



Caring Ambassadors Lung Cancer Program

Literature Review April 2017

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Distinct Afatinib Resistance Mechanisms Identified in Lung Adenocarcinoma Harboring an EGFR Mutation.](#)

Yamaoka T1, Ohmori T2, Ohba M2, et al. Mol Cancer Res. 2017 Mar 13. pii: molcanres.0482.2016. doi: 10.1158/1541-7786.MCR-16-0482. [Epub ahead of print]

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are associated with significant responses in non-small cell lung cancer (NSCLC) patients harboring EGFR-activating mutations. However, acquired resistance to reversible EGFR-TKIs remains a major obstacle. In particular, while the second-generation irreversible EGFR-TKI afatinib is currently used for treating NSCLC patients, the mechanisms underlying acquired afatinib resistance remain poorly understood. Here, heterogeneous mechanisms of acquired resistance were identified following long-term exposure to increasing doses of afatinib in EGFR mutant lung adenocarcinoma PC9 cells. Notably, three resistant cell lines, PC-9AFR1, PC-9AFR2, and PC-9AFR3 (AFR1, AFR2, and AFR3, respectively), employed distinct mechanisms for avoiding EGFR inhibition, with increased EGFR expression being detected in all resistant cell lines. Moreover, an activating EGFR mutation was partially lost in AFR1 and AFR2 cells. AFR1 cells exhibited afatinib resistance as a result of wild-type KRAS amplification and overexpression; however, these cells showed a progressive decrease and eventual loss of the acquired KRAS dependence, as well as resensitization to afatinib, following a drug holiday. Meanwhile, AFR2 cells exhibited increased expression of insulin-like growth factor-binding protein 3 (IGFBP3), which promoted insulin-like growth factor 1 receptor (IGF1R) activity and subsequent AKT phosphorylation, thereby indicating a potential bypass signaling pathway associated with IGF1R. Finally, AFR3 cells harbored the secondary EGFR mutation T790M. Our findings constitute the first report showing acquired wild-type KRAS overexpression and attenuation of afatinib resistance following a drug holiday.

[Gli1 expression in cancer stem-like cells predicts poor prognosis in patients with lung squamous cell carcinoma.](#)

Cui Y1, Cui CA2, Yang ZT2, Ni WD2, Jin Y3, Xuan YH4. Exp Mol Pathol. 2017 Mar 9;102(2):347-353. doi: 10.1016/j.yexmp.2017.03.004. [Epub ahead of print]

PURPOSE: Glioma-associated oncogene homolog 1 (Gli1) is involved in cancer stem cell (CSC) maintenance in various tumors; however, its expression and clinical significance in lung squamous cell

carcinoma (LSCC) has not been reported. In this study, we aimed to reveal the clinical significance of Gli1 in LSCC and investigate the potential of Gli1 as a CSC marker by comparing its expression with that of other stemness-related genes in LSCC. **METHODS:** We assessed the expressions of Gli1, LSD1, CD44, Sox9 and Sox2 by immunohistochemistry in the tissue specimens obtained from 101 patients with LSCC. The relationship of Gli1 expression with clinicopathological parameters and cell-cycle regulating genes was investigated. **RESULTS:** Gli1 expression was significantly correlated with T stage ($P<0.001$), lymph node metastasis ($P=0.002$), and clinical stage ($P=0.005$) of LSCC. The Kaplan-Meier survival analysis revealed that the expression of Gli1 in LSCC was all significantly associated with poor overall survival (OS: $P=0.005$). Cox regression analysis further confirmed that Gli1 is a prognostic marker of unfavorable clinical outcome of LSCC. Gli1 expression was significantly correlated with the expression of stemness-related genes such as LSD1 ($P=0.009$) and CD44 ($P<0.001$), but not with those of Sox2 and Sox9. However, Gli1 expression was associated with the expression of hypoxia-inducible factors1 α (HIF1 α ; $P<0.001$) and Cyclin D1 ($P=0.002$), respectively. In additionally, microvessel density (MVD) was significantly higher in Gli1-positive LSCC than in the negative LSCC ($P=0.026$). **CONCLUSIONS:** Our results suggest that Gli1 may be a potential LSCC stem cell marker and an independent indicator of poor prognosis for patients with LSCC.

SCREENING, DIAGNOSIS AND STAGING

[Identifying Community Perspectives for a Lung Cancer Screening Awareness Campaign in Appalachia Kentucky: The Terminate Lung Cancer \(TLC\) Study.](#)

Cardarelli R1, Roper KL2, Cardarelli K3, et al. J Cancer Educ. 2017 Mar;32(1):125-134. doi: 10.1007/s13187-015-0914-0.

Lung cancer screening with low-dose computed tomography (LDCT) scan is now covered by Centers for Medicare & Medicaid Services following an evidence-based recommendation, but a shared decision making process should inform patients of risks and limitations. An awareness campaign promoting LDCT screenings is an opportunity to elicit patient engagement with health providers about the risks and benefits. Focus groups representing three regions of Appalachian Kentucky known for high lung cancer rates discussed development of a lung cancer screening campaign. Recommendations included messaging content, appeals or design, campaign implementation, and trusted information or communication sources. Community health workers (CHWs) from three Eastern Kentucky regions recruited individuals from their local communities using established client files. CHWs hosted six total focus groups (7-11 participants each) using questions guided by the Communication-Persuasion Matrix framework. All sessions were recorded and transcribed for independent content analysis. A total of 54 individuals (61.1 % female; >55 pack year history) were participated. Prior to discussion, most participants had not heard of lung cancer screening. Cited needs for content of a campaign included benefits of early detection and payment information. Messages considered most persuasive were those that include personal testimony, messages of hope, prolonged life, and an emphasis on family and the ambition to survive. Having information come from one's family doctor or specialty provider was considered important to message communication. Messages about survivorship, family, and prolonged life should be considered in lung cancer screening awareness campaigns. Our results provide community input about messages regarding screening options.

[Evaluation of Promotional Materials To Promote Low-Dose Computed Tomography \(LDCT\) Screening to High-Risk Consumers and Health Care Providers.](#)

Hudson JN1, Quinn GP1,2, Wilson LE1, Simmons VN3,4,5. J Cancer Educ. 2017 Mar 11. doi: 10.1007/s13187-017-1204-9. [Epub ahead of print]

Low-dose computed tomography (LDCT) screening is a promising screening modality for increasing the detection rate of early stage lung cancers among high-risk individuals. Despite being recommended by the US Preventative Services Task Force, uptake of LDCT remains low. The objective of the current study

was to gather feedback from high-risk consumers and health care providers on LDCT promotional materials. Focus group discussions were conducted with high-risk individuals (8 focus groups; N = 38) and primary care providers (9 focus groups; N = 23). Participants reviewed existing LDCT promotional materials to assess their perceptions of media materials created to publicize LDCT. Data were analyzed using the constant comparative method. Several key themes emerged from focus groups that can be used to inform development of future LDCT promotional materials. High-risk (HR) participants expressed greater receptivity for promotional materials that did not further stigmatize lung cancer and/or smoking and expressed preferences for materials that clearly outlined the risks/benefits of screening. Primary care providers (PCPs) offered suggestions to facilitate the referral process such as diagnostic codes and requested a design that clearly outlined eligibility criteria. A clear and thorough explanation of LDCT eligibility, cost, harms, and benefits was of chief importance for both PCP and HR audiences. Given that PCPs and HR audiences are not well informed on the specifics of LDCT screening eligibility and insurance coverage, creating provider and patient education opportunities will aid in shared decision-making opportunities. Promotional materials that meet the needs of the target audience are needed to facilitate discussions of risks/benefits of screening with HR individuals.

[Implementation of Lung Cancer Screening in the Veterans Health Administration.](#) Kinsinger LS1, Anderson C2, Kim J1, et al. JAMA Intern Med. 2017 Mar 1;177(3):399-406. doi: 10.1001/jamainternmed.2016.9022.

IMPORTANCE: The US Preventive Services Task Force recommends annual lung cancer screening (LCS) with low-dose computed tomography for current and former heavy smokers aged 55 to 80 years. There is little published experience regarding implementing this recommendation in clinical practice. **OBJECTIVES:** To describe organizational- and patient-level experiences with implementing an LCS program in selected Veterans Health Administration (VHA) hospitals and to estimate the number of VHA patients who may be candidates for LCS. **DESIGN, SETTING, AND PARTICIPANTS:** This clinical demonstration project was conducted at 8 academic VHA hospitals among 93 033 primary care patients who were assessed on screening criteria; 2106 patients underwent LCS between July 1, 2013, and June 30, 2015. **INTERVENTIONS:** Implementation Guide and support, full-time LCS coordinators, electronic tools, tracking database, patient education materials, and radiologic and nodule follow-up guidelines. **MAIN OUTCOMES AND MEASURES:** Description of implementation processes; percentages of patients who agreed to undergo LCS, had positive findings on results of low-dose computed tomographic scans (nodules to be tracked or suspicious findings), were found to have lung cancer, or had incidental findings; and estimated number of VHA patients who met the criteria for LCS. **RESULTS:** Of the 4246 patients who met the criteria for LCS, 2452 (57.7%) agreed to undergo screening and 2106 (2028 men and 78 women; mean [SD] age, 64.9 [5.1] years) underwent LCS. Wide variation in processes and patient experiences occurred among the 8 sites. Of the 2106 patients screened, 1257 (59.7%) had nodules; 1184 of these patients (56.2%) required tracking, 42 (2.0%) required further evaluation but the findings were not cancer, and 31 (1.5%) had lung cancer. A variety of incidental findings, such as emphysema, other pulmonary abnormalities, and coronary artery calcification, were noted on the scans of 857 patients (40.7%). **CONCLUSIONS AND RELEVANCE:** It is estimated that nearly 900 000 of a population of 6.7 million VHA patients met the criteria for LCS. Implementation of LCS in the VHA will likely lead to large numbers of patients eligible for LCS and will require substantial clinical effort for both patients and staff.

