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Effects of volume CT lung cancer screening: mortality results of the NELSON randomized, controlled population-based screening trial.

Authors: de Koning HJ et al.

Reference: J Thorac Oncol. 2018; 13(10):S185

URL: https://doi.org/10.1016/j.jtho.2018.08.012

Comments:
The US Preventive Services Task Force (USPSTF) recommends annual low-dose CT scans of the chest for adults aged 55-80 years with at least a 30 pack-year smoking history who either currently smoke, or quit within the last 15 years. This recommendation was informed by the large, randomized, controlled phase III National Lung Screening Trial (NLST) of 53,454 US smokers, which observed a 20% relative reduction in lung cancer mortality with annual low-dose CT vs chest radiography. The NELSON study was a controlled trial that evaluated the efficacy of low-dose CT scan screening for lung cancer in Belgium and the Netherlands. It used a population-based registry to recruit 15,822 individuals aged 50-74 years (with a smoking history of more than 10 cigarettes per day for more than 30 years or more than 15 cigarettes per day for more than 25 years with no previous lung cancer diagnosis or ongoing treatment, no CT chest examination in the last year, and no renal cancer, melanoma, or breast cancer who were either current smokers or had stopped smoking in the past 10 years) who were randomized 1:1 to low-dose chest CT screening at baseline and then in Years 1, 2, 4, and 6.5 years versus no low-dose chest CT screening. The trial, initially powered (80%) for high risk males, to detect a reduction in lung cancer mortality of ≥ 25% at Year 10 of follow-up (the primary endpoint), also included a small subgroup of women (16%).

The results of the NELSON study were presented at the International Association for the Study of Lung Cancer 19th World Conference on Lung Cancer, September 23-26, 2018; Toronto, Canada (Abstract PL02.05). Although rates of first lung cancer diagnosis through Year 10 were similar between patients who did and did not receive CT scan screening, up to December 2011, approximately 50% of lung cancer cases in men were detected at stage Ia in the CT screening arm vs approximately 75% at stage III/IV in the control arm. 69% of screen-detected lung cancers were found to be stage Ia or Ib. In addition, more than half of patients in the study arm were eligible for surgical treatment versus fewer than one-quarter of those in the control arm (67.7% vs 24.5%; P <.001). At 10 years of follow-up, longitudinal low-dose CT screening resulted in a 26% reduction in lung cancer deaths in asymptomatic men [HR of 0.74 (95% CI: 0.60-0.91); P = 0.003] and a 39% reduction in women [HR of 0.61 (95% CI: 0.35-1.04); P = 0.0543] compared to controls that were not screened. These results show an even bigger reduction in deaths from lung cancer than was seen in the NLST conducted in the United States and suggest gender differences. Volume CT lung cancer screening of high risk former and current smokers results in a very substantial reduction in lung cancer mortality in both genders.

Most cited articles:
Best practices recommendations for diagnostic immunohistochemistry in lung cancer.

Authors: Yatabe Y et al.


URL: https://doi.org/10.1016/j.jtho.2018.12.005

Comments:
The histological subtyping of non-small cell lung cancer (NSCLC), namely adenocarcinoma and squamous cell carcinoma, is of therapeutic importance because of the choice of chemotherapy regimens and the testing for targetable molecular alterations. The 2015 World Health Organization Classification of Lung Tumors first introduced the importance of immunohistochemical (IHC) stains as an ancillary test to separate NSCLC subtypes, especially in small biopsy and cytology samples that account for most specimens for lung cancer diagnosis. Although the classification of lung cancer remains based on histological features, immunohistochemistry (IHC) is recommended in cases with no morphologic evidence of differentiation to improve diagnostic accuracy. However, the prioritization of molecular testing means the use of IHC should be limited. However, interpretation of IHC can be challenging. The pathologists must be aware of the many pitfalls that can involve selection of antibody panels, clones, and staining patterns. The recommendations by the IASLC Pathology Committee to 11 questions that summarise the most pressing issues with on diagnostic IHC in lung cancer are as follows:

1. What is the best combination of markers to use in daily practice?
   Recommendation: When IHC is needed for the subtyping of NSCLC, thyroid transcription factor 1 (TTF1) and p40 are the criterion standard, and these two markers are usually sufficient in clinical practice if there are no morphologic features of neuroendocrine (NE) differentiation. p40 is preferable to p63 to identify squamous cell carcinoma

