# Appendix E – Clinical evidence tables

| Short Title | | Title | Study Characteristics | Risk of Bias: quality assessment |
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| Gore (2017) | | Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extracranial Irradiation for Extensive-Disease Small Cell Lung Cancer (ED SCLC): NRG Oncology RTOG 0937 | **Study type**<br>• Randomised controlled trial<br><br>**Study details**<br>• Study location<br>*USA*<br>• Study setting<br>*Various hospitals in the USA*<br>• Study dates<br>*Recruitment was between 2010 to 2015*<br>• Duration of follow-up<br>*Trial was stopped prematurely because futile. Median follow-up was 9 months. At planned interim analysis, the study crossed the futility boundary for OS and was closed before meeting the accrual target. The original plan was to evaluate participants after therapy at 2 weeks; at 1, 2, 6, 9, and 12 months; every 6 months for 2 to 3 years; and then annually. CT of the chest/abdomen or PET/CT and brain imaging were to be required at each visit starting at 2 months.*<br>• Sources of funding<br>*National Cancer Institute*<br>• Details of first-line treatment with systemic anti-cancer therapy<br>*4 to 6 cycles of platinum-based chemotherapy at a minimum of one site of disease.*<br><br>**Inclusion criteria**<br>• Pathologically proven SCLC | **Quality assessment (RCT)**<br>Random sequence generation<br>• High risk of bias<br>*Although the randomisation technique use have worked, in practice those randomised cRT + PCI arm were on average 5 years o (comparing median ages of the two groups cRT + PCI arm, 54.5% of the participants v years old or over, compared to 28.6% for t only group.*<br><br>Allocation concealment<br>• High risk of bias<br>*Not mentioned*<br><br>Blinding of participants and personnel<br>• Unclear risk of bias<br>*Not possible*<br><br>Blinding of outcome assessment<br>• High risk of bias<br>*None*<br><br>Incomplete outcome data<br>• Low risk of bias |

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| | | | • Staging CT of chest and abdomen showing extensive SCLC<br>• Bone scan or PET/CT<br>• Brain imaging<br>• Partial or complete response to chemotherapy<br>• Restaging within 8 weeks of study entry (CT of chest & abdomen or PET/CT, bone scan or PET, MRI brain or CT brain if contraindicated)<br><br>**Exclusion criteria**<br>• Brain metastases<br>• 5 or more (extracranial) metastases<br>• Evidence of progression at any site<br>• Evidence of progression at the 8-week re-staging<br>• Zubrod performance status above 2<br>• Serum aspartate transaminase level beyond 2.5 times the upper limit of normal<br>• Aspartate transaminate level beyond 2.5 times the upper limit of normal<br>• Bilirubin level 1.5 times or greater than the upper limit of normal<br>• Serum creatinine level 1.5 times or more than the upper limit of normal for people with renal or perirenal metastases<br>• Absolute neutrophil count of lower than 1000 cells/mm3<br>• Platelet count of lower than 75,000 cells/mm3<br>• Haemoglobin level lower than 8 g/dL<br><br>**Sample characteristics**<br>• Sample size<br>*86 participants*<br>• Split between study groups | Selective reporting<br>• Low risk of bias<br><br>Other sources of bias<br>• Low risk of bias<br><br>Overall risk of bias<br>• High<br><br>Directness<br>• Directly applicable |

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| | | | *Consolidative extracranial irradiation + PCI group = 44; PCI group = 42*<br>• Loss to follow-up<br>*2 participants were lost to follow-up in the PCI group.*<br>• %female<br>*Consolidative extracranial irradiation + PCI group = 52.3%; PCI group = 57.1%*<br>• Average age<br>*Median age (range): consolidative extracranial irradiation + PCI group = 66 years (35-86); PCI group = 60.5 years (47-81)*<br>• Performance status<br>*Zubrod performance status (0, 1, 2): consolidative extracranial irradiation + PCI group = 40.9%, 56.8%, 2.3%; PCI group = 50%, 50%, 0%*<br>• Response to first-line treatment with systemic anti-cancer therapies<br>*Complete response, complete thoracic response and partial metastatic response elsewhere, partial thoracic response and partial metastatic response elsewhere or stable: consolidative extracranial irradiation + PCI group = 15.9%, 13.6%, 70.5%; PCI group = 23.8%, 11.9%, 64.3%*<br>• Number of metastatic lesions<br>*1, 2-4: consolidative extracranial irradiation + PCI group = 31.8%, 68.2%; PCI group = 40.5%, 59.5%*<br><br>**Interventions**<br>• Consolidative extracranial irradiation (cRT) + prophylactic cranial irradiation (PCI)<br>*25 Gy of PCI at 2.5 Gy per fraction. Thoracic radiation therapy to the primary and involved regional nodes was required for all participants unless they had had palliative radiation therapy to the primary at diagnosis. Radiation was delivered to postchemotherapy volumes,* | |