[Routine genetic testing of lung cancer specimens derived from surgery, bronchoscopy and fluid aspiration by next generation sequencing.](#) Yamamoto G1, Kikuchi M1, Kobayashi S1, et al. Int J Oncol. 2017 Mar 27. doi: 10.3892/ijo.2017.3935. [Epub ahead of print]

After the development of EGFR tyrosine kinase inhibitors (TKIs), genetic testing of EGFR became required for effective treatment of lung cancer. Initially, the testing was conducted separately for each mutated region. However, many EGFR mutations have since been identified that determine the efficacy of EGFR-TKIs. Therefore, genetic testing of EGFR by next generation sequencing (NGS) may be a suitable strategy for lung cancer. Here we examined the applicability of the NGS method in regard to sensitivity, time and cost. A total of 939 specimens were obtained from 686 lung cancer patients at our hospital. DNA and RNA were simultaneously extracted from specimens derived from surgery, bronchoscopy, and fluid aspiration. Specimens included cerebrospinal fluid, pleural effusion, abdominal fluid, and pericardial effusion. From RNA, target regions (EGFR, KRAS, ALK fusion and RET fusion) were enriched by RT-PCR and sequenced with MiSeq. From DNA, PCR or PCR-RFLP conventional methods were performed. NGS and conventional methods were carried out routinely per week. Among the total 939 specimens, 38 specimens could not be examined with NGS. Among these, 34 specimens were analyzed by conventional testing with simultaneously extracted DNA. The remaining four specimens could not be tested with either method. Compared with the conventional method, the concordance rate of mutations was 99% (892/901), excluding specimens with NGS failure. The time period required from processing of specimens to results was 4 days, and the cost per sample was sufficiently low. In conclusion, the genetic testing with NGS method was useful for lung cancer treatment. The cost, sensitivity and time were able to tolerate routine examinations.

[**A Prospective, Multi-institutional, Pathologist-Based Assessment of 4 Immunohistochemistry Assays for PD-L1 Expression in Non-Small Cell Lung Cancer.**](#) Rimm DL1, Han G2, Taube JM3, et al. JAMA Oncol. 2017 Mar 9. doi: 10.1001/jamaoncol.2017.0013. [Epub ahead of print]

IMPORTANCE: Four assays registered with the US Food and Drug Administration (FDA) detect programmed cell death ligand 1 (PD-L1) to enrich for patient response to anti-programmed cell death 1 and anti-PD-L1 therapies. The tests use 4 separate PD-L1 antibodies on 2 separate staining platforms and have their own scoring systems, which raises questions about their similarity and the potential interchangeability of the tests. **OBJECTIVE:** To compare the performance of 4 PD-L1 platforms, including 2 FDA-cleared assays, 1 test for investigational use only, and 1 laboratory-developed test. **DESIGN, SETTING, AND PARTICIPANTS:** Four serial histologic sections from 90 archival non-small cell lung cancers from January 1, 2008, to December 31, 2010, were distributed to 3 sites that performed the following immunohistochemical assays: 28-8 antibody on the Dako Link 48 platform, 22c3 antibody on the Dako Link 48 platform, SP142 antibody on the Ventana Benchmark platform, and E1L3N antibody on the Leica Bond platform. The slides were scanned and scored by 13 pathologists who estimated the percentage of malignant and immune cells expressing PD-L1. Statistical analyses were performed from December 1, 2015, to August 30, 2016, to compare antibodies and pathologists' scoring of tumor and immune cells. **MAIN OUTCOMES AND MEASURES:** Percentages of malignant and immune cells expressing PD-L1. **RESULTS:** Among the 90 samples, the SP142 assay was an outlier, with a significantly lower mean score of PD-L1 expression in both tumor and immune cells (tumor cells: 22c3, 2.96; 28-8, 3.26; SP142, 1.99; E1L3N, 3.20; overall mean, 2.85; and immune cells: 22c3, 2.15; 28-8, 2.28; SP142, 1.62; E1L3N, 2.28; overall mean, 2.08). Pairwise comparisons showed that the scores from the 28-8 and E1L3N tests were not significantly different but that the 22c3 test showed a slight (mean difference, 0.24-0.30) but statistically significant reduction in labeling of PD-L1 expression in tumor cells. Evaluation of intraclass correlation coefficients (ICCs) between antibodies to quantify interassay variability for PD-L1 expression in tumor cells showed high concordance between antibodies for tumor cell scoring (0.813; 95% CI, 0.815-0.839) and lower levels of concordance for immune cell scoring (0.277; 95% CI, 0.222-0.334). When examining variability between pathologists for any single assay, the concordance between pathologists' scoring for PD-L1 expression in tumor cells ranged from

ICCs of 0.832 (95% CI, 0.820-0.844) to 0.882 (95% CI, 0.873-0.891) for each assay, while the ICCs from immune cells for each assay ranged from 0.172 (95% CI, 0.156-0.189) to 0.229 (95% CI, 0.211-0.248). **CONCLUSIONS AND RELEVANCE:** The assay using the SP142 antibody is an outlier that detected significantly less PD-L1 expression in tumor cells and immune cells. The assay for antibody 22c3 showed slight yet statistically significantly lower staining than either 28-8 or E1L3N, but this significance was detected only when using the mean of 13 pathologists' scores. The pathologists showed excellent concordance when scoring tumor cells stained with any antibody but poor concordance for scoring immune cells stained with any antibody. Thus, for tumor cell assessment of PD-L1, 3 of the 4 tests are concordant and reproducible as read by pathologists.

Lung Cancer Diagnosis by Fine Needle Aspiration Is Associated With Reduction in Resection of Nonmalignant Lung Nodules. Barta JA1, Henschke CI2, Flores RM3, Yip R2, Yankelevitz DF2, Powell CA4. *Ann Thorac Surg.* 2017 Mar 5. pii: S0003-4975(16)31776-3. doi: 10.1016/j.athoracsur.2016.11.055. [Epub ahead of print]

BACKGROUND: The rates of resection of nonmalignant lung nodules suspected preoperatively to be lung cancer vary widely and are reported to be as high as 40%. We determined the impact of the frequent use of computed tomography (CT)-guided fine needle aspiration (FNA) on the resection rate of nonmalignant nodules and frequency of resections of benign disease among patients undergoing evaluation for lung cancer resection operation in an academic medical center. **METHODS:** Eligible patients underwent CT-guided FNA, surgical resection, or both during the 12-month period between July 2013 and July 2014 for known or suspected first primary resectable stage I-III lung cancer. Patient data were extracted from the electronic medical records. **RESULTS:** One hundred ninety-seven patients underwent surgical resection; among them the overall resection rate of nonmalignant lesions was 13.1% (26/197). For those with preoperative FNA, the rate was 7.9% (11/139), and for those with no biopsy, the rate was 25.9% (15/58) ($p = 0.001$). The sensitivity and specificity of FNA biopsy were 96% and 98%, respectively. The false-negative rate was 3.9% (5/128). **CONCLUSIONS:** The resection rate of nonmalignant nodules was significantly lower for patients with preoperative CT-guided FNA biopsy than in those without. The diagnostic accuracy of FNA in these patients at moderate to high risk for lung cancer is higher than that of positron emission tomography, with a low rate of adverse events. These findings suggest that the frequent use of preoperative diagnostic confirmation by FNA results in a low rate of nonmalignant resection.

Clinical Impact of Single Nucleotide Polymorphism in PD-L1 on Response to Nivolumab for Advanced Non-Small-Cell Lung Cancer Patients. Nomizo T1, Ozasa H1, Tsuji T1, et al. *Sci Rep.* 2017 Mar 23;7:45124. doi: 10.1038/srep45124.

This study was intended to determine the efficacy of nivolumab, we evaluated treatment response with respect to PD-1/PD-L1 SNPs among patients with NSCLC. A total of 50 patients with NSCLC were treated with nivolumab and were also evaluated for PD-1/PD-L1 single nucleotide polymorphisms (SNPs) from plasma DNA. We investigated the association among PD-1/PD-L1 SNPs, objective response rate (ORR) and progression-free survival (PFS). Two of seven SNPs studied showed association with ORR and PFS, with maximum evidence at the marker rs2282055. The ORR was 25%, 15%, and 0% for the G/G, G/T and T/T genotypes of PD-L1 rs2282055, respectively. The G allele of PD-L1 rs2282055 was significantly associated with better clinical response compared with the T allele ($P = 0.0339$ [Cochran-Armitage trend test]). The median PFS time was 2.6 months (95% confidence interval [CI], 1.8 months to 4.3 months) for the G/G and G/T genotypes and 1.8 months (95% confidence interval [CI], 0.4 months to 2.2 months) for the T/T genotype ($P = 0.0163$). Moreover, the C/C and C/G genotypes of PD-L1 rs4143815 were significantly associated with better ORR and PFS in NSCLC patients treated with

nivolumab. These results suggest that rs2282055 and rs4143815 may be a biomarker for the efficacy of nivolumab.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Extended surgery for T4 lung cancer: a 30 years' experience.](#) Darteville PG1, Mitilian D2, Fadel E2. *Gen Thorac Cardiovasc Surg.* 2017 Mar 27. doi: 10.1007/s11748-017-0752-6. [Epub ahead of print] T4 non-small cell lung carcinomas (NSCLC) were deemed unresectable. Advances in surgery have challenged this dogma. We describe technical aspects and result on superior vena cava (SVC), carinal, thoracic inlet tumor surgeries, and resection under cardiopulmonary bypass (CPB). SVC reconstruction requires hemodynamic control to reverse SVC clamping cerebral effects and excellent cephalic venous bed patency. Among 50 SVC resections, including 25 carinal pneumonectomies, post-operative mortality rate was 8%. In the N0-N1 group, 5- and 10-year survival rates were 46.6 and 37.7%, respectively. Right carinal pneumonectomy was performed through right thoracotomy. Sternotomy was favored for left carinal pneumonectomy or carinal resection alone. Among 138 carinal resections, including eight right upper lobectomies, 123 right pneumonectomies, four left pneumonectomies, and three isolated carinal resections, the post-operative mortality rate was 9.4%. In the N0-N1 patients, 5-year survival rate was 47%. 191 patients underwent resections of thoracic inlet tumors through a transclavicular cervicothoracic anterior approach combined in 63 patients with a posterior midline incision for limited spine invasion. In N0-N1 group, 5- and 10-year survival rates were 41.5 and 29.7%, respectively. CPB allowed resection of tumors invading the heart or great vessels in 13 patients. R0 resection and post-operative mortality rate were 94.4 and 5.5%, respectively. In this series of 388 T4 NSCLC, the post-operative mortality rate was 4%. In the R0 and N0-N1 groups, the 5-year survival rates were 44 and 41%, respectively. Surgical resection of T4 locally advanced NSCLC is worth being performed in selected N0-N1 patients, provided that a radical resection is expected.

