/293 (68%) | yes | Yes: 125/293 (43%) |
| 441 | Tai, 2013(29) | Clin Lung Cancer | LD-SCLC:  PCI vs  no PCI | 1981 ~ 2007 | 289 analyzed | NI | 65 years (range, 38-86 years) | NI | 168/289 (58.1%) | NI | Yes | Yes | PCI: 177/289 (61.2%); |
| 461 | van der Linden, 2001(30) | Respir Med | LD-SCLC with CR:  PCI vs  no PCI | 01.1985 ~ 10.1994 | 135 screened,  102 analyzed | 17 months (range 7 - 117 months) | NI | NI | NI | 9/135 | yes: 67/102 (65.7%): PCI: 55/65; No PCI: 12/37. | Yes | PCI: 65/102; No PCI: ˆ37/102. |
| 491 | Wu, 2017(31) | Radiother Oncol | LD-SCLC,  TNM vs BM | 1993-2013 | 333 screened, 283 eligible | 21.4 months | NI | KPS: ≥ 80: 241/283 (85.2%);  < 80: 42/283 (14.8%) | 127/283 (44.9%) | Yes: 69/283 (24.4%) | Yes: 236/283 (83.4%) | Yes: 264/283 (93.3%) | Yes: 116/283 (41.0%) |
| 493 | Xu, 2017(32) | J Thorac Oncol | Resected SCLC:  PCI vs  no PCI | 01.2006 ~ 01.2014 | 438 screened,  349 eligible | NI | median: NI (range, 38–79); <60 years: 155/349 (44.4%) ≥60 years: 194/349 (55.6%). | NI | 337/389 (85.1%) | Yes, all | yes: 229 (65.6%); median: 52 Gy (range 30–80 Gy). | Yes: 321 (92%); No: 28 (8.0%) | PCI: 115/349; No PCI: 234/349 |
| 513 | Zeng, 2019(33) | JAMA Netw Open | SCLC, with TRT, chemo, and PCI:  TDRT vs ODRT | 01-07-2003 ~  30-6-2016 | 894 screened,  778 eligible,  338 matched (1:1 PSM) | 23.6 months (interquartile range, 14.2-38.2 months), | 55 (interquartile range, 48-61), | 0: 127/778(16.3%); 1: 624/778(80.2%); 2: 27/778 (3.5%) | 574/778 (73.8%) | Yes: 44 (5.7%) | ODRT: 609/778 (78.3%); TDRT: 169/778 (21.7%) | Yes | Yes |
| 514 | Zeng, 2017(34) | Sci Rep | SCLC with PCI:  Risk factors for BM | 2003 ~  2014 | 204 screened, 175 eligible | 42.1 months (range, 7.4–119.4) | 55 (29-76) | 0: 10/175(5.7%); 1: 162/175(92.6%); 2: 3/175(1.7%) | 129/175 (73.7%) | NI | ODRT: 123/175; TDRT: 46/175 | Yes | Yes |
| 519 | Zheng, 2018(35) | Strahlenther Onkol | LD-SCLC without PCI:  Risk factors for BM | 01.2010 ~ 12.2016 | 153 | 42.5 months (range, 5.8–93.2 months). | 59 (23–80); | 0: 64/153 (41.8%); 1: 75/153 (49.0%); 2: 6/153 (3.9%) | 104/153 (68%) | NI | ODRT (mean: 56.9Gy, range:50–66Gy): 120; TDRT (45Gy/ bid): 19 | Yes | No |
| 520 | Zhu, 2014(36) | Radiat Oncol | Resected SCLC:  Risk factors for BM | 01.2003 ~ 12.2009 | 211 screened,  126 eligible | 56.0 months (range, 30.4–96.8 months). | 55 (34–74); <65 years: 91/126 (72.2%); ≥65 years: 35/126 (27.8%). | KPS: ≥ 80: 80/126 (64.0%);   < 80: 46/126 (36.0%) | 101/126 (80.2%) | Yes, all | yes:55/126; 50–60 Gy | yes | No |
| 521 | Zhu, 2014(37) | Lung Cancer | Resected SCLC:  PCI vs no PCI | 01.2003 ~ 12.2009 | 211 screened,  193 eligible | All: 39.4 months (range,4.0–96.8 months); surviving patients: 52.7 months (range,30.4–96.8 months). | 56 (34-78); <65 years: 143/193 (74.1%); ≥65 years: 50/193 (25.9%). | KPS:  ≥ 80: 126/193 (65.3%);  < 80: 67/193 (34.7%) | 150/193 (77.7%) | Yes, all | Yes: 94/193; 50–60 Gy | Yes | PCI: 67/193; No PCI: 126/193 |
|  | Prospective observation studies | | |  |  |  |  |  |  |  |  |  |  |
| 397 | Seute, 2004(38) | Cancer | SCLC,  Observe neurologic disorders | 10.1980 -  09. 2001 | 432 (11 were diagnosed SCLC with BM at autopsy) | NI | 66 (32–89) | NI | 347/432 (80.3%) | NI | occasionally applied | yes | 45/432 (10.4%) |
| 122 | Fu, 2014(39) | Jpn J Clin Oncol | SCLC with PCI | 11.2006 -02.2010 | 129 enrolled, 112 eligible | 25 months (5–66 months) | 58.5 years (IQR 49–69 years) | NI | NI | NI | Yes | Yes | Yes |
| *Abbreviations:* BM, brain metastasis; CCRT, concurrent chemoradiotherapy; chemo, chemotherapy; CR, complete response; CRT, chemoradiotherapy; ED-SCLC, extensive-stage disease small cell lung cancer; IQR, interquartile range; HT: Hypertension; KPS, Karnofsky performance status scale; LD-SCLC, limited-stage disease small cell lung cancer; MRI, magnetic resonance imaging; NI, no information; ODRT, once-daily radiotherapy; OS, overall survival; PCI, prophylactic cranial irradiation; PET-CT, positron emission tomography and computed tomography; PR, partial response; PS, performance status; SCLC, small cell lung cancer; SCRT, sequential chemoradiotherapy; TDRT, twice-daily radiotherapy; TRT, thoracic radiotherapy. | | | | | | | | | | | | | |

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