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| | | | *including to the site of the primary and involved nodal regions at diagnosis. Metastases were treated if they did not have a complete response to chemotherapy. The recommended radiation dose to all extracranial sites was 45 Gy delivered in 15 daily fractions of 3 Gy. From 30 to 40 Gy was acceptable if dose reduction was necessary to meet normal tissue dose constraints. It was recommended that PCI be started concurrently with cRT, although sequential therapy was allowed at the discretion of the treating physician. The median time from diagnosis to start of radiation was 22 weeks. The median time from end of chemotherapy to start of radiation was 6.9 weeks. Of the participants treated with cRT, 90.5% received thoracic radiation per protocol (30–45 Gy). Two participants received less than 30 Gy (22.5 Gy and 24 Gy) and two participants received more than 45 Gy (50 and 65 Gy), with 95.3% of all participants receiving PCI per protocol.*<br>• Prophylactic cranial irradiation<br>*25 Gy of PCI at 2.5 Gy per fraction. The median time from diagnosis to start of radiation was 22 weeks. The median time from end of chemotherapy to start of radiation was 5.9 weeks.*<br><br>**Outcome measures**<br>• Mortality: hazard ratio<br>• Mortality: 1 year overall survival<br>• Response to treatment: hazard ratio for time to progression<br>• Response to treatment: percentage whose cancer had progressed at 3 months<br>• Response to treatment: percentage whose cancer had progressed at 1 year<br>• Adverse events: number of people who experienced a grade 3 or higher adverse event | |

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| Jeremic (1999) | | Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study | **Study type**<br>• Randomised controlled trial<br>*Participants who had the best response to chemotherapy, in other words, those who had a complete response outside the thorax, were randomised to either (group 1:) accelerated hyperfractionated radiation therapy and concurrent low-dose daily chemotherapy consisting of carboplatin and etoposide, followed by prophylactic cranial irradiation and then by two additional cycles of cisplatin/etoposide or (group 2:) four additional cycles of cisplatin/etoposide and PCI.*<br><br>**Study details**<br>• Study location<br>*Yugoslavia*<br>• Study setting<br>*University Hospital, Kragujevac, Yugoslavia*<br>• Study dates<br>*1988 to 1993*<br>• Duration of follow-up<br>*Follow-up was ongoing - no follow-up stop duration. Participants were examined fully at the end of their treatment, every month for 6 months after the end of the treatment, every 2 months for 2 years thereafter, and every 4 to 6 months thereafter.*<br>• Sources of funding<br>*Japanese Ministry of Education*<br>• Details of first-line treatment with systemic anti-cancer therapy<br>*Three cycles of a standard-dose cisplatin/etoposide regimen given at 3-week intervals (cisplatin 80 mg/m2 on day 1 and etoposide 80 mg/m2 on days 1 through 3). No dose reductions were allowed for the first three cycles of cisplatin/etoposide. After three cycles of* | **Quality assessment (RCT)**<br>Random sequence generation<br>• Unclear risk of bias<br>*The method of randomisation is not given. the characteristics of the participants in gro 2 are reasonably well balanced.*<br><br>Allocation concealment<br>• High risk of bias<br>*Not performed*<br><br>Blinding of participants and personnel<br>• Unclear risk of bias<br>*Not performed. However, this is probably n possible.*<br><br>Blinding of outcome assessment<br>• High risk of bias<br>*Not performed*<br><br>Incomplete outcome data<br>• Low risk of bias<br><br>Selective reporting<br>• Low risk of bias<br><br>Other sources of bias |