[Addition of Surgery After Radiation Significantly Improves Survival in Stage IIIB Non-small Cell Lung Cancer: A Population-Based Analysis.](#) Herskovic A1, Chitti B2, Christos P3, Wernicke AG1, Parashar B4. *World J Surg.* 2017 Mar;41(3):758-762. doi: 10.1007/s00268-016-3764-y.

OBJECTIVES: Limited work, either retrospective or prospective, has been done to investigate whether or not there is a cause-specific mortality (CSM) or all-cause mortality (ACM) benefit to adding surgery following neoadjuvant treatment for Stage IIIB NSCLC. **METHODS:** We extracted patients with Stage IIIB NSCLC from the Survival, Epidemiology, and End Results Program (SEER) database treated from 2004 to 2012 with either radiation alone or radiation followed by surgery. Other variables extracted were age, sex, race, and tumor location. The impact of patient and treatment variables on CSM and ACM was explored using Cox multivariable regression analysis. **RESULTS:** A total of 14,065 patients were extracted from the SEER database. On multivariable analysis, even after adjustment for age, gender, race, and site, radiation followed by surgery was associated with a reduction in cause-specific mortality compared to radiation alone (adjusted HR 0.46; 95 % CI 0.41, 0.52; $p < 0.0001$). Median overall survival was 11 months in the radiotherapy alone arm versus 29 months in the radiotherapy plus surgery arm ($p < 0.0001$ by log-rank test). After adjustment for these same factors, radiation followed by surgery was also associated with a reduction in all-cause mortality compared with radiation alone (adjusted HR 0.47; 95 % CI 0.42, 0.52; $p < 0.0001$). Median cause-specific survival was 12 months in the radiotherapy alone arm versus 33 months in the radiotherapy plus surgery arm ($p < 0.0001$ by log-rank test). **DISCUSSION:** In the SEER database, there appears to be both a CSM and ACM benefit to adding surgery following radiation for Stage IIIB NSCLC.

[Lobectomy for Lung Cancer at Veterans Administration Medical Center Versus Academic Medical Center.](#) Geraci T1, Baratta V1, Young J1, Milman S1, Dunican AM2, Jones RN3, Ng T4. *Ann Thorac Surg.* 2017 Mar 24. pii: S0003-4975(17)30012-7. doi: 10.1016/j.athoracsur.2016.12.040. [Epub ahead of print]

BACKGROUND: Hospital and surgeon volume each have an association with postoperative outcomes. The volume of lung cancer surgery at our Veterans Administration Medical Center (VAMC) is lower than at our academic medical center (AMC). We compared the outcomes after lobectomy at VAMC versus AMC to identify specific areas of clinical care requiring quality improvement. **METHODS:** To keep surgeon experience constant, data were derived from a prospective database from a single surgeon. Included were all male patients undergoing lobectomy for non-small cell lung cancer. Postoperative morbidity, mortality, and overall survival were compared after propensity score matching. **RESULTS:** From 2004 to 2013, 419 patients were evaluated (338 AMC, 81 VAMC). Outcomes comparison after propensity score matching of 81 AMC patients with 81 VAMC patients found a higher rate of major complications (12% versus 27%, $p = 0.02$) and longer hospital stay (median 6.0 versus 7.5 days, $p < 0.001$) for VAMC, but no difference in 90-day mortality (AMC 5% versus VAMC 6%, $p > 0.99$). Pneumonia was the specific complication found to be higher at VAMC (11% versus AMC 1.2%, $p = 0.01$). There was no difference in 5-year overall survival for stage I disease (AMC 68% versus VAMC 69%, $p = 0.95$). **CONCLUSIONS:** Keeping surgeon experience constant, and after adjusting for patient factors, the rate of major complication after lobectomy is higher at VAMC. The difference is largely attributable to a higher rate of postoperative pneumonia at VAMC. Complications after pulmonary resection at VAMC could be reduced by implementing quality improvement initiatives aimed at reducing the rate of postoperative pneumonia.

[Standardizing Robotic Lobectomy: Feasibility and Safety in 128 Consecutive Lobectomies Within a Single Healthcare System.](#) Lazar JF1, Spier LN, Hartman AR, Lazzaro RS. *Innovations (Phila).* 2017 Mar 23. doi: 10.1097/IMI.0000000000000352. [Epub ahead of print]

OBJECTIVE: Single-surgeon cohorts assessing robotically assisted video-assisted thoracic (RA-VATS) lobectomy have reported good outcomes, but there are little data regarding multiple surgeons applying a standard technique in separate hospitals. The purpose of this study was to show how a standardized robotic technique is both safe and reproducible between surgeons and institutions. **METHODS:** From July 1, 2012, to October 1, 2013, patients undergoing RA-VATS lobectomy for both benign and malignant disease were identified from a prospectively collected database of two thoracic surgeons from different hospitals within the same healthcare system and retrospectively analyzed. Each surgeon employed an identical "rule of 10" completely port-based approach through all 128 cases. The primary end points of the study were in-hospital and 30-day mortality. Secondary end points were differences in morbidity and perioperative outcomes between the two surgeons based on their "rule of 10" technique. **RESULTS:** A total of 128 cases were performed with 121 lobectomies, 3 bilobectomies, and 4 pneumonectomies for both malignant and benign disease. Each surgeon had 64 cases without a single in-hospital or 30-day mortality. Overall morbidity was 16.4%. Each surgeon had one readmission and take back to operating room (a washout and a mechanical pleurodesis). The most common complication was prolonged air leak (38.1%, 8/21 patients). There was no statistical difference in length of stay, complications, severity of illness, and clinical staging between the two surgeons. There was a significant difference in resected lymph nodes (11.79 vs 14.45, $P = 0.0086$). Compared with published national meta-analysis on RA-VAT lobectomies, there was a significantly reduced length of stay (4.2 vs 6 days, $P = 0.0436$) and bleeding (0.8 vs 1.8%, $P = 0.0003$). Nodal upstaging from cN0 to pN1 was 8% and cN0 to pN2 was 2% for an overall nodal upstaging of 10% for stage I nonsmall cell lung cancer. **CONCLUSIONS:** By standardizing how a robotic lobectomy is performed, we were able to show that

RA-VATS lobectomy is safe and may allow for the expansion of minimally invasive lobectomy to surgeons who otherwise have failed to adopt traditional VATS. When compared with the most recent national meta-analysis, we had reduced morbidity, mortality, bleeding, and length of stay. Robotic nodal upstaging for stage I nonsmall lung cancer was consistent with larger multicenter study. We hope that these results will help lead to the standardization robotic lobectomy and a larger multisurgeon/institutional study that could pave the way for greater adoption of minimally invasive lobectomy.

[Role of Segmentectomy in Treatment of Early-Stage Non-Small Cell Lung Cancer.](#) Hennon M1,2, Landreneau RJ3. *Ann Surg Oncol.* 2017 Mar 1. doi: 10.1245/s10434-017-5787-5. [Epub ahead of print]

PURPOSE AND DESIGN: Standard treatment for early-stage non-small cell lung cancer has traditionally involved lobectomy. Historical data that demonstrates suboptimal results for sublobar resection compared to lobectomy have been challenged in recent years with retrospective data for patients with T1a disease. For patients who are not candidates for lobectomy, options for sublobar resection include wedge resection or anatomic segmentectomy. Segmentectomy has long been held to be a better cancer operation than wedge resection, and its role in treating early-stage lung cancer remains controversial in patients who are candidates for lobectomy. A review of available literature involving segmentectomy and possible predictors of failure for segmentectomy was performed in an attempt to clarify the role of segmentectomy for early-stage lung cancer. **RESULTS AND CONCLUSIONS:** Current evidence is conflicting regarding the optimal scenario for sublobar resection with segmentectomy. Two large-scale randomized trials are currently addressing the question. In the meantime, certain preoperative and intraoperative considerations should be taken into account when considering segmentectomy for the treatment of early-stage non-small cell lung cancer.

NSCLC – SYSTEMIC THERAPIES (CHEMOTHERAPY, TARGETED THERAPY, AND IMMUNOTHERAPY)

[Prognostic significance of nestin expression in patients with resected non-small cell lung cancer treated with platinum-based adjuvant chemotherapy; relationship between nestin expression and epithelial to mesenchymal transition related markers.](#) Ryuge S1, Sato Y2, Nagashio R2, et al. *PLoS One.* 2017 Mar 30;12(3):e0173886. doi: 10.1371/journal.pone.0173886. eCollection 2017.

INTRODUCTION: Although adjuvant platinum-based chemotherapy (AC) has been shown to improve survival of patients with completely resected stage II and stage IIIA non-small cell lung cancer (NSCLC), its effect is limited. Nestin is a class VI intermediate filament protein expressed in neural stem cells and several cancer cells including NSCLC. In the present study, we aimed to determine its prognostic significance concerning survival in NSCLC patients receiving AC. **METHODS:** Nestin expression in cancer cells was immunohistochemically studied in 90 patients with completely resected stage II and stage IIIA NSCLC treated with AC and its association with clinicopathologic parameters, including ABCG2, E-cadherin, and vimentin expression, was evaluated. Kaplan-Meier survival analysis and Cox proportional hazards models were used to estimate the effect of nestin expression on survival.

RESULTS: Nestin expression was observed in 28 of the 90 (31.1%) NSCLCs. Clinicopathologically, nestin expression was associated with loss of E-cadherin expression ($P = 0.006$) and vimentin positive expression ($P < 0.001$). In survival analysis, nestin expression was significantly associated with a poorer prognosis ($P = 0.028$). Multivariable analysis confirmed that nestin expression is an independent prognostic indicator in NSCLC patients receiving AC (HR = 2.56; 95% CI, 1.23-5.30, $P = 0.01$).

CONCLUSION: The present study reveals that nestin expression is a prognostic indicator of a poorer survival probability in NSCLC patients receiving AC, although its prognostic significance still requires confirmation with larger patient populations.

[A phase Ib/II study of cabozantinib \(XL184\) with or without erlotinib in patients with non-small cell lung cancer.](#) Wakelee HA1, Gettinger S2, Engelman J3, et al. *Cancer Chemother Pharmacol.* 2017 Mar 28. doi: 10.1007/s00280-017-3283-z. [Epub ahead of print]

PURPOSE: Cabozantinib is a multi-kinase inhibitor that targets MET, AXL, and VEGFR2, and may synergize with EGFR inhibition in NSCLC. Cabozantinib was assessed alone or in combination with erlotinib in patients with progressive NSCLC and EGFR mutations who had previously received erlotinib.