2. What extent of TTF1- and p40-positive reactions should we consider to be positive?
   Recommendation: Focal positivity for TTF1 is considered a positive reaction indicating pulmonary adenocarcinoma in the proper clinical context, whereas for p40 the cutoff rate should be positivity in more than 50% of tumor nuclei. Focal or weak positivity for p40 is not diagnostic of squamous cell carcinoma

3. Are there any staining differences in lung adenocarcinoma between among TTF1 clones (SPT24, SP141, and 8G7G3/1)?
   Recommendation: The staining performance of TTF1 varies among the clones. Among the most commonly used antibodies, 8G7G3/1 is the most specific antibody to identify lung adenocarcinoma

4. Should an NSCLC that is diffusely positive for cytokeratin 7 (CK7) but negative for TTF1 and p40 be regarded as probably adenocarcinoma?
   Recommendation: CK7 is not specific for adenocarcinoma; the marker can be seen in squamous cell carcinoma. The use of CK7 is discouraged for subtyping of NSCLC

5. When should NE markers be applied to an NSCLC?
   Recommendation: NE markers should be applied only in support of NE morphology
6. What is the best antibody panel to differentiate NE tumors from other types of NSCLC, and which one is the most reliable?

**Recommendation:** A panel of chromogranin A, synaptophysin, and CD56 is the best combination to identify NE tumors. The staining significance of each antibody varies among the sample types, histologic subtypes, and extent and/or intensity of positive reactions.

7. When should a proliferation marker be used in diagnosis?

**Recommendation:** The main established role of Ki-67 in lung carcinomas is to help distinguish carcinoids from high-grade NE carcinomas (large cell NE carcinoma and small cell carcinomas), especially in small or crushed biopsy or cytologic samples. The role of Ki-67 in separating typical from atypical carcinoids is not established and needs more investigation.

8. Is IHC useful to render a specific diagnosis of uncommon lung cancer subtypes (sarcomatoid carcinoma, salivary gland-type tumors, and nuclear protein in testis (NUT) carcinoma)?

**Recommendation:** Currently, IHC and molecular testing are needed to achieve the definitive diagnoses of uncommon lung cancers such as sarcomatoid carcinoma, salivary gland-type tumors, and NUT carcinoma and to distinguish from the mimics.

9. What portion of the cytologic sample is best for immunostaining: the cell block, the air-dried smears, or the ethanol-fixed smears? Can destained smears be used adequately?

**Recommendation:** All cytologic preparations, including cell blocks and ethanol-fixed and air-dried slides, can principally be used for immunostaining. Formalin-fixed cell blocks are most straightforward, whereas rigorous protocol optimization, validation, and quality control are required in immunostaining in cytologic examination.

10. Which IHC panel is recommended to differentiate lung mucinous adenocarcinoma from metastatic mimics?

**Recommendation:** There is no useful marker to differentiate pulmonary mucinous adenocarcinoma from metastatic mimics. A clinicopathologic tumor board is crucial for this clinical context.

11. Are there any IHC or other markers to differentiate between primary lung cancers and metastases; between squamous cell carcinomas of lung primary and metastases from thymic, head and neck, endocervical, and the other cancers; and between adenocarcinomas of primary and metastases from gynecologic, mammary, uroepithelial, nonpulmonary NE, prostate, and liver cancers?

**Recommendation:** In this clinical context, morphologic comparison with prior tumor is crucial. There are no absolute IHC markers to make the differential diagnosis, and pathologists should be aware of the pitfalls of IHC.
Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer.

Authors: Soria JC et al.