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| | | | *cisplatin/etoposide, complete patient re-evaluation and restaging were performed. Depending on how they responded, they were allocated different interventions.*<br><br>**Inclusion criteria**<br>• Pathologically proven SCLC<br>• Staging procedures: chest X-rays, tomography, bronchoscopy, bone marrow biopsy, radionuclide scans of brain, bone, liver. Abdominal ultrasonography. CT abdomen, thorax and brain. Showed extensive SCLC<br>*CT abdomen, thorax and brain were performed in all participants since 1989. Extensive SCLC was defined as tumour beyond the confines of the hemithorax, mediastinum, and ipsilateral or contralateral supraclavicular nodes. Participants with tumours that could not be encompassed within a tolerable RT field were also considered to have ED SCLC, as were participants who had an "isolated" pleural effusion with positive cytology.*<br><br>**Exclusion criteria**<br>• Brain metastases<br>• Negative cytology in an isolated pleural effusion<br>• Previous or concurrent malignancy except skin nonmelanoma<br>• Karnofsky performance score <70<br>• Age <18 years<br>• Age >70 years<br>• WBC count <4,000/mm3<br>• Platelet count <150,000/mm3<br>• Serum creatinine 2.0 mg/dL or more<br>• Bilirubin level 2.0 mg/dL or more | • High risk of bias<br>*The RCT aspect of the trial does not look a radiotherapy in isolation: the chemotherap are not quite the same. Group 1 had 1x carboplatin/etoposide (+ radiotherapy) and cisplatin/etoposide. Group 2 had 2x cisplatin/etoposide and 2x cisplatin/etopos*<br><br>Overall risk of bias<br>• High<br>*A total radiotherapy dose of 54 Gy is relati compared to UK practice.* |

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| | | | *Unless low because of liver metastases*<br>• Recent or concurrent severe, uncontrolled, cardiovascular or pulmonary disease<br>• Impairment of mental status<br><br>**Sample characteristics**<br>• Sample size<br>*171 participants*<br>• Split between study groups<br>*Group 1 = 55; group 2 = 54; group 3 = 34; group 4 = 28*<br>• Loss to follow-up<br>*None*<br>• %female<br>*Group 1 = 40%; group 2 = 40.7%; group 3 = 38.2%; group 4 = 39.3%*<br>• Average age<br>*Median age (range): group 1 = 59 years (38-70); group 2 = 59 years (39-71); group 3 = 58 (41-70); group 4 = 60 (44-69)*<br>• Performance status<br>*No meaningful data provided*<br>• Response to first-line treatment with systemic anti-cancer therapies<br>*See 'Split between study groups' heading above*<br><br>**Interventions**<br>• Group 1 (RCT): For participants who had a complete response outside the thorax: accelerated hyperfractionated radiation therapy + carboplatin/etoposide + PCI + 2x cisplatin/etoposide<br>*Participants who had the best response to chemotherapy, in other words, those who had a complete response outside the thorax (and* | |

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| | | | *had either a complete or partial response inside the thorax), were randomised to group 1 and group 2.*<br>*A complete response was defined as the disappearance of all disease for at least 4 weeks, including negative bone marrow examination results, and the absence of new lesions (for all measurable or assessable disease). For bone metastasis, bone lesions visible on plane radiographs were required only to be improved or stable, and no finding on radionuclide bone scan could have interfered with the designated type of response. For measurable disease, a partial response was defined as a 4-week reduction of greater than 50% of the sum of the products of the cross-sectional diameters of all measurable disease, together with the absence of new lesions. For assessable lesions, a partial response was defined as a decrease in tumour size for at least 8 weeks.*<br>*Group 1 had accelerated hyperfractionated radiation therapy and concurrent low-dose daily chemotherapy consisting of carboplatin and etoposide, followed by prophylactic cranial irradiation and then by two additional cycles of cisplatin/etoposide. PCI was administered to the whole brain at a total tumour dose of 25 Gy in 10 daily fractions in 2 weeks via two parallel-opposed lateral fields.*<br>• Group 2 (RCT): For participants who had a complete response outside the thorax: 2x cisplatin/etoposide + PCI + 2x cisplatin/etoposide<br>*Participants who had the best response to chemotherapy, in other words, those who had a complete response outside the thorax (and had either a complete or partial response inside the thorax). Group 2 had four additional cycles of cisplatin/etoposide and PCI. PCI was administered to the whole brain at a total tumour dose of 25 Gy in 10 daily fractions in 2 weeks via two parallel-opposed lateral fields.*<br>• Details of accelerated hyperfractionated radiation therapy for groups 1, 3 and 4 | |

