An evaluation study of EGFR mutation tests utilized for non-small-cell lung cancer in the diagnostic setting

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Background: Epidermal growth factor receptor (EGFR) mutation is predictive for the efficacy of EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer (NSCLC) treatment. We evaluated the performance, sensitivity, and concordance between five EGFR tests.

Materials and methods: DNA admixtures (n = 94; 1%–50% mutant plasmid DNA) and samples from NSCLC patients [116 formalin-fixed paraffin-embedded (FFPE) tissue, 29 matched bronchoscopically brushing (BB) cytology, and 20 additional pleural effusion (PE) cytology samples] were analyzed. EGFR mutation tests were PCR-Invader®, peptide nucleic acid-locked nucleic acid PCR clamp, direct sequencing, Cycleave™, and Scorpion Amplification Refractory Mutation System (ARMS)®. Analysis success, mutation status, and concordance rates were assessed.

Results: All tests except direct sequencing detected four mutation types at ≥1% mutant DNA. Analysis success rates were 91.4%–100% (FFPE) and 100% (BB and PE cytology), respectively. Inter-assay concordance rates of successfully analyzed samples were 94.3%–100% (FFPE; kappa coefficients: 0.88–1.00), 93.1%–100% (BB cytology; 0.86–1.00), and 85.0%–100% (PE cytology; 0.70–1.00), and 93.1%–96.6% (0.86–0.93) between BB cytology and matched FFPE.

Conclusions: All EGFR assays carried out comparably in the analysis of FFPE and cytology samples. Cytology-derived DNA is a viable alternative to FFPE samples for analyzing EGFR mutations.

Key words: cytology, EGFR mutation, FFPE, NSCLC, PCR

introduction

Epidermal growth factor receptor (EGFR) mutation is a key predictive factor for the efficacy of EGFR tyrosine kinase inhibitors in the treatment of patients with advanced non-small-cell lung cancer (NSCLC) [1–3]. EGFR mutation testing is necessary to enable the physician to offer the most suitable therapy for a patient with advanced NSCLC.

Four EGFR mutation tests, PCR-Invader® [4], peptide nucleic acid-locked nucleic acid (PNA-LNA) PCR clamp [5], PCR direct sequencing [6], and Cycleave PCR™ [7] are used commercially in Japan, with testing generally carried out by centralized contracted laboratories. The Scorpion Amplification Refractory Mutation System (ARMS)® [8] is another sensitive globally available method and in particular was used in the phase III Iressa Pan-Asia Study (IPASS) to determine EGFR mutation status [1, 9]. A variety of methods, including direct sequencing, PCR-Invader, PNA-LNA PCR clamp, fragment analysis, and Cycleave PCR, were used in the WJTOG3405 phase III study to select EGFR mutation-positive patients [2], and the PNA-LNA PCR clamp method was used in the NEJ002 study [3]. To date, a study to compare the sensitivity and concordance of methods for EGFR mutation testing in Japan has not been conducted.

Diagnostic practices, and therefore, samples available for EGFR mutation analysis, differ between laboratories and countries. Large surgical samples are optimal for EGFR mutation analysis but small tissue from a tumor biopsy is the most commonly used and preferred sample type for diagnosis by clinicians [10, 11]. In clinical practice, tissue samples are not always available for diagnosis, and cytology samples, including bronchofiberscopic brushing (BB) cytology and pleural effusion cytology samples, are used in Japan and increasingly globally.

The aim of this study was to evaluate the sensitivity and performance of different EGFR mutation tests using artificial DNA admixtures, and clinical samples including formalin-fixed...
paraffin-embedded (FFPE) tissue, BB cytology, and pleural effusion cytology samples from patients with NSCLC.

**materials and methods**

This was an observational study using control DNA admixtures and clinical samples. Patients provided written informed consent for samples to be used in research. The study was conducted as a collaborative research of AstraZeneca KK with National Cancer Center Hospital East (NCCHE) and Hyogo Cancer Center (HCC) after protocol approval by each Institutional Review Board and was conducted in accordance with ethical guidelines for epidemiological studies.