URL: https://www.nejm.org/doi/10.1056/NEJMoa1713137

Comments: Osimertinib, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), has effectively overcome the T790M resistance mechanism associated with earlier-generation EGFR TKIs, but patients with EGFR-positive non-small cell lung cancer (NSCLC) are still experiencing disease progression on the third-generation drug. Based on positive data from the phase III FLAURA study, osimertinib has become the frontline standard of care for this patient population. Results from the FLAURA study showed that osimertinib significantly improved median progression-free survival (PFS) at 18.9 months versus 10.2 months with the earlier TKIs, erlotinib and gefitinib (HR, 0.46; 95% CI, 0.37-0.57; P <0.001). While objective response rates were similar at 80% with osimertinib versus 76% on standard TKIs, the median duration of response was 17.2 months versus 8.5 months in favour of osimertinib (95% CI, 7.3-9.8). The PFS hazard ratio for about 20% of the patients with brain metastases enrolled in the study was similar to that of the overall patient population. These patients also experienced less disease progression in the brain with osimertinib. Despite the clear survival benefit, patients are now developing resistance mechanisms that are unique to osimertinib. Data presented at the 2018 ESMO Congress by Suresh S. Ramalingam suggested that MET amplification and EGFR C797S mutations were key alterations associated with resistance to first-line osimertinib. (Ramalingam SS et al. Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study. In: Proceedings from the 2018 ESMO Congress; October 19-23, 2018; Munich, Germany. Abstract LBA50. https://oncologypro.esmo.org/Meeting-Resources/ESMO-2018-Congress/Mechanisms-of-acquired-resistance-to-first-line-osimertinib-preliminary-data-from-the-phase-III-FLAURA-study) Plasma samples analysed through next-generation sequencing at baseline and at the time of progression in the FLAURA study showed that MET amplification was the most common acquired resistance mechanism in patients who progressed on osimertinib (15%), followed by C797S (7%), and PI3KCA mutations (7%). The mechanisms of resistance to first-line osimertinib are therefore much more heterogeneous than what are observed with progression on first- and second-generation EGFR TKIs where in 60% of patients treatment failure is due to an acquired T790M mutation. In addition, the resistance mechanisms at osimertinib treatment failure are often happening concurrently. Combination strategies targeting some of these resistance mechanisms are being investigated in ongoing studies.
**Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC.**

Authors: Antonia SJ et al.  
URL: https://www.nejm.org/doi/10.1056/NEJMoa1809697

Comments:  
For more than a decade, concurrent chemoradiotherapy (CCRT) has been the standard of care for fit patients with unresectable locally advanced (LA) non-small cell lung cancer (NSCLC). Between 30% and 50% of newly diagnosed cases of LA-NSCLC are unresectable. Although multiple clinical trials have associated CCRT with greater clinical benefit than radiotherapy alone or sequential radiotherapy and chemotherapy, prognosis after CCRT has remained poor. Approximately 10% of patients die within 6 months of CCRT, overall survival (OS) ranges from 18 to 28 months, and the estimated 5-year OS rate is 15% to 25%.

The phase III PACIFIC trial was a placebo-controlled trial which evaluated the role of durvalumab [a monoclonal antibody against programmed death-ligand 1 (PD-L1)] as consolidation therapy in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after completing CCRT. This practice-changing trial showed that durvalumab significantly improved overall survival (OS) with an increase in toxicity which is acceptable. A total of 709 patients from 235 sites in 26 countries were randomly assigned in a 2:1 ratio to receive either durvalumab (n=473) or placebo (n=236) every 2 weeks within 42 days of their last radiation dose. Durvalumab was administered intravenously at a dose of 10 mg/kg until disease progression or up to 12 months. The median progression-free survival (PFS) was 3 times longer in the durvalumab arm than in the placebo arm (17.2 vs 5.6 months, respectively; HR for disease progression or death, 0.51; (95% CI, 0.41-0.63). The benefit was seen irrespective of gender, smoking status, PD-L1 expression, and tumour histology type. In addition, the development of new lesions was less frequent in the durvalumab arm (20.4% vs 32.1%). Median OS was 28.7 months in the control arm and not reached in the durvalumab arm (HR for death, 0.68; 99.73% CI, 0.470-0.997; 2-sided P = 0.0025). Median time to death or distant metastasis was significantly longer in the durvalumab arm than in the placebo arm (28.3 vs 16.2 months, respectively; HR, 0.53; 95% CI, 0.41-0.68). The brain is a common metastatic site for NSCLC, and has been historically associated with decreased OS and poor quality of life. The rate of new brain metastases in the PACIFIC trial was almost halved with durvalumab compared with placebo (6.3% vs 11.8%, respectively). OS benefit, a PFS benefit of almost a year and a significant decrease in the occurrence of new lesions including brain lesions, are compelling reasons for consolidation treatment with durvalumab to be considered a new standard of care following CCRT in patients with stage III unresectable NSCLC.