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| | | | *Radiotherapy was administered with 6 to 10 MV photons from linear accelerators. The target volume included all gross disease and ipsilateral hilum with a 2-cm margin and the entire mediastinum with a 1-cm margin. Both supraclavicular fossae were routinely irradiated, and anteroposterior/posteroanterior fields were used to deliver 36 Gy in 24 fractions in 12 treatment days over 2.5 weeks. After this, the anterior, lateral, and/or posterior oblique fields were used to give an additional 18 Gy in 12 fractions in 6 treatment days. The total TD was 54 Gy in 36 fractions in 18 treatment days in 3.5 weeks. Doses were specified at middepth at the central axis for parallel-opposed fields and at the intersection of the central axes for oblique techniques. The maximum dose was 36 Gy for the spinal cord and the entire heart, 54 Gy for the oesophagus, and 18 Gy for the contralateral lung. Two daily fractions of 1.5 Gy were used with an interfraction interval of 4.5 to 6 hr. No dose corrections were made for lung inhomogeneities. During accelerated hyperfractionated radiation therapy, 50 mg of carboplatin and 50 mg of etoposide were given on each RT day between the two daily fractions (3 to 4 hr after the first one, ie, 1 to 2 hr before the second one).*<br>• Details of cisplatin/etoposide treatment for groups 1, 2, 3 and 4<br>*Dose reductions and/or treatment delays were allowed during any subsequent treatment. Adjustments in drug dosage were made according to nadir and treatment-day blood counts. A 25% reduction in the dosage of both drugs was made if the nadir granulocyte count was less than 0.5 x 10 9/L or the nadir platelet count was less than 75 x 10 9/L. A similar reduction was made if the pretreatment granulocyte count was between 1.5 and 2.0 x 10 9/L or the pretreatment platelet count was between 100 and 125 x 10 9/L. If the pretreatment granulocyte count or platelet count fell below these levels that required a 25% dosage reduction, treatment was delayed for 1 week until the blood counts recovered.* | |

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| | | | **Outcome measures**<br>• Mortality: yearly survival rates for 5 years<br>*Participants who died during cycles 1 through 3 were considered induction deaths and were included in all analyses.*<br>• Response to treatment: percentage thoracic and extra-thoracic recurrence-free survival each year for 5 years<br>*Participants were evaluated for response after three cycles of cisplatin/etoposide (week 9), then after either accelerated hyperfractionated radiation therapy or two additional cisplatin/etoposide cycles (week 15), and at the end of treatment (week 21). A complete response was defined as the disappearance of all disease for at least 4 weeks, including negative bone marrow examination results, and the absence of new lesions (for all measurable or assessable disease). For bone metastasis, bone lesions visible on plane radiographs were required only to be improved or stable, and no finding on radionuclide bone scan could have interfered with the designated type of response. For measurable disease, a partial response was defined as a 4-week reduction of greater than 50% of the sum of the products of the cross-sectional diameters of all measurable disease, together with the absence of new lesions. For assessable lesions, a partial response was defined as a decrease in tumor size for at least 8 weeks. Stable disease was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the cross-sectional diameters of all measurable lesions and no clear pattern of either regression or progression of disease for at least 8 weeks. Disease progression was defined as an increase of greater than 25% in the sum of the products of the cross-sectional diameters of measured lesions, together with an increase in assessable disease or the appearance of new lesions.*<br>• Response to treatment: median time to first relapse | |

Lung cancer: diagnosis and management for the clinical and cost-effectiveness of first use of thoracic radiotherapy for people with extensive-stage SCLC who have had first-line treatment with systemic anti-cancer therapies (March 2019)

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| | | | • Response to treatment: complete response rate at thoracic and extra-thoracic sites<br>• Response to treatment: duration of response<br>• Adverse events<br>*Chemotherapy-induced toxicity was evaluated using the criteria of the Eastern Cooperative Oncology Group. Toxicity attributable to accelerated hyperfractionated radiation therapy was evaluated according to the criteria of the Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer.* | |
| Slotman (2015) | | Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial | **Study type**<br>• Randomised controlled trial<br><br>**Study details**<br>• Study location<br>*The Netherlands, UK, Norway and Belgium.*<br>• Study setting<br>*42 hospitals: 16 in Netherlands, 22 in the UK, 3 in Norway and 1 in Belgium.*<br>• Study dates<br>*Recruitment was from 2009 to 2012*<br>• Duration of follow-up<br>*Participants in both groups were followed up at 6 weeks and 12 weeks, then once every 3 months, then once every 6 months after 1 year. All participants were followed up until death. The median follow-up was 24 months.*<br>• Sources of funding<br>*Dutch Cancer Society (CKTO), Dutch Lung Cancer Research Group, Cancer Research UK, Manchester Academic Health Science Centre* | Random sequence generation<br>• Low risk of bias<br><br>Allocation concealment<br>• High risk of bias<br>*No allocation concealment.*<br><br>Blinding of participants and personnel<br>• Unclear risk of bias<br>*No blinding but this is probably not possibl situation.*<br><br>Blinding of outcome assessment<br>• High risk of bias<br>*No blinding of outcome assessment.*<br><br>Incomplete outcome data<br>• Low risk of bias |