**samples and DNA extraction**

**DNA admixtures**

Four types of mutant plasmids were prepared including the *EGFR* mutation L858R, T790M, and E746-A750 deletion (nt del 2234-2249) in the Blue Heron PUC plasmid by Invitrogen Inc. (Tokyo, Japan). The sequence inserted into each plasmid corresponded with the longest sequence requirements spanning the exons across all of the methods to be evaluated, from −300 to +220 bp for exon 18 (for G719S) and from −200 to +200 bp for exons 19, 20, and 21 (for E746-A750 deletion, T790M, and L858R, respectively). Admixtures were prepared at Saitama Medical University Hospital. The plasmid preparations (5.4 ng/μl) were diluted with water and whole-human genomic DNA (12.5 ng/μl) (Promega Inc., Madison, WI) to prepare an admixture containing a 1:1 ratio (confirmed by Sanger sequencing) of copies of mutated and wild-type *EGFR* (5.4 fg/μl plasmid DNA, 10 ng/μl genomic DNA; referred to here as a 100% admixture). The 100% admixture solution was then diluted with genomic DNA to provide DNA solutions simulating those isolated from a clinical sample containing *EGFR*-mutated and wild-type cells at ratios of 50:50 (50% admixture), 25:75 (25%), 10:90 (10%), 5:95 (5%), 2:98 (2%), and 1:99 (1%). The samples were divided into aliquots for each laboratory, randomized and assigned an identification code, and 20 μl of each sample sent to the laboratories for mutation testing in a blinded manner. Ten wild-type control samples (from a single stock of genomic DNA) (10 ng/μl) were also distributed for testing.

**formalin-fixed paraffin-embedded samples**

In total, 120 FFPE NSCLC samples collected at NCCHE (*n* = 100) and HCC (*n* = 20) between December 2005 and October 2009 were used. Twelve consecutive sections (5-μm thickness), prepared by Sanritsu Co. Ltd (Tokyo, Japan) from each FFPE tissue block, were allocated as follows: sections 1 and 12, hematoxylin–eosin (H&E) staining; sections 2 and 7, PCR direct sequencing; sections 3 and 8, Scorpione PCR; sections 4 and 9, PCR-Invader; sections 5 and 10, PNA-LNA PCR clamp; sections 6 and 11, Scorpion ARMS. Samples were randomly assigned an identification code by Sanritsu Co. Ltd, with separate identification codes for the samples for PCR direct sequencing and Scorpione PCR (as they were to be analyzed by the same laboratory). A table of corresponding randomized identification codes was retained by AstraZeneca KK until analysis. H&E-stained sections (Sanritsu Co. Ltd) were reviewed by a single pathologist at NCCHE for histological type, tumor cell content, and tumor dimension in a blinded manner. DNA was extracted at each testing laboratory using their own standard operating procedures (SOPs), all of which utilized the QIAamp kit (QIAGEN Japan, Tokyo, Japan) (see supplemental Methods, available at Annals of Oncology online).

**bronchoscopibercoscopic brushing cytology samples**

Thirty BB cytology samples (with matched FFPE samples available) obtained at NCCHE (*n* = 10) and HCC (*n* = 20) between 2006 and 2009 were used. Samples were collected by exfoliative cytodiagnosis brushing or curette washing in saline solution, without anticoagulant, and stored frozen. The BB cytology samples were randomized and assigned an identification code. The presence of tumor cells and histological type were confirmed by a pathologist at each center. DNA was extracted (QIAamp DNA Mini kit, QIAGEN Japan) at Kinki University of Medicine (Department of Genome Biology) and divided into 22 μl aliquots for analysis by the testing laboratories (direct sequencing was excluded due to the small amount of DNA anticipated, and for Scorpion ARMS, if the DNA concentration was <1 ng/μl, only exon 19 deletions, L858R, and T790M mutations were analyzed—see supplemental Methods, available at Annals of Oncology online).