Approximately 30% of patients in the durvalumab arm had a grade 3/4 adverse event compared with 26% of patients in the placebo arm. These rates are higher than those observed in studies of ICI monotherapy for stage IV disease. The similar rates in both arms suggest these are probably CCRT-related delayed toxicities. Pneumonitis, a frequent complication of both thoracic radiation and PD-1/ PD-L1 inhibitors, is a concern and distinguishing radiation pneumonitis from immune-related pneumonitis in the context of recent CCRT can be difficult. However, the PACIFIC results were reassuring because although pneumonitis or radiation pneumonitis was slightly more frequent in the durvalumab arm (33.9% vs 24.8%), rates of grade 3/4 pneumonitis were similar in the durvalumab and placebo arms (3.4% vs 2.6%, respectively).
Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer.

Authors: Gandhi L et al.


Comments: Due to low or absent PD-L1 tumour expression, the majority of patients with metastatic non-squamous NSCLC are not eligible for pembrolizumab [a monoclonal antibody against programmed death-1 (PD-1)] monotherapy. Patients with metastatic non-squamous NSCLC with PD-L1 <50% and those with PD-L1 >50% were enrolled in KEYNOTE-189, which compared the combination of pembrolizumab + platinum + pemetrexed to platinum + pemetrexed. Patients with activating EGFR mutations or ALK rearrangements were excluded. Platinum and pemetrexed were administered together for 4 cycles, followed by maintenance pemetrexed. Pembrolizumab 200 mg was given every 3 weeks for up to 35 cycles. All efficacy endpoints [overall survival (OS), progression-free survival (PFS) and objective response rate (ORR)] were improved with the addition of pembrolizumab to platinum/pemetrexed chemotherapy across PD-L1 subgroups: PD-L1 negative, PD-L1 1-49% and PD-L1 >50%, except for PFS in PD-L1 negative patients. For the entire cohort, the ORR was 47.6% with pembrolizumab + chemotherapy and 18.9% with chemotherapy alone (p < 0.001). Triplet therapy improved PFS and OS vs. chemotherapy, (HR 0.52, p < 0.001 and HR 0.49, p < 0.01, respectively). Of note, the benefits of pembrolizumab + chemotherapy were more pronounced in the PD-L1 >50% subgroup. The ORR was 61.4% with pembrolizumab + chemotherapy (n = 132) vs. 22.9% (n = 70) with chemotherapy (p <0.0001). The PFS and OS were also prolonged with pembrolizumab + chemotherapy [HR 0.36 (95% CI 0.25–0.52)] and HR 0.42 (95% CI 0.24–0.68), respectively.

The addition of pembrolizumab in this trial resulted in a minimal increase in the overall adverse event rate compared to chemotherapy (grade >3 in 67.2% vs. 65.8%) and this did not appear to differ significantly by the type of platinum used. As expected, the immune-mediated adverse event rate was higher with the addition of pembrolizumab (all grades 22.7% vs. 11.9%, grade >3 in 8.9% vs. 4.5%). Diarrhoea and rash were significantly more common with the addition of pembrolizumab. The incidence of febrile neutropenia was higher with pembrolizumab.

Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC.

Authors: Socinski MA et al.


Comments: Atezolizumab [a monoclonal antibody against programmed death-ligand 1 (PD-L1)] is another check-point inhibitor approved for first-line treatment in metastatic NSCLC based on the IMpower150 study (N=1202) which compared atezolizumab + bevacizumab + carboplatin + paclitaxel (ABCP) (n=400) to bevacizumab + carboplatin + paclitaxel (BCP) (n=400) in patients with metastatic non-squamous
NSCLC with any level of PD-L1 expression. Chemotherapy + bevacizumab was administered for 4-6 cycles. Bevacizumab ± atezolizumab was administered every 3 weeks until disease progression or death. Unlike most other studies, patients with activating *EGFR* mutations or *ALK* rearrangements were allowed to enroll if they had progressed on or were unable to tolerate at least one tyrosine kinase inhibitor but were excluded from the primary endpoint assessment. All efficacy endpoints were improved with ABCP versus BCP. Across all PD-L1 subgroups, ABCP significantly improved progression-free survival (PFS) compared to BCP. Patients with tumour PD-L1 expression ≥50% or immune cell PD-L1 expression >10%, had a greater magnitude of benefit with the addition of atezolizumab. Adding atezolizumab did not increase the incidence of any grade treatment-related adverse events (TRAEs) but did cause an increase in grade 3-4 TRAEs (55.7% vs. 45.7%). Immune-related adverse events were more frequent with the addition of atezolizumab. The addition of atezolizumab lead to a higher incidence of rash and febrile neutropenia.