METHODS: This was a phase Ib/II study (NCT00596648). The primary objectives of phase I were to assess the safety, pharmacokinetics, and pharmacodynamics and to determine maximum tolerated dose (MTD) of cabozantinib plus erlotinib in patients who failed prior erlotinib treatment. In phase II, patients with prior response or stable disease with erlotinib who progressed were randomized to single-agent cabozantinib 100 mg qd vs cabozantinib 100 mg qd and erlotinib 50 mg qd (phase I MTD), with a primary objective of estimating objective response rate (ORR). **RESULTS:** Sixty-four patients were treated in phase I. Doses of 100 mg cabozantinib plus 50 mg erlotinib, or 40 mg cabozantinib plus 150 mg erlotinib were determined to be MTDs. Diarrhea was the most frequent dose-limiting toxicity and the most frequent AE (87.5% of patients). The ORR for phase I was 8.2% (90% CI 3.3-16.5). In phase II, one patient in the cabozantinib arm (N = 15) experienced a partial response, for an ORR of 6.7% (90% CI 0.3-27.9), with no responses for cabozantinib plus erlotinib (N = 13). There was no evidence that co-administration of cabozantinib markedly altered erlotinib pharmacokinetics or vice versa.

CONCLUSIONS: Despite responses with cabozantinib/erlotinib in phase I, there were no responses in the combination arm of phase II in patients with acquired resistance to erlotinib. Cabozantinib did not appear to re-sensitize these patients to erlotinib.

[Long-term Outcomes of Induction Carboplatin and Gemcitabine Followed by Concurrent Radiotherapy With Low-dose Paclitaxel and Gemcitabine for Stage III Non-small-cell Lung Cancer.](#) Guilbault C1, Garant A2, Faria S2, Owen S3, Ofiara L4, Duclos M2, Hirsh V3, Kopeck N2. *Clin Lung Cancer.* 2017 Mar 1. pii: S1525-7304(17)30046-3. doi: 10.1016/j.clcc.2017.02.003. [Epub ahead of print]

BACKGROUND: Standard treatment for unresectable stage III non-small-cell lung cancer (NSCLC) is concurrent chemo-radiation (CRT). A regimen of induction carboplatin and gemcitabine followed by CRT was developed at the McGill University Health Centre to prevent delays in treatment initiation. We report the long-term outcomes with this regimen based on a pooled analysis of both protocol patients from a phase II study and nonprotocol patients. **METHODS AND MATERIALS:** Outcomes and toxicity data were retrieved for 142 patients with stage III NSCLC: 43 patients treated on protocol between January 2003 and November 2004, and 101 patients treated off-protocol between December 2004 and August 2013. Patients received 2 cycles of carboplatin with an area under the curve of 5 intravenously (IV) on day 1 and gemcitabine 1000 mg/m² IV on days 1 and 8 every 3 weeks, followed on day 50 by CRT, 60 Gy/30 over 6 weeks, concomitantly with 2 cycles of paclitaxel 50 mg/m² IV and gemcitabine 100 mg/m² IV on days 1 and 8 every 3 weeks. **RESULTS:** The median overall survival was 23.2 months. With a median follow-up of 23.8 months, the 3-, 4-, and 5-year overall survival was 38%, 30%, and 26%, respectively. The median and 5-year progression-free survival rates were 12.5 months and 25%, respectively. Rates of grade \geq 3 hematologic, esophageal, and respiratory toxicity were 20%, 10%, and 10%, respectively. Forty-eight patients received further lines of chemotherapy. **CONCLUSION:** The present analysis affirms the favorable toxicity profile of this novel induction chemotherapy, without apparent compromise in clinical outcomes, when compared with regimens using immediate concurrent CRT.

[Efficacy and safety of nivolumab in Japanese patients with advanced or recurrent squamous non-small cell lung cancer.](#) Hida T1, Nishio M2, Nogami N3, et al. *Cancer Sci.* 2017 Mar 7. doi: 10.1111/cas.13225. [Epub ahead of print]

Limited treatment options are available for stage IIIB/IV non-small cell lung cancer (NSCLC). Nivolumab, a programmed cell death-1 immune checkpoint inhibitor antibody, has been shown to be effective for the treatment of NSCLC. This study investigated the effectiveness and safety of nivolumab in Japanese patients with advanced or recurrent squamous NSCLC that progressed after platinum-containing chemotherapy. In this multicenter phase II study, patients were treated with nivolumab (3mg/kg, intravenously) every 2 weeks until progressive disease or unacceptable toxicity was seen. The primary endpoint was overall response rate (ORR) assessed by independent radiology review committee (IRC) and secondary endpoints included a study site-assessed ORR, overall survival (OS), progression-free survival (PFS), duration of response, time to response, best overall response (BOR), and safety. The study included 35 patients from 17 sites in Japan. Patients had IRC-assessed ORR of 25.7% (95% CI 14.2, 42.1) and the study site-assessed ORR was 20.0% (95% CI 10.0, 35.9). The median OS, median time to response and median PFS were 16.3 (95% CI 12.4-25.4), 2.7 (range 1.2-5.5) and 4.2 (95% CI 1.4-7.1) months, respectively. The IRC-assessed BOR was partial response, stable disease, and progressive disease for 25.7%, 28.6%, and 45.7% of patients, respectively. Treatment-related adverse events were reported in 24 patients (68.6%), most of which resolved with appropriate treatment including steroid therapy or discontinuation of nivolumab. Nivolumab was effective and well tolerated in Japanese patients with advanced or recurrent squamous NSCLC that progressed after platinum-containing chemotherapy.

[Randomized phase II study comparing weekly docetaxel-cisplatin vs. gemcitabine-cisplatin in elderly or poor performance status patients with advanced non-small cell lung cancer.](#)

Jang J1, Kim HK2, Cho BC3, et al. *Cancer Chemother Pharmacol.* 2017 Mar 24. doi: 10.1007/s00280-017-3289-6. [Epub ahead of print]

BACKGROUND: Docetaxel/cisplatin (DP) and gemcitabine/cisplatin (GP) are standard treatment regimens for advanced non-small cell lung cancer (NSCLC). In spite of potent efficacy, the conventional 1-day DP is regarded as having more toxicity as compared with GP. There is increasing interest in a biweekly split administration of DP to reduce its toxicity. Hypothesis was that first-line biweekly DP is as safe as GP in the elderly or poor performance status (PS) patients. **METHODS:** Chemotherapy-naïve patients with advanced NSCLC (IIIB/IV) who were elderly (65<) or PS (ECOG 2) were randomized to DP or GP arm by balancing for ECOG (0-1 vs. 2) and stage (IIIB vs. IV). DP comprised docetaxel (35 mg/m²)/cisplatin (30 mg/m²) iv on days 1 and 8, every 3 weeks. GP comprised gemcitabine (1000 mg/m²)/cisplatin (30 mg/m²) iv on days 1 and 8, every 3 weeks. Chemotherapy lasted up to 4-6 cycles or until progression. Primary endpoint was safety (proportion of grade 3/4 toxicities). Planned sample size was 49 patients in each arm. **RESULTS:** From November 2009 to August 2012, a total of 99 patients were randomized (DP 50/GP 49) from nine institutions. Adenocarcinoma and squamous cell carcinoma were observed in 62% and 33% of patients, respectively. Toxicity profiles were comparable for both arms and the differences were not statistically significant except for anemia and leucocytopenia. Any grade of anemia (86 vs. 98%) and of leucocytopenia (18 vs. 43%) was more common in the GP arm with statistical significance. Oral mucositis tended to be predominant in the DP arm. Patients in the DP arm (51%) suffered grade 3 or higher toxicities as did 47% in the GP arm (47%). The most common grade 3 or higher toxicities were as follows: In the DP arm, neutropenia (8%), leucopenia (8%), anemia (4%), pneumonia with normal ANC (4%) and febrile neutropenia (2%) were observed. In the GP arm, anemia (15%), neutropenia (15%), pneumonia with normal ANC (4%), thrombocytopenia (4%) and leucopenia (2%) were observed. The best overall response rates (CR + PR) for the DP and GP arms were 20.0 and 21% with no CR, respectively, and disease control rates (CR + PR + SD) were 70.0 and 76%, respectively. Median progression-free survival and median overall survival were 3.7 and 14.9 months in the DP arm

and 5.6 and 20.8 months in the GP arm, respectively. **CONCLUSION:** This study showed that DP is similar to GP in terms of efficacy and toxicity in treatment of elderly or poor performance patients. Both regimens showed similar grade 3/4 toxicities with different profiles.

[Safety of alectinib for the treatment of metastatic ALK-rearranged non-small cell lung cancer.](#)

Zhu V1,2, Ou SH1. Expert Opin Drug Saf. 2017 Apr;16(4):509-514. doi: 10.1080/14740338.2017.1299706. Epub 2017 Mar 3.

INTRODUCTION: Patients with anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC) may derive significant clinical benefit from targeted therapies against this driver mutation, but progression is virtually inevitable. Alectinib is a next-generation ALK inhibitor that provides a novel treatment option for this group of patients. Areas covered: In this review, we summarize the overall safety and tolerability of alectinib. Specifically, we cover cardiovascular, gastrointestinal, hepatic, musculoskeletal, and respiratory adverse events. The safety profile of alectinib is also described in special populations and in comparison with other ALK inhibitors. Expert opinion: Alectinib is a well-tolerated tyrosine kinase inhibitor and should be considered for patients with ALK-rearranged NSCLC. The question then arises as to how to choose a next-generation ALK inhibitor in the second-line setting. Understanding acquired resistant mechanisms has become essential. Whether or not to use alectinib in the first-line setting is extremely controversial, but we anticipate its approval for this indication and availability in more countries in the near future.