**pleural effusion cytology samples**

Pleural effusion cytology samples were provided by NCCHE. Twenty pleural effusion cytology samples were collected from patients diagnosed with NSCLC (adenocarcinoma) between February 2009 and February 2010 and confirmed by a pathologist to contain tumor cells. Samples were frozen within 10 and 30 min of sampling and stored at −80°C. Frozen samples were thawed at 37°C and refrozen rapidly three times to disrupt the cells and ensure an even distribution and then divided into five equal aliquots that were sent to each of the testing laboratories. Samples were randomly assigned an identification code as for the FFPE samples. DNA was extracted at each laboratory using their own SOPs, all of which were based on the use of the QIAamp kit (see supplemental Methods, available at Annals of Oncology online).

**EGFR mutation analysis**

Samples were analyzed using five different *EGFR* mutation tests carried out by four different testing laboratories: PCR-Invader [4, 12] by BML Inc. (Tokyo, Japan); PNA-LNA PCR clamp [5] by Mitsubishi Chemical Medience Corp. (Tokyo, Japan); PCR direct sequencing (with the exception of the BB cytology samples, due to the anticipated tumor DNA yield based on published evidence regarding the detection limit of this method [13]) [6] by SRL Inc. (Tokyo, Japan), Cyctave PCR [7] also by SRL Inc., and Scorpion ARMS [14, 15] by Genzyme Analytical Services (Los Angeles, CA). Scorpion ARMS analysis employed the Dxs *EGFR* Mutation Test Kit for research use only [QIAGEN Manchester (formerly Dxs Ltd), UK] and was carried out according to the manufacturer’s instructions with modifications described in the supplemental Methods (available at Annals of Oncology online). The other methods were carried out using each of the laboratories’ experimental set up, with data analysis and quality control completed according to their own specific protocols (further details in the supplemental Methods, available at Annals of Oncology online). Samples were defined as mutation negative where sufficient material was present to generate a result but the presence of a mutation was not observed within the detection limit of the assay. The *EGFR* mutations detected by each *EGFR* mutation test are shown in supplemental Table S1 (available at Annals of Oncology online).

Analysis data (positive, negative, not detected, mutation type) and any supplemental information (e.g. failure of PCR amplification) were reported to AstraZeneca KK (Osaka, Japan).

**statistical analysis**

The correct determination rates (whether or not the positive/negative *EGFR* mutation assessment result was correct) and sensitivity (lowest percentage DNA admixture detected) by *EGFR* mutation type were assessed using DNA admixture samples for each *EGFR* mutation test. The success and positive rates of each *EGFR* mutation test were determined using FFPE, and BB and pleural effusion cytology samples. The success rate was defined as the proportion of samples successfully analyzed.
where it was possible to determine the mutation status. Samples were classified as unsuccessful where it was not possible to determine the mutation status, the PCR amplification failed, or if values of samples exceeded the cut-off value of Scorpion ARMS. The positive rate was defined as the number of samples analyzed as positive by each method as a proportion of the number of samples successfully analyzed. False-positive and false-negative rates were not determined, as no reference or ‘gold standard’ has been defined for EGFR mutation analysis.

The concordance rates and Cohen’s kappa coefficients were determined between different methods of detection and between FFPE versus BB cytology sample types for mutation types commonly detectable by all assessed methods. Cohen’s kappa coefficient was calculated as: kappa = (Po−Pe)/(1−Pe), where Po is the observed concordance rate and Pe is the expected probability of chance agreement.

results

patient samples

In total, 116 FFPE samples were evaluable for analysis, as four samples were confirmed not to contain NSCLC cells. The majority of samples were of adenocarcinoma histology and had a tumor cell content of at least 50%. Both tissue and tumor dimensions were ≤19 mm in most samples.

Of the 30 BB cytology samples (24 adenocarcinoma, four squamous, one adenosquamous, one large cell), one sample was excluded from the analysis because its matching FFPE sample was not judged as NSCLC. The samples were taken at a mean of 39 days (range 20–70 days) before operation and the mean DNA concentration was 8.73 ng/μl (range 0.2–40.3 ng/μl). All 20 pleural effusion cytology samples were assessable for analysis. Volumes of pleural effusion cytology samples used for each test method were 0.7–0.8 ml.