Lung cancer patients with liver metastasis have shorter survival and reduced response to immune checkpoint blockade because of the immunosuppressive environment of the liver. In the IMpower150 study, subgroup analyses showed that the addition of bevacizumab to atezolizumab and chemotherapy prolonged overall survival (OS) of patients with liver metastases (13% of patients in the ABCP arm and 14% of patients in the BCP arm) in the intention-to-treat *EGFR* and *ALK* wild-type patients [13.2 vs 9.1 months; HR 0.54 (95% CI, 0.33-0.88)]. In the subpopulation of patients with *EGFR* mutations or *ALK* rearrangements, the addition of bevacizumab to atezolizumab and chemotherapy (45 patients in the ABCP arm and 65 patients in the BCP arm) prolonged median PFS (9.7 vs 6.1 months; HR: 0.59; 95% CI: 0.37-0.94) and prolonged median OS [not reached vs 17.5 months; HR 0.52 (95% CI, 0.29-1.03)].

**IMpower130: efficacy and safety from a randomized phase 3 study of carboplatin and nab-paclitaxel with or without atezolizumab in 1L advanced non-squamous NSCLC.**

Authors: Cappuzzo F et al.


Comments:

In the IMpower130 study, atezolizumab + carboplatin + nab-paclitaxel was compared to carboplatin + nab-paclitaxel in patients with non-squamous NSCLC regardless of PD-L1 expression, including patients with activating *EGFR* mutations or *ALK* rearrangements after first-line tyrosine kinases inhibitors. Carboplatin + nab-paclitaxel was administered for 4-6 cycles. Patients receiving chemotherapy alone were treated with either placebo or pemetrexed every 3 weeks. Atezolizumab was administered every 3 weeks until disease progression or death. Enrolled *EGFR*-mutant, or *ALK*+ patients were not included in the primary analysis. Adding atezolizumab to chemotherapy significantly improved progression-free survival (PFS) by 1.5 months and overall survival (OS) by 4.7 months in the entire intention-to-treat wildtype population (N=679). Subgroup analyses according to PD-L1 expression levels observed a PFS improvement regardless of PD-L1 expression, but none experienced a significant OS benefit with the addition of atezolizumab. The incidence of grade ≥3 treatment-related adverse events were 74.9% with atezolizumab + chemotherapy vs. 60.7% with chemotherapy alone.
Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel with or without pembrolizumab (pembro) for patients (pts) with metastatic squamous (sq) non-small cell lung cancer (NSCLC).

Authors: Paz-Ares LG et al.

Reference: J Clin Oncol. 2018; 36(suppl 15); abstr 105


Comments:
KEYNOTE-407 was a large, multinational phase III study with over 150 participating centres, in which treatment-naïve patients with metastatic squamous NSCLC were randomised to receive either carboplatin and paclitaxel or nab-paclitaxel plus pembrolizumab versus placebo followed by single-agent pembrolizumab or placebo. The study demonstrated a 36% reduction in the risk of death with the addition of pembrolizumab to standard chemotherapy versus chemotherapy alone (more than 50% of the patients received nab-paclitaxel). Survival benefit was observed across PD-L1 subgroups. Objective response rate was 58% in those who received pembrolizumab versus 35% in the control arm. At a median follow-up of 7.7 months, median overall survival (OS) was 15.9 months versus 11.3 months in favour of the pembrolizumab arm. The addition of pembrolizumab also led to an improved median progression-free survival (PFS) of 6.4 months versus 4.8 months. Positive data were most clearly seen in patients who had high PD-L1 expression, and secondarily, in those who had intermediate PD-L1 expression. The PFS in the PD-L1-negative group does not seem very impressive, but there was OS benefit.

Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden.

Authors: Hellmann MD et al.


URL: https://www.nejm.org/doi/10.1056/NEJMoa1801946

Comments:
The randomised phase III study (CheckMate-227) compared the immune checkpoint inhibitor combination of nivolumab [a monoclonal antibody against programmed death-1 (PD-1)] + ipilimumab [a monoclonal antibody against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)] to histology-based platinum-doublet chemotherapy as first-line treatment in both PD-L1 positive and PD-L1 negative advanced squamous and non-squamous NSCLC patients without activating EGFR mutations or ALK rearrangements. In the overall study population of CheckMate227, nivolumab + ipilimumab modestly improved 1-year progression-free survival (PFS) compared to platinum-doublet chemotherapy, HR 0.83 (95%CI, 0.72–0.96) but did not improve median PFS or overall survival (OS). The incidence of grade 3-4 treatment-related adverse events were similar with nivolumab + ipilimumab at 31.2% compared to platinum-based doublets at 36.1%.