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| | | | *Trials Coordination Unit, and the UK National Cancer Research Network.*<br>• Details of first-line treatment with systemic anti-cancer therapy<br>*4 to 6 cycles of platinum etoposide chemotherapy, which was standard chemotherapy. 488/495 participants had this, 7/495 received other platinum-based regimens.*<br><br>**Inclusion criteria**<br>• Extensive SCLC<br>*Defined as disease beyond the hemithorax, hilar, mediastinal, and supraclavicular nodes.*<br>• Partial or complete response to chemotherapy<br>*Assessed by the local investigators using the RECIST 1.1 criteria.*<br><br>**Exclusion criteria**<br>• Brain metastases<br>*Or leptomeningeal metastases*<br>• Age <18 years<br>• WHO performance status >2<br>• Not considered treatable using acceptable radiation fields as judged by a radiation oncologist<br>• More than 6 weeks between chemotherapy and randomisation<br>• Pleural metastases<br>• Previous radiotherapy to the brain or thorax<br>• Ability to comply with protocol and follow-up schedules<br><br>**Sample characteristics**<br>• Sample size | Selective reporting<br>• Low risk of bias<br><br>Other sources of bias<br>• High risk of bias<br>*After the intervention, treatment for diseas progression was not part of the protocol ar to each centre's policy. The potential differ might have an effect on the outcomes. Wh study was registered, the investigators onl to report on data at 1 year follow-up. There is the prospect of cherry-picking data.*<br><br>Overall risk of bias<br>• High<br><br>Directness<br>• Directly applicable |

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| | | | *495 participants*<br>• Split between study groups<br>*Thoracic radiotherapy + PCI group = 247; PCI group = 248*<br>• Loss to follow-up<br>*None*<br>• %female<br>*Thoracic radiotherapy + PCI group = 45%; PCI group = 45%*<br>• Average age<br>*Median age (interquartile range): thoracic radiotherapy + PCI group = 63 years (58-69); PCI group = 63 (57-69)*<br>• Performance status<br>*WHO performance score (0, 1, 2): thoracic radiotherapy + PCI group = 39%, 49%, 12%; PCI group = 28%, 63%, 9%*<br>• Response to first-line treatment with systemic anti-cancer therapies<br>*Complete response, partial response, good response: thoracic radiotherapy + PCI group = 5%, 73%, 22%; PCI group = 5%, 69%, 26%.*<br><br>**Interventions**<br>• Thoracic radiotherapy + PCI<br>*Thoracic radiotherapy was delivered to a dose of 30 Gy in 10 fractions. The planning target volume included the post-chemotherapy volume with a 15 mm margin to account for microscopic disease and setup errors. Hilar and mediastinal nodal stations that were considered involved pre-chemotherapy were always included, even in case of response. Both 2D and 3D radiotherapy planning techniques were allowed. For 3D planning, the volume of normal lung tissue, minus planning target volume receiving more than 20 Gy, should be less than 35% and correction for tissue heterogeneity was mandatory. Treatment* | |

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| | | | *was delivered with a linear accelerator (4–10 MV) and all fields were treated daily (4 or 5 fractions per week). Prophylactic cranial irradiation was given as 20 Gy in 5 fractions, 25 Gy in 10 fractions, or 30 Gy in 10, 12, or 15 fractions. Each centre had to preselect one prophylactic cranial irradiation scheme for all participants. Treatment was delivered with two opposed lateral fields (4–10 MV). Prophylactic cranial irradiation and thoracic radiotherapy preferably had to start within 6 weeks, but not later than 7 weeks after chemotherapy, and not within 2 weeks after chemotherapy or if acute grade 2 or higher toxic effects of chemotherapy had not yet resolved. In the thoracic radiotherapy group, 7 participants did not receive and 6 did not complete thoracic radiotherapy, because of disease progression (n=5), deterioration of general condition (n=3), patient refusal (n=4), or treatment-related toxic effects (n=1).*<br>• Prophylactic cranial irradiation<br>*Prophylactic cranial irradiation (PCI) was given as 20 Gy in 5 fractions, 25 Gy in 10 fractions, or 30 Gy in 10, 12, or 15 fractions. Each centre had to preselect one prophylactic cranial irradiation scheme for all participants. Treatment was delivered with two opposed lateral fields (4–10 MV). PCI preferably had to start within 6 weeks, but not later than 7 weeks after chemotherapy, and not within 2 weeks after chemotherapy or if acute grade 2 or higher toxic effects of chemotherapy had not yet resolved.*<br><br>**Outcome measures**<br>• Mortality: hazard ratio<br>• Mortality: 1 year overall survival<br>• Mortality: 1.5 year overall survival<br>• Mortality: 2 year overall survival<br>• Response to treatment: intrathoracic control | |

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| | | | • Response to treatment: pattern of failure<br>• Response to treatment: progression-free survival<br>• Adverse events | |