Table 1. Success rate and EGFR mutation status determined by different EGFR mutation tests in FFPE, BB, and pleural effusion samples

<table>
<thead>
<tr>
<th>Sample type and method</th>
<th>No. of samples successfully analyzed (%)</th>
<th>No. of mutation-positive samples (%)</th>
<th>No. of mutation-negative samples (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FFPE samples (n = 116)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scorpion ARMS</td>
<td>115 (99.1)</td>
<td>65 (56.5)</td>
<td>50 (43.5)</td>
</tr>
<tr>
<td>PCR-Invader</td>
<td>116 (100.0)</td>
<td>65 (56.0)</td>
<td>51 (44.0)</td>
</tr>
<tr>
<td>PNA-LNA PCR clamp</td>
<td>106 (91.4)</td>
<td>61 (57.5)</td>
<td>45 (42.5)</td>
</tr>
<tr>
<td>PCR direct sequencing</td>
<td>110 (94.8)</td>
<td>64 (58.2)</td>
<td>46 (41.8)</td>
</tr>
<tr>
<td>Cycleave PCR</td>
<td>116 (100.0)</td>
<td>63 (54.3)</td>
<td>53 (45.7)</td>
</tr>
<tr>
<td><strong>BB cytology samples (n = 29)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scorpion ARMS</td>
<td>29 (100.0)</td>
<td>15 (51.7)</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>PCR-Invader</td>
<td>29 (100.0)</td>
<td>17 (58.6)</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>PNA-LNA PCR clamp</td>
<td>29 (100.0)</td>
<td>17 (58.6)</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>Cycleave PCR</td>
<td>29 (100.0)</td>
<td>16 (55.2)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td><strong>Pleural effusion cytology samples (n = 20)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scorpion ARMS</td>
<td>20 (100.0)</td>
<td>11 (55.0)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>PCR-Invader</td>
<td>20 (100.0)</td>
<td>11 (55.0)</td>
<td>9 (45.0)</td>
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<tr>
<td>PNA-LNA PCR clamp</td>
<td>20 (100.0)</td>
<td>10 (50.0)</td>
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<td>Cycleave PCR</td>
<td>20 (100.0)</td>
<td>11 (55.0)</td>
<td>9 (45.0)</td>
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</table>

*Percentage calculated based on the number of samples successfully analyzed; EGFR mutation status was determined before the study and samples were selected to allow for an ∼1:1 ratio of mutation-positive:mutation-negative samples.

ARMS, Amplification Refractory Mutation System; BB, bronchofiberscopic brushing; FFPE, formalin-fixed paraffin-embedded; PNA-LNA, peptide nucleic acid–locked nucleic acid.

discordance of five EGFR mutation tests

DNA admixtures

PCR-Invader, PNA-LNA PCR clamp, Cycleave PCR, and Scorpion ARMS methods detected each of the EGFR mutation types L858R, T790M, G719S, and the in-frame deletion E746-A750 type 1 at ratios ranging from 1% to 50% of mutant/wild-type allele. PCR direct sequencing detected all types of mutations in samples containing 5%–50% of plasmid DNA but could not detect any of the mutations in the 1% mutant DNA admixture, nor exon 19 deletion or L858R in the 2% mutant DNA admixture. There were no false positives in wild-type samples.

formalin-fixed paraffin-embedded samples

Success rates of all five EGFR mutation tests were over 90% in FFPE samples (Table 1). Concordance rates between any two methods ranged from 85.3% to 99.1% including samples unsuccessfully analyzed and from 94.3% to 100% excluding samples unsuccessfully analyzed (supplemental Table S2, available at Annals of Oncology online). The rate of type 1 discordance (different mutations detected between the methods) was 3.4% (4/116 samples) and the rate of type 2 discordance (mismatch of mutation status between the methods) was 6.9% (8/116 samples) in FFPE samples (supplemental Table S3, available at Annals of Oncology online).

Unsuccessful rates of mutation analyses and discordance rates by tumor/sample characteristics for FFPE samples are shown in supplemental Figure S1 (available at Annals of Oncology online). Higher unsuccessful rates were associated with histological subtype [squamous cell carcinoma, 4/7 (57.1%)], older sample age [year of surgery 2006, 9/10 (90.0%)], and larger tumor dimension [20–29 mm, 3/15 (57.1%)].
Discordances between the two major mutation types in FFPE samples were 81.8% (18/22) for exon 19 deletions and 87.2% (34/39) for L858R.

PCR direct sequencing identified rare mutations in six patients that were not detected by any other methods. In one of the other 17 samples, PCR direct sequencing detected an additional mutation [exon 18 deletion (E709_T710>D)], which the other methods were not designed to assess.

**Discussion**

Analysis of the control DNA admixture samples showed that the EGFR mutation tests had comparable sensitivity, with the exception of direct sequencing. The sensitivity of direct sequencing, although higher than expected and reported elsewhere [15], was lower than the other techniques.

The results of this study showed that all five EGFR mutation tests had comparable success rates (over 90%) in FFPE samples. These were consistently high success rates given that the fixation of some of the samples was not ideal (e.g., long fixation times). The success rates of direct sequencing were higher than anticipated based on previous studies of clinical samples. For example, in a recent study, ARMS and direct sequencing were used to detect known EGFR mutations in NSCLC FFPE samples, and ARMS was found to be a more sensitive and robust technique [13]. However, it should be recognized that even when utilizing the same technologies, differences in reagents, DNA quality, software, and crucially, primer design and amplicon size have a huge influence on direct sequencing success rates and mutation detection potential. Our results show that the processes implemented by the laboratory in this study are highly optimized for the detection of EGFR mutations from tumor DNA using direct sequencing. As the testing laboratories also carried out the DNA extraction (with the exception of BB cytology samples), the slight differences in DNA extraction and processes across the different laboratories could also impact on the overall performance of the test methods.

All the FFPE samples were examined by a pathologist and generally found to be of high quality and tumor content. The numbers of samples with different tumor/sample characteristics were too low to make any definitive conclusions regarding unsuccessful and discordance rates by these characteristics. However, sample unsuccessful rates appear to be associated with squamous cell carcinoma, older samples, and samples with long tumor dimension, all of which can make it difficult to extract DNA. In addition, discordance rates appeared higher in older samples or samples of low tumor cell content, short tumor dimension or short tissue dimension, where the quantities of DNA are small.

Concordance rates were generally over 85% (>94%, excluding samples unsuccessfully analyzed) between any two EGFR mutation tests in FFPE samples. The lowest concordance rates between the five methods were in comparison with the PNA-LNA PCR clamp method. As the PNA-LNA PCR clamp method also had a higher unsuccessful rate than the other methods, concordance rates were lower in comparison with other methods when including samples unsuccessfully analyzed. However, all kappa statistics were ≥0.70, indicating a high concordance of analysis results. Concordance rates for the two major EGFR mutation types, exon 19 deletions and L858R, across all five mutation tests in FFPE samples were also high (81.8% and 87.2%, respectively), illustrating the suitability of all
five methods for EGFR mutation analysis in clinical studies and diagnostic applications. However, as the concordance rates were not 100% for any one method, we would advocate the selection of a single method for consistent use during a clinical study. With regard to daily practice, the decision to select and adopt a particular technology is at the discretion of individual laboratories and may be influenced by the diagnostic environment in which they reside. Selection factors may include technical expertise of operators, cost, test status (in vitro diagnostic versus laboratory-developed test), or availability of instrumentation.

Several factors may have contributed to the discordances between the EGFR mutation tests. These factors may have included differences in sensitivity and specificity, different DNA extraction procedures between laboratories, variation in tumor cell content within and across samples, and tumor heterogeneity within an FFPE block [10, 11, 16].

The performance of all five EGFR mutation tests was comparable in the analysis of both BB and pleural effusion cytology samples, with 100% success rates. BB cytology samples showed high concordance rates (>93%, excluding samples unsuccessfully analyzed) between pairs of EGFR mutation tests and versus FFPE samples by each detection method. Using the PNA-LNA PCR clamp method, analysis of BB cytology samples was successful where the matched FFPE sample failed analysis. Some mutations were detected in cytology samples of low DNA concentrations where matching FFPE samples were assessed as mutation negative. This result suggests that cytology samples can be useful in mutation analysis when tissue samples cannot be used, are in a small quantity, or degradation of FFPE samples is suspected. Pleural effusion cytology samples may be particularly suitable for analysis as they can be obtained easily, non-invasively and repeatedly, and generally contain plenty of cancer cells, relative to other sample types.

To our knowledge, this is the first high-quality comparison study of EGFR mutation tests in both FFPE and cytology samples. The results of the current study indicate that cytology-derived DNA is a suitable alternative to FFPE samples for the analysis of EGFR mutations and may be useful when FFPE samples are unavailable for molecular analysis. Other studies have also shown that ARMS can be used to detect EGFR mutations in cytology samples from transbronchial needle aspirates [17] or pleural effusion [18] and that this technique appeared to be more sensitive than direct sequencing in this sample type. Other methods for EGFR mutation testing, including pyrosequencing [19] and high-resolution melting analysis [20], also exist.

In summary, the performance of all five EGFR mutation tests was comparable in the analysis of FFPE and cytology samples. Where EGFR mutation tests and standard operating procedures are used in a reliable robust way, with trained operators, in a well-developed diagnostic setting, comparable results are obtained across mutation tests and sample types. FFPE specimens are currently the sample of choice for determining EGFR mutation status [11]. However, the ability to use cytology samples allows additional patients to be tested for EGFR mutations, and therefore, more appropriate treatment of their disease.

acknowledgements

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funding

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disclosure

KG has received honoraria from Ono Pharmaceutical and Chugai Pharmaceutical and fees for consultancy/advisory boards from Ono Pharmaceutical. MS has received honoraria from Chugai Pharmaceutical and AstraZeneca. KN has received research grants from Daiichi Sankyo, Chugai Pharmaceutical, AstraZeneca, Glaxo SmithKline, and Solasia Pharma KK, research support from Chugai Pharmaceutical, and honoraria from Kyowa Hakko Kirin, Sumitomo Bakelite, Taiho Pharmaceutical, and Qiagen. KH has received patent fees from Mitsubishi Chemical Medience. TM has received honoraria from AstraZeneca and Chugai Pharmaceutical. JW, ED, RM, and TT are employees of AstraZeneca and hold stock in AstraZeneca. GI has declared no conflicts of interest.

references

Prophylactic cranial irradiation in small-cell lung cancer: Findings from a North Central Cancer Treatment Group Pooled Analysis


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Background: This pooled analysis evaluated the outcomes of prophylactic cranial irradiation (PCI) in 739 small-cell lung cancer (SCLC) patients with stable disease (SD) or better following chemotherapy ± thoracic radiation therapy (TRT) to examine the potential advantage of PCI in a wider spectrum of patients than generally participate in PCI trials.

Patients and methods: Three hundred eighteen patients with extensive SCLC (ESCLC) and 421 patients with limited SCLC (LSCLC) participated in four phase II or III trials. Four hundred fifty-nine patients received PCI (30 Gy/15 or 25 Gy/10) and 280 did not. Survival and adverse events (AEs) were compared.

Results: PCI patients survived significantly longer than non-PCI patients [hazard ratio [HR] = 0.61 [95% confidence interval (CI): 0.52–0.72]; P < 0.0001]. The 1- and 3-year survival rates were 56% and 18% for PCI patients versus 32% and 5% for non-PCI patients. PCI was still significant after adjusting for age, performance status, gender, stage, complete response, and number of metastatic sites (HR = 0.82, P = 0.04). PCI patients had significantly more grade 3+ AEs (64%) compared with non-PCI patients (50%) (P = 0.0004). AEs associated with PCI included alopecia and lethargy. Dose fractionation could be compared only for LSCLC patients and 25 Gy/10 was associated with significantly better survival compared with 30 Gy/15 (HR = 0.67, P = 0.018).

Conclusions: PCI was associated with a significant survival benefit for both ESCLC and LSCLC patients who had SD or a better response to chemotherapy ± TRT. Dose fractionation appears important. PCI was associated with an increase in overall and specific grade 3+ AE rates.

Key words: PCI, prophylactic cranial irradiation, radiotherapy, small-cell lung cancer, survival