In a selected subgroup of study patients with a high tumour mutational burden (TMB), defined as ≥10 mutations/megabase determined by the FoundationOne CDx assay (irrespective of PD-L1 expression level), PFS was significantly longer with the combination of nivolumab + ipilimumab than with platinum-doublet chemotherapy [median PFS, 7.2 vs 5.5 months (HR, 0.58; 95.7% CI (0.41-0.81); P=0.0002)]
year PFS was 42.6% vs 13.2%). Among those with low TMB, there was no PFS benefit from the combination of nivolumab + ipilimumab compared to chemotherapy. The results of this study validate the role of TMB as an emerging, independent biomarker of outcomes with immunotherapy. The lack of relationship between tumour PD-L1 expression and TMB has been observed in several different studies, highlighting the potential complementary role for both biomarkers. Limitations for the use of TMB as a biomarker in clinical practice include non-standardised platforms for sample type and analysis, differences in the cut-off values that designate a tumour as having a high versus low TMB, and whether TMB can be used to identify patients who may derive benefit from immunotherapy-chemotherapy combinations.

**Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial.**

Authors: Takahashi T et al.


URL: [https://doi.org/10.1016/S1470-2045(17)30230-9](https://doi.org/10.1016/S1470-2045(17)30230-9)

Comments: The effectiveness of prophylactic cranial irradiation (PCI) has been well established in patients with limited-stage (LS) small cell lung cancer (SCLC) after response to first-line chemotherapy. The role of PCI is controversial in patients with extensive stage (ES) SCLC. The pivotal study on the impact of PCI in patients with ES-SCLC who responded to initial chemotherapy, published in 2007 by the European Organization for Research and Treatment of Cancer (EORTC), showed that PCI reduced the incidence of symptomatic brain metastases (BM) (14.6% vs. 40% at 1 year); and prolonged overall survival (OS) compared with observation (27% vs. 13.3% at 1 year). CT or MRI was not required at staging or during follow-up, unless patients had symptoms suggestive of BM. The more recent Japan Clinical Oncology Group (JCOG) prospective randomized controlled trial showed that in patients with ES-SCLC who had no BM on baseline MRI, PCI at a standard dose of 25 Gy in 10 fractions also reduced the risk of developing BM (symptomatic or asymptomatic) by almost 2-fold (33.6% vs 59.7% at 1 year) but did not improve OS compared to routine surveillance MRI and treatment of symptomatic BM upon detection. Based on the results of the EORTC study the 2013 American College of Chest Physicians guideline on the treatment of SCLC stated that PCI was recommended in ES- as well as LS-SCLC patients who had a complete or partial response to initial chemotherapy. However, with the publication of the JCOG study results, the current National Comprehensive Cancer Network guidelines state that in patients with ES-SCLC, either PCI or brain MRI surveillance should be considered.

In the EORTC study, since brain imaging was not required to exclude BM before randomisation, a substantial number of the patients might have had asymptomatic BM before PCI and could have benefitted from PCI. In contrast, the JCOG study enrolled patients who had been confirmed not to have BM by MRI after chemotherapy before randomisation. In addition, patients underwent active brain MRI surveillance every 3 months during the first year and at 18 and 24 months after enrolment. Patients who developed BM during follow-up underwent radiation therapy. A pre-planned interim analysis of the JCOG study showed that the chance of PCI improving survival was 0.011% and the study was terminated early after 224 out of the planned 330 patients were enrolled. The JCOG study may be underpowered for OS in view of the early termination and it being designed as a non-inferiority trial. In the JCOG study, 47.8% (54 of 113 patients) of patients in the PCI group developed BM, and 46.3% (25 of 54 patients) of these patients underwent repeat cranial irradiation, mostly stereotactic radiotherapy instead of whole-brain radiotherapy. The EORTC study reported that symptomatic BM
were observed in 16.8% (24 of 143 patients) of patients in the PCI group, and repeat cranial irradiation was administered in only 8.4% (2 of 124 patients) of these patients. In summary, PCI unequivocally results in a significant reduction in the incidence of BM in ES-SCLC. However, the benefit of PCI on OS may be debatable if patients receive routine brain MRI surveillance with an option of salvage brain radiotherapy for BM upon detection.