[A randomized phase III study of combining erlotinib with bevacizumab and panitumumab versus erlotinib alone as second-line therapy for Chinese patients with non-small-cell lung cancer.](#)

Wang Y1, Wang H1, Jiang Y1, Zhang Y1, Wang X2. Biomed Pharmacother. 2017 Mar 6;89:875-879. doi: 10.1016/j.biopha.2017.02.097. [Epub ahead of print]

PURPOSE: In this phase III clinical study, we assessed the clinical outcomes of combining erlotinib with bevacizumab and panitumumab as second-line chemotherapy for patients with non-small-cell lung cancer (NSCLC). **METHODS:** Chinese NSCLC patients, who received first-line platinum-based chemotherapy but still experienced disease progression, were assigned to receive second-line treatment of erlotinib plus bevacizumab and panitumumab (arm I), or erlotinib plus placebo (arm II). The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall survival (OS) and response rates. **RESULTS:** 150 patients were enrolled in arm I, and 147 in arm II. Median PFS of arm I was 4.6 months (95% CI, 2.3-9.4 months), much longer than the median PFS in arm II (1.9 months, 95% CI 0.8-5.2 months) (P=0.003). The median OS of arm I was 10.4 months (95% CI, 7.5-13.1 months), also significantly longer than the median OS in arm II (8.9 months, 95% CI 3.3-10.9 months) (P=0.031). Partial response in arm I was 38%, significantly higher than the partial response rate of 15% in arm II (P=0.014). The occurrence rates of adverse events, including diarrhea, fatigue and rash, were higher in arm I than in arm II. **CONCLUSIONS:** Erlotinib plus bevacizumab and panitumumab is an efficient second-line treatment option for patients with NSCLC.

NSCLC - RADIOTHERAPY

[7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial.](#)

Sun B1, Brooks ED1, Komaki RU1, et al. Cancer. 2017 Mar 27. doi: 10.1002/cncr.30693. [Epub ahead of print]

BACKGROUND: The authors evaluated the efficacy, patterns of failure, and toxicity of stereotactic ablative radiotherapy (SABR) for patients with medically inoperable, clinical stage I non-small cell lung cancer (NSCLC) in a prospective clinical trial with 7 years of follow-up. Clinical staging was performed according to the seventh edition of the American Joint Committee on Cancer TNM staging system.

METHODS: Eligible patients with histologically confirmed NSCLC of clinical stage I as determined using positron emission tomography staging were treated with SABR (50 grays in 4 fractions). The primary endpoint was progression-free survival. Patients were followed with computed tomography and/or positron emission tomography/computed tomography every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually thereafter. **RESULTS:** A total of 65 patients were eligible for analysis. The median age of the patients was 71 years, and the median follow-up was 7.2 years. A total of 18 patients (27.7%) developed disease recurrence at a median of 14.5 months (range, 4.3-71.5 months) after SABR. Estimated incidences of local, regional, and distant disease recurrence using competing risk analysis were 8.1%, 10.9%, and 11.0%, respectively, at 5 years and 8.1%, 13.6%, and 13.8%, respectively, at 7 years. A second primary lung carcinoma developed in 12 patients (18.5%) at a median of 35 months (range, 5-67 months) after SABR. Estimated 5-year and 7-year progression-free survival rates were 49.5% and 38.2%, respectively; the corresponding overall survival rates were 55.7% and 47.5%, respectively. Three patients (4.6%) experienced grade 3 treatment-related adverse events. No patients developed grade 4 or 5 adverse events (toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 3.0]). **CONCLUSIONS:** With long-term follow-up, the results of the current prospective study demonstrated outstanding local control and low toxicity after SABR in patients with clinical stage I NSCLC. Regional disease recurrence and distant metastases were the dominant manifestations of failure. Surveillance for second primary lung carcinoma is recommended. Cancer 2017. © 2017 American Cancer Society.

[Long-Term Outcomes of Salvage Stereotactic Ablative Radiotherapy for Isolated Lung Recurrence of Non-Small Cell Lung Cancer: A Phase II Clinical Trial.](#) Sun B1, Brooks ED1, Komaki R1, et al. J Thorac Oncol. 2017 Mar 1. pii: S1556-0864(17)30129-6. doi: 10.1016/j.jtho.2017.02.018. [Epub ahead of print]

OBJECTIVES: Our goal was to evaluate stereotactic ablative radiotherapy (SABR) as a salvage option for isolated recurrence of NSCLC in the lung parenchyma after definitive treatment of stage I to III disease. **METHODS:** Patients who had histologically confirmed, positron emission tomography-staged, isolated NSCLC recurring locally or metastasis in the lung parenchyma (≤ 3 cm, suitable for SABR) after previous definitive treatment were prospectively enrolled in this trial and treated with volumetric, image-guided SABR to 50 Gy in four fractions. Patients were then followed with computed tomography or positron emission tomography/computed tomography. Primary end points included the pattern of failure after salvage SABR, overall survival (OS), and progression-free survival (PFS). **RESULTS:** Fifty-nine patients with recurrent disease were treated with salvage SABR. The median age was 70 years (range 45-86 years), and the median follow-up time after salvage SABR was 58.3 months. Re-recurrence after salvage SABR developed in 19 patients (32%). Measuring from the date of salvage SABR, the estimated 5-year rates of local, regional, and distant failure were 5.2%, 10.3%, and 22.4%, respectively; the estimated PFS was 46.2% at 3 years and 41.1% at 5 years; and the OS rates were 63.5% at 3 years and 56.5% at 5 years. A high post-SABR neutrophil-to-lymphocyte ratio was found to predict poor survival. Grade 3 treatment-related adverse events developed in three patients (5%). No patient had a grade 4 or 5 event. **CONCLUSION:** Our study showed that salvage SABR provides excellent 5-year OS, local control, and PFS rates with minimal toxicity for patients with isolated NSCLC recurrence in the lung parenchyma. These results are striking and comparable to historically reported outcomes of patients with primary early-stage NSCLC treated with definitive SABR. SABR appears to be a very effective and safe salvage option for patients with isolated lung parenchyma recurrent disease after definitive treatment and should be considered along with surgery as a potential first-line option for patients with local lung parenchymal recurrent disease.

[TTF-1- and/or CD56-positive Circulating Tumor Cells in patients with small cell lung cancer \(SCLC\).](#) Messaritakis I1, Stolidis D1, Kotsakis A1,2, et al. Sci Rep. 2017 Mar 28;7:45351. doi: 10.1038/srep45351.

The aim of the study was to evaluate the phenotypic CTCs heterogeneity (TTF-1+ and/or CD56+) in SCLC patients and correlate it with the CellSearch. Peripheral blood was obtained from 108 consecutive patients. CTCs were detected by CellSearch and double-immunofluorescence using anti-CD45, anti-TTF-1 and anti-CD56 antibodies. Before chemotherapy TTF-1+/CD45-, CD56+/CD45- and TTF-1+/CD56+ CTCs were detected in 66(61.1%), 55(50.9%) and 46(42.6%) patients, respectively; 60.2% of patients were CellSearch+. Among the 22 patients with 0 CTCs/7.5 ml on CellSearch, TTF-1+/CD45-, CD56+/CD45- and TTF-1+/CD56+ CTCs were detected in 8(36.4%), 6(27.3) and 6(27.3%) patients, respectively; no CK+/EpCAM+ or TTF1+/EpCAM+ CTCs were detected in these patients. One-chemotherapy cycle decreased both the number of positive patients ($p < 0.001$) and their CTC number ($p < 0.001$), irrespectively of their phenotype and the detection method. The incidence and number of the different CTC subpopulations on PD, was significantly increased at their baseline levels. Multivariate analysis revealed that the increased number of CTCs at baseline and on PD were significantly associated with decreased PFS ($p = 0.048$) and OS ($p = 0.041$), respectively. There is an important CTC heterogeneity in such patients according to the expression of TTF-1 and CD56 which could detect EpCAM- CTC subpopulations and, thus, undetectable by CellSearch. These CTC subpopulations are dynamically correlated with treatment efficacy and disease-progression.

[Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial.](#) Takahashi T1, Yamanaka T2, Seto T3, et al. Lancet Oncol. 2017 Mar 23. pii: S1470-2045(17)30230-9. doi: 10.1016/S1470-2045(17)30230-9. [Epub ahead of print]

BACKGROUND: Results from a previous phase 3 study suggested that prophylactic cranial irradiation reduces the incidence of symptomatic brain metastases and prolongs overall survival compared with no prophylactic cranial irradiation in patients with extensive-disease small-cell lung cancer. However, because of the absence of brain imaging before enrolment and variations in chemotherapeutic regimens and irradiation doses, concerns have been raised about these findings. We did a phase 3 trial to reassess the efficacy of prophylactic cranial irradiation in the treatment of extensive-disease small-cell lung cancer. **METHODS:** We did this randomised, open-label, phase 3 study at 47 institutions in Japan. Patients with extensive-disease small-cell lung cancer who had any response to platinum-based doublet chemotherapy and no brain metastases on MRI were randomly assigned (1:1) to receive prophylactic cranial irradiation (25 Gy in ten daily fractions of 2.5 Gy) or observation. All patients were required to have brain MRI at 3-month intervals up to 12 months and at 18 and 24 months after enrolment. Randomisation was done by computer-generated allocation sequence, with age as a stratification factor and minimisation by institution, Eastern Cooperative Oncology Group performance status, and response to initial chemotherapy. The primary endpoint was overall survival, analysed in the intention-to-treat population. This trial is registered with the UMIN Clinical Trials Registry, number UMIN000001755, and is closed to new participants. **FINDINGS:** Between April 3, 2009, and July 17, 2013, 224 patients were enrolled and randomly assigned (113 to prophylactic cranial irradiation and 111 to observation). In the planned interim analysis on June 18, 2013, of the first 163 enrolled patients, Bayesian predictive probability of prophylactic cranial irradiation being superior to observation was 0.011%, resulting in early termination of the study because of futility. In the final analysis, median overall survival was 11.6 months (95% CI 9.5-13.3) in the prophylactic cranial irradiation group and 13.7 months (10.2-16.4) in the observation group (hazard ratio 1.27, 95% CI 0.96-1.68; $p=0.094$). The most frequent grade 3 or worse adverse

events at 3 months were anorexia (six [6%] of 106 in the prophylactic cranial irradiation group vs two [2%] of 111 in the observation group), malaise (three [3%] vs one [$<1\%$]), and muscle weakness in a lower limb (one [$<1\%$] vs six [5%]). No treatment-related deaths occurred in either group.

INTERPRETATION: In this Japanese trial, prophylactic cranial irradiation did not result in longer overall survival compared with observation in patients with extensive-disease small-cell lung cancer. Prophylactic cranial irradiation is therefore not essential for patients with extensive-disease small-cell lung cancer with any response to initial chemotherapy and a confirmed absence of brain metastases when patients receive periodic MRI examination during follow-up. **FUNDING:** The Ministry of Health, Labour and Welfare of Japan.

Indications for Adjuvant Mediastinal Radiotherapy in Surgically Resected Small Cell Lung Cancer.

Wakeam E1, Giuliani M2, Leighl NB3, Finlayson SR4, Varghese TK4, Darling GE5. *Ann Thorac Surg.* 2017 Mar 3. pii: S0003-4975(16)31758-1. doi: 10.1016/j.athoracsur.2016.11.039. [Epub ahead of print]

BACKGROUND: Adjuvant mediastinal radiotherapy (AMR) is used after surgical resection for patients with small cell lung cancer (SCLC), but data guiding its use are scant. We sought to examine whether AMR was associated with an improvement in survival for resected SCLC patients and to define subpopulations who should be selected for AMR. **METHODS:** Patients undergoing lobectomy, pneumonectomy, and sublobar resection for SCLC were identified in the National Cancer Database (2004 to 2013). Kaplan-Meier survival curves and Cox proportional hazards were used to evaluate associations between AMR and survival. Hazard ratios were adjusted for patient comorbidity, demographics, tumor characteristics, such as stage, grade, histology, and margin status, and receipt of adjuvant chemotherapy. **RESULTS:** We identified 3,101 patients. Those receiving AMR were younger, more likely to have greater pathologic T and N stage, to undergo sublobar resection, and to have a positive margin. Kaplan-Meier curves showed better median survival for patients with pN1 or pN2 disease who received AMR. After adjustment, Cox models showed AMR was associated with a lower risk of death for pN1 (hazard ratio, 0.79; 95% confidence interval, 0.63 to 1.00; $p = 0.05$) and pN2 (hazard ratio, 0.60; 95% confidence interval, 0.48 to 0.75; $p < 0.0001$). In the overall cohort, AMR was not associated with better survival in node-negative patients. AMR was, however, associated with improved survival for patients receiving sublobar resection (hazard ratio, 0.72; 95% confidence interval, 0.57 to 0.90; $p = 0.004$).

CONCLUSIONS: AMR is associated with longer survival for node-positive patients after resection for SCLC, especially those with pN2. AMR may also be associated with longer survival in patients undergoing sublobar resections.

Comparative Analysis for Diagnostic Yield of Small Cell Lung Cancer by Cytology and Histology During the Same Bronchoscopic Procedure.

Li WN1, Wang DF2, Zhao YB3, Qiu XS1, Wang EH1, Wu GP4. *Clin Lung Cancer.* 2017 Mar 2. pii: S1525-7304(17)30052-9. doi: 10.1016/j.clcc.2017.02.009. [Epub ahead of print]

BACKGROUND: Biopsy, brushing, and transbronchial needle aspiration (TBNA) are the most common methods used for the diagnosis of small cell lung cancer during the same diagnostic bronchoscopic procedure. However, it is not clear which method provides better results. **PATIENTS AND METHODS:** A retrospective analysis was performed of 140 patients who had undergone video bronchoscopy for diagnostic purposes. Bronchial brushings were obtained from all subjects. Biopsy specimens were also obtained from all subjects, except for 6 cases that could not be sampled; the TBNA method was used for some special lesions. The results were analyzed separately by histology and cytology.

RESULTS: The diagnostic yield of cytology was significantly greater than that of histology ($P < .01$) and that of conventional smear preparations in cytology was obviously greater than that of hematoxylin and eosin stains in histology ($P < .01$). The false-negative results were significantly lower with cytology than with histology ($P < .01$). Also, the cases of sampling site restriction with cytology were distinctly less

than those with histology ($P < .05$). Stretch deformation of the tissue structure and cell morphology was the main reason for the false-negative results in the histologic diagnosis. The use of TBNA resolved all 4 cases of hilar adenopathy and 2 cases of lesions outside the bronchus. Multiple brushings of the tissue adjacent to cancer tissue and liquid-based preparations of cancerous necrotic tissue can significantly reduce the false-negative results from biopsy. **CONCLUSIONS:** The diagnostic yield of cytologic examination of brushings and TBNA for small cell lung cancer was superior to that of histologic examination of hematoxylin and eosin stains and immunohistochemistry.

Chemotherapy in combination with cytokine-induced killer cell transfusion: An effective therapeutic option for patients with extensive stage small cell lung cancer. Huang J1, Kan Q2, Lan1, et al. *Int Immunopharmacol.* 2017 Mar 11;46:170-177. doi: 10.1016/j.intimp.2016.12.005. [Epub ahead of print]

BACKGROUND AND AIMS: In the past decade of clinical studies, the combination of chemotherapy with cytokine induced killer (CIK) cell transfusion has confirmed a promised efficacy in several types of cancer. CIK cells are a mixture of T lymphocytes, generated from peripheral blood mononuclear cells induced by multiple cytokines. This study was aimed to evaluate the clinical efficacy of chemotherapy combined with CIK- cell therapy in patients with extensive stage small cell lung cancer (ES SCLC).

PATIENTS AND METHODS: Forty four patients with ES SCLC were enrolled in this study. All the patients received treatment from Oct 2010 to Sep 2013 in the First Affiliated Hospital of Zhengzhou University. Included patients were equally divided into 2 groups according to the treatment strategies. Patients in the combined treatment group received chemotherapy combined with CIK-cell transfusion and patients in the control group received chemotherapy alone. The short-term effects, overall survival (OS), progress free survival (PFS) and therapy-related adverse events were analyzed retrospectively.

RESULTS: Short-term efficacy evaluation indicated that the total response rates in the combined treatment group and control group were 40.9% (9/22) and 9.1% (2/22), respectively. There was a significant difference between the two groups ($p=0.0339$). Furthermore, the PFS of the combined treatment group was significantly longer than that of the control group (8 vs. 4months, $P=0.005$). No severe side effect was observed after transfusion of CIK cells. **CONCLUSION:** These results indicated that chemotherapy combined with CIK-cell immunotherapy might provide a safe and effective treatment for patients with ES SCLC.

Hypo- or conventionally fractionated radiotherapy combined with chemotherapy in patients with limited stage small cell lung cancer. Zhang J1, Fan M2, Liu D1, Zhao KL1, Wu KL1, Zhao WX1, Zhu ZF1, Fu XL1. *Radiat Oncol.* 2017 Mar 11;12(1):51. doi: 10.1186/s13014-017-0788-x.

BACKGROUND: Previous data from our institution showed that hypofractionated thoracic radiotherapy (HypoTRT) with concurrent etoposide/platinum chemotherapy yielded favorable survival in patients with limited-stage small cell lung cancer (LS-SCLC). The present study retrospectively compared the survival outcomes, failure patterns and toxicities between groups of LS-SCLC patients treated with conventionally fractionated thoracic radiotherapy (ConvTRT) or HypoTRT combined with chemotherapy. **METHODS:** Medical records of LS-SCLC patients between January 2010 and December 2013 at Fudan University Shanghai Cancer Center were retrospectively reviewed. All patients treated with chemotherapy and ConvTRT (2 Gy per fraction daily, $DT \geq 56$ Gy) or HypoTRT (2.5 Gy per fraction daily, $DT = 55$ Gy) were eligible for analysis. Progression-free survival (PFS) and overall survival (OS) were generated for different populations using the Kaplan-Meier method and compared using the log-rank test. Comparisons of failure patterns and toxicity were analyzed using the χ^2 test. **RESULTS:** A total of 170 patients treated with HypoTRT ($n = 69$) or ConvTRT ($n = 101$) were eligible for analysis. The median PFS and OS were 13.7 and 25.3 months, respectively, in the ConvTRT cohort, which was similar to the HypoTRT cohort (PFS 18.2 months, $p = 0.991$, and OS 27.2 months, $p = 0.698$), with a median follow-up of 30

months. Multivariate analysis revealed that PCI and TNM stage were prognostic factors for PFS and that PCI was prognostic for OS. The patterns of failure (stratified by local-regional recurrence, distant metastasis or both as first relapse) were similar between the dose cohorts ($p = 0.693$, $p = 0.330$, $p = 0.572$). Distant metastasis remained the main failure pattern. The brain was the most frequent remote failure site, followed by bone, liver and adrenal gland. PCI improved the 2-year survival rate from 46.1% to 70.0% and the 2-year PFS rate from 20.9% to 45.3%, respectively ($p < 0.001$). Grade ≥ 3 esophagitis and pneumonitis occurred in 9.9% and 11.9%, respectively, of the patients in the ConvTRT cohort and in 11.6% and 10.0%, respectively, of those in the HypoTRT cohort ($p = 0.815$). **CONCLUSION:** This retrospective analysis demonstrated that HypoTRT or ConvTRT combined with etoposide/platinum chemotherapy yielded statistically similar survival, treatment failure outcomes, and toxicity profiles. PCI correlated with improved PFS and OS.

Thoracic irradiation in 3weeks for limited-stage small cell lung cancer: Is twice a day fractionation really needed? Turgeon GA1, Souhami L1, Kopek N1, Hirsh V2, Ofiara L3, Faria SL4. Cancer Radiother. 2017 Mar 18. pii: S1278-3218(17)30038-0. doi: 10.1016/j.canrad.2016.09.015. [Epub ahead of print]

PURPOSE: Many Canadian institutions treat limited-disease small cell lung cancer with 40Gy in 15 fractions delivered once-a-day in 3weeks concomitantly with chemotherapy. This regimen is convenient and seems to be effective. Here, we report and compare with a literature review the outcomes of patients with limited-stage small cell lung cancer treated in our institution with this hypofractionated regimen. **PATIENTS AND METHODS:** From January 2004 to December 2012, patients with limited-stage small cell lung cancer treated curatively with platinum-based chemotherapy and concurrent thoracic radiotherapy at a dose of 40Gy in 16 fractions once-a-day were eligible for this review. **RESULTS:** Sixty-eight patients fit the analysis criteria, including ten patients with small pleural effusion. The median age was 66years old. After a median follow-up of 77months for those alive, the median survival was 28months. At 3 and 5years respectively, the locoregional control rates were 67 and 64%, while the overall survival rates were 40 and 35%. Prophylaxis cranial irradiation was delivered to 68% of the patients. Grade 2 and 3 acute esophagitis occurred in respectively 49 and 9% of the patients. There was no grade 4 radiation-induced toxicity. All patients, except for one, completed their thoracic irradiation course without interruption. **CONCLUSION:** Once-a-day hypofractionated radiation with concurrent chemotherapy followed by prophylactic cranial irradiation is a practical regimen. Based on our experience and the published literature, it appears to be similarly effective as regimens using twice-daily fractionation in 3weeks, or once-daily in 6 to 7weeks with higher radiotherapy doses. Further prospective comparisons of hypofractionation with the current recommendations are needed.

PALLIATIVE AND SUPPORTIVE CARE

Patient Experience of Symptoms and Side Effects when Treated with Osimertinib for Advanced Non-Small-Cell Lung Cancer: A Qualitative Interview Substudy. Rydén A1, Blackhall F2,3, Kim HR4, Pillai RN5, Braam L6, Martin ML6, Walding A7. Patient. 2017 Mar 28. doi: 10.1007/s40271-017-0229-9. [Epub ahead of print]

INTRODUCTION: Capturing the patient experience during treatment is important to both regulatory authorities and to patients starting treatment. We identified the symptoms and side effects experienced by patients with advanced non-small-cell lung cancer during osimertinib treatment, to understand treatment expectations, satisfaction, and the level of difficulty coping with the side effects experienced during treatment. **METHODS:** Qualitative interviews (approximately 4-6 weeks after treatment initiation and again after approximately 4 months of treatment) were conducted during the phase I/II AURA clinical trial of osimertinib, a tyrosine kinase inhibitor of epidermal growth factor receptor-sensitizing and T790M

resistance mutations. **RESULTS:** During the first interview (23 patients), the most commonly reported symptoms/side effects were coughing, itching, tiredness (each reported by 56.5% of patients), and rash (43.5%). During the second interview (21 patients), compared with the first interview, shortness of breath and diarrhea were reported by more patients (57.1 and 38.1%, respectively; both increased from 34.8%); tiredness remained predominant (42.9%); and itching (38.1%), coughing (38.1%), and rash (14.3%) were reported by fewer patients. At both interviews, the most frequently reported symptoms/side effects were also those most often rated by patients for bothersomeness and severity, and generally received mean scores in the low-to-moderate range. However, several rarely expressed symptoms/side effects (e.g., abdominal pain, frequent day time urination) received high bothersomeness ratings. At the second interview, patients were highly satisfied with osimertinib and had a low level of difficulty in coping with side effects during treatment. **CONCLUSIONS:** These data enhance our understanding of patients' experiences of symptoms/side effects, which could increase the accuracy of the osimertinib benefit-risk assessment, guide management of adverse events, and improve the information given to patients receiving the drug.

[Cancer Communication and Family Caregiver Quality of Life](#), Wittenberg E1, Borneman T2, Koczywas M3, Del Ferraro C4, Ferrell B5. *Behav Sci (Basel)*. 2017 Mar 2;7(1). pii: E12. doi: 10.3390/bs7010012.

Family caregivers have enormous communication responsibilities tied to caregiving, such as sharing the patient's medical history with providers, relaying diagnosis and prognosis to other family members, and making decisions about care with the patient. While caregiver stress and burden has been widely documented in the caregiving literature, little is known about how communication burden, real or perceived communication challenges, impacts caregiver quality of life. In family caregiving, the City of Hope (COH) Quality of Life model proposes that the caregiving experience is reciprocal to the patient experience, impacting physical, social, psychological, and spiritual quality of life. We used data from a pilot study testing a communication coaching call intervention with family caregivers of lung cancer patients to analyze caregiver reported communication burden and quality of life. We found variances in each quality of life domain, suggesting that caregiver interventions should range from self-care skill building for physical care to psycho-educational interventions that support caregiver coping and communication skill building. These findings demonstrate the importance of caregiver assessment and attention to communication burden in quality cancer care.

[The self-care practices of family caregivers of persons with poor prognosis cancer: differences by varying levels of caregiver well-being and preparedness](#), Dionne-Odom JN1, Demark-Wahnefried W2, Taylor RA3, et al. *Support Care Cancer*. 2017 Mar 1. doi: 10.1007/s00520-017-3650-7. [Epub ahead of print]

PURPOSE: Little is known about the impact of family caregiving for adults with poor prognosis cancer on caregivers' own individual self-care practices. We explored differences in caregivers' discrete self-care practices associated with varying levels of caregiver well-being, preparedness, and decision-making self-efficacy. **METHODS:** Cross-sectional survey within eight community-based southeastern U.S. cancer centers was conducted. Family caregivers of Medicare beneficiaries ≥ 65 years with pancreatic, lung, brain, ovarian, head and neck, hematologic, or stage IV cancer completed measures of individual self-care practices (health responsibility, physical activity, nutrition, spiritual growth, interpersonal relations, stress management, and sleep), well-being (anxiety, depression, and health-related quality of life [HRQoL]), preparedness, and decision-making self-efficacy. **RESULTS:** Caregivers (n = 294) averaged 66 years, were mostly female (72.8%), white (91.2%), Protestant (76.2%), retired (54.4%), and patients' spouse/partner (60.2%). Approximately, half were rural-dwellers (46.9%) with incomes $< \$50,000$ (53.8%). Most provided support 6-7 days/week (71%) for > 1 year (68%). Nearly a quarter (23%) reported

high depression and 34% reported borderline or high anxiety. Low engagement in all self-care practices was associated with worse caregiver anxiety, depression, and mental HRQoL (all p values < .05). Caregivers with lower health responsibility, spiritual growth, interpersonal relation, and stress management scores had lower preparedness and decision-making self-efficacy. **CONCLUSIONS:** A significant proportion of caregivers simultaneously report low engagement in all forms of self-care practices, high depression and anxiety, and low HRQoL mental health scores. Caregiver well-being, preparedness, and decision-making self-efficacy might be optimized through interventions targeted at enhancing health responsibility, stress management, interpersonal relationships, and spiritual growth self-care practices.

Plasma Ghrelin Levels Are Associated with Anorexia but Not Cachexia in Patients with NSCLC.

Blauwhoff-Buskermolen S1, Langius JA2, Heijboer AC3, Becker A4, de van der Schueren MA5, Verheul HM6. *Front Physiol.* 2017 Mar 1;8:119. doi: 10.3389/fphys.2017.00119. eCollection 2017.

BACKGROUND AND AIMS: The ghrelin receptor is one of the new therapeutic targets in the cancer anorexia-cachexia syndrome. Previous studies revealed that plasma ghrelin levels were high in patients with anorexia nervosa and low in obese subjects. We studied to what extent ghrelin levels are related with anorexia and cachexia in patients with cancer. **MATERIALS AND METHODS:** Fasted ghrelin levels were determined as well as anorexia and cachexia in patients with stage III/IV non-small cell lung cancer before chemotherapy. Total plasma ghrelin was measured by radioimmunoassay. Anorexia was measured with the FAACT-A/CS questionnaire (cut-off value ≤ 37). Cachexia was determined as $>5\%$ weight loss (WL) in 6 months or $>2\%$ WL in 6 months in combination with low BMI or low muscle mass. The Kruskal-Wallis test was performed to assess differences in plasma ghrelin levels between four groups: patients with (+) or without (-) anorexia (A) or cachexia (C). Multiple regression analyses were performed to assess differences in plasma ghrelin levels between patients C+ and C- and patients with A+ and A- (adjusted for age and sex). **RESULTS:** Forty patients with stage III (33%) or stage IV (68%) were recruited, of which 50% was male. Mean age was 59.6 ± 10.3 years. Sixteen patients had no anorexia or cachexia (A-C-), seven patients had both anorexia and cachexia (A+C+), ten patients had anorexia without cachexia (A+C-) and seven patients had cachexia without anorexia (A-C+). The levels of total plasma ghrelin were significantly different between the four groups of patients with or without anorexia or cachexia ($p = 0.032$): the A+C- patients had significantly higher ghrelin levels [median (IQR): 1,754 (1,404-2,142) compared to the A-C+ patients 1,026 (952-1,357), $p = 0.003$]. A+ patients had significantly higher ghrelin levels compared A- patients (C+ and C- combined, $\beta: 304$, $p = 0.020$). Plasma ghrelin levels were not significantly different in C+ patients compared to C- patients (A+ and A- combined, $\beta: -99$, $p = 0.450$). **CONCLUSIONS:** Patients with anorexia had significantly higher ghrelin levels compared to patients without anorexia. We therefore hypothesize that patients with cancer anorexia might benefit from treatment with a ghrelin receptor agonist to prevent WL and deterioration in physical functioning.

Does Educating Patients About the Early Palliative Care Study Increase Preferences for Outpatient Palliative Cancer Care? Findings From Project EMPOWER.

Hoerger M, Perry LM, Gramling R, Epstein RM, Duberstein PR. *Health Psychol.* 2017 Mar 9. doi: 10.1037/hea0000489. [Epub ahead of print]

OBJECTIVES: Randomized controlled trials, especially the Early Palliative Care Study (Temel et al., 2010), have shown that early outpatient palliative cancer care can improve quality of life for patients with advanced cancer or serious symptoms. However, fear and misconceptions drive avoidance of palliative care. Drawing from an empowerment perspective, we examined whether educating patients about evidence from the Early Palliative Care Study would increase preferences for palliative care.

METHOD: A sample of 598 patients with prostate, breast, lung, colon/rectal, skin, and other cancer diagnoses completed an Internet-mediated experiment using a between-group prepost design. Intervention

participants received a summary of the Early Palliative Care Study; controls received no intervention. Participants completed baseline and posttest assessments of preferences of palliative care. Analyses controlled for age, gender, education, cancer type, presence of metastases, time since diagnosis, and baseline preferences. **RESULTS:** As hypothesized, the intervention had a favorable impact on participants' preferences for outpatient palliative cancer care relative to controls ($d = 1.01$, $p < .001$), while controlling for covariates. Intervention participants came to view palliative care as more efficacious ($d = 0.79$, $p < .001$) and less scary ($d = 0.60$, $p < .001$) and exhibited stronger behavioral intentions to utilize outpatient palliative care if referred ($d = 0.60$, $p < .001$). Findings were comparable in patients with metastatic disease, those with less education, and those experiencing financial strain. **CONCLUSIONS:** Educating patients about the Early Palliative Care Study increases preferences for early outpatient palliative care. This research has implications for future studies aimed at improving quality of life in cancer by increasing palliative care utilization.

Changes in the sleep-wake rhythm, sleep quality, mood, and quality of life of patients receiving treatment for lung cancer: A longitudinal study. Chang WP1,2, Lin CC2,3. *Chronobiol Int.* 2017 Mar 10:1-11. doi: 10.1080/07420528.2017.1293678. [Epub ahead of print]

Studies on the diurnal sleep-wake rhythm of patients with lung cancer have mostly examined patients cross-sectionally, whereas the effects of lung cancer treatment over time have rarely been considered. Through long-term longitudinal tracking of patients with lung cancer, this study examined changes in their sleep-wake rhythm, sleep quality, anxiety, depressive symptoms, fatigue and quality of life (QoL) at various treatment stages. In addition, factors affecting their QoL were explored. Hierarchical linear modeling was adopted to analyze a convenience sample of 82 patients with lung cancer. The changes in their sleep-wake rhythm, sleep, mood (anxiety, depressive symptoms and fatigue) and QoL were observed at five time points: prior to treatment and at weeks 6, 12, 24 and 48 after the start of the treatment. The effects of sex, age, cancer stage, treatment type, comorbidities and time were controlled to determine the predictors of patients' QoL. The results showed that patients' sleep-wake rhythms were poor before treatments. Compared with baseline, the sleep-wake rhythms of the patients significantly improved at week 48, and anxiety significantly improved at weeks 6, 12, 24 and 48. By contrast, their fatigue became exacerbated at weeks 8 and 48. Moreover, QoL improved significantly from week 6 until the end of the treatment period. QoL was negatively affected by poor sleep quality ($\beta = -0.69$, $p = 0.00$) and depressive symptoms ($\beta = -2.59$, $p < 0.001$) and positively affected by regular sleep-wake rhythms ($\beta = 0.23$, $p = 0.001$). Therefore, clinical health-care professionals should focus more attention to the fatigue levels of patients with lung cancer before, during and after treatment. Health-care professionals may also need to provide such patients with health education regarding sleep hygiene and with emotional support to assist them in maintaining regular sleep-wake rhythms in order to improve their QoL.

Modifiable and non-modifiable characteristics associated with sleep disturbance in oncology outpatients during chemotherapy. Mark S1, Cataldo J1, Dhruva A2, et al. *Support Care Cancer.* 2017 Mar 9. doi: 10.1007/s00520-017-3655-2. [Epub ahead of print]

PURPOSE: In a sample of outpatients with breast, gastrointestinal, gynecological, and lung cancer who received at least two cycles of chemotherapy (CTX), the purposes were to evaluate for inter-individual differences in the severity of sleep disturbance and determine which demographic, clinical, and symptom characteristics were associated with initial levels as well as the trajectories of sleep disturbance.

METHODS: A total of 1331 patients completed study questionnaires in their homes, at six time points over two cycles of CTX (prior to CTX administration, approximately 1 week after CTX administration, and approximately 2 weeks after CTX administration). Questionnaires included demographic, clinical, and symptom assessments (i.e., General Sleep Disturbance Scale, Lee Fatigue Scale, Center for Epidemiological Studies-Depression Scale, Spielberger State-Trait Anxiety Inventories, Attentional

Function Index). Hierarchical linear modeling based on full maximum likelihood estimation was performed. **RESULTS:** Characteristics associated with higher initial levels of sleep disturbance included higher body mass index, poorer functional status, higher trait anxiety, higher depressive symptoms, and higher evening fatigue. Characteristics associated with the worse trajectories of sleep disturbance were higher levels of education and higher sleep disturbance at enrollment. Characteristics associated with both higher initial levels and worse trajectories of sleep disturbance were higher morning fatigue and worse attentional function. **CONCLUSIONS:** A large amount of inter-individual variability exists in sleep disturbance during CTX. The modifiable and non-modifiable characteristics found in this study can be used to identify higher risk patients and provide earlier interventions to reduce sleep disturbance.

Cancer Cachexia-Induced Muscle Atrophy: Evidence for Alterations in microRNAs important for Muscle Size. Lee DE1, Brown JL, Rosa-Caldwell ME, et al. *Physiol Genomics*. 2017 Mar

24:physiolgenomics.00006.2017. doi: 10.1152/physiolgenomics.00006.2017. [Epub ahead of print]

Muscle atrophy is a hallmark of cancer cachexia resulting in impaired function and quality of life and cachexia is the immediate cause of death for 20-40% of cancer patients. Multiple microRNAs (miRNAs) have been identified as being involved in muscle development and atrophy, however less is known specifically on miRNAs in cancer cachexia. **PURPOSE:** The purpose of this investigation was to examine the miRNA profile of skeletal muscle atrophy induced by cancer cachexia to uncover potential miRNAs involved with this catabolic condition. **METHODS:** Phosphate buffered saline (PBS) or Lewis-Lung carcinoma cells (LLC) were injected into C57BL/6J mice at 8 weeks of age. LLC animals were allowed to develop tumors for 4 weeks to induce cachexia. Tibialis anterior muscles were extracted and processed to isolate small RNAs which were used for miRNA sequencing. Sequencing results were assembled with mature miRNAs and functions of miRNAs were analyzed using Ingenuity Pathway Analysis. **RESULTS:** LLC animals developed tumors that contributed to significantly smaller tibialis anterior muscles (18.5%) and muscle cross-sectional area (40%) compared to PBS. 371 miRNAs were present in the muscle above background levels. Of these, nine miRNAs were found to be differentially expressed. Significantly altered groups of miRNAs were categorized into primary functionalities including cancer, cell-to-cell signaling, and cellular development among others. Gene network analysis predicted specific alterations of factors contributing to muscle size including Akt, FOXO3 and others. **CONCLUSION:** These results create a foundation for future research into the sufficiency of targeting these genes to attenuate muscle loss in cancer cachexia.

Mindfulness-Based Stress Reduction added to care as usual for lung cancer patients and/or their partners: A multi-centre randomized controlled trial.

Schellekens MP1, van den Hurk DG2, Prins JB3, Donders AR4, Molema J2, Dekhuijzen R2, van der Drift MA2, Speckens AE1. *Psychooncology*. 2017 Mar 23. doi: 10.1002/pon.4430. [Epub ahead of print]

BACKGROUND: Lung cancer patients report among the highest distress rates of all cancer patients. Partners report similar distress rates. The present study examined the effectiveness of additional Mindfulness-Based Stress Reduction (CAU + MBSR) versus solely care as usual (CAU) to reduce psychological distress in lung cancer patients and/or their partners. **METHODS:** We performed a multicentre, parallel-group, randomized controlled trial. MBSR is an 8-week group-based intervention, including mindfulness practice and teachings on stress. CAU included anti-cancer treatment, medical consultations and supportive care. The primary outcome was psychological distress. Secondary outcomes included quality of life, caregiver burden, relationship satisfaction, mindfulness skills, self-compassion, rumination and post-traumatic stress symptoms. Outcomes were assessed at baseline, post-intervention and 3-month follow-up. Linear mixed modeling was conducted on an intention-to-treat sample. Moderation (gender, disease stage, baseline distress, participation with/without partner) and mediation analyses were performed. **RESULTS:** 31 patients and 21 partners were randomized to CAU + MBSR and

32 patients and 23 partners to CAU. After CAU + MBSR patients reported significantly less psychological distress ($p = .008$, $d = .69$) than after CAU. Baseline distress moderated outcome: those with more distress benefitted most from MBSR. Additionally, after CAU + MBSR patients showed more improvements in quality of life, mindfulness skills, self-compassion and rumination than after CAU. In partners, no differences were found between groups. **CONCLUSION:** Our findings suggest that psychological distress in lung cancer patients can be effectively treated with MBSR. No effect was found in partners, possibly because they were more focused on patients' wellbeing rather than their own.

[Reflection of illness and strategies for handling advanced lung cancer - a qualitative analysis in patients and their relatives.](#) Sparla A1, Flach-Vorgang S2, Villalobos M3, et al. BMC Health Serv Res. 2017 Mar 2;17(1):173. doi: 10.1186/s12913-017-2110-x.

BACKGROUND: Lung cancer patients are often diagnosed in an advanced stage of disease. In a situation of palliative treatment, both patients and their relatives experience existential burden. Evidence suggests that multi-professional teams should deal with them as dyads. However, little is known about differences in their individual situation. The purpose of this study is to explore and compare reflections that arise out of the context of diagnosis and to compare how patients and their relatives try to handle advanced lung cancer. **METHODS:** Data was collected by qualitative interviews. A total of 18 participants, 9 patients diagnosed with advanced lung cancer (ICD- 10 C-34, stage IV) starting or receiving palliative treatment and 9 relatives were interviewed. Data was interpreted using qualitative content analysis. **RESULTS:** Reflection aspects were "thoughts about the cause", "meaning of belief" and "experience of inequity". Patients often experienced the diagnosis as inequity and were more receptive for believing in treatment success. The main strategies found were "repression", "positive attitude", "strong focus on the present" and "adjustment of life terms". Patient and relative dyads used the same strategies, but with different emphasis. That life time is limited was more frequently realized by relatives than by patients. **CONCLUSION:** While strategies used by relatives are similar to those of patients', they are less reflective and more pragmatic in terms of handling daily life and organizing care. The interviewed patients were mostly not able to takeover these tasks. To strong was their belief in treatment success, their repression of the future and the focus on the present. This implicates, that in terms of end-of-life care, relatives are important to reach patients who are often not receptive to this topic.

COMPLEMENTARY & ALTERNATIVE THERAPY

[AKR1B10-inhibitory Selaginella tamariscina extract and amentoflavone decrease the growth of A549 human lung cancer cells in vitro and in vivo.](#) Jung YJ1, Ha Lee E1, Gun Lee C2, Rhee KJ2, Jung WS1, Choi Y3, Pan CH4, Kang K4. J Ethnopharmacol. 2017 Mar 9. pii: S0378-8741(17)30125-3. doi: 10.1016/j.jep.2017.03.010. [Epub ahead of print]

ETHNOPHARMACOLOGICAL RELEVANCE: Selaginella tamariscina (P.Beauv.) Spring is a traditional medicinal plant used to treat various human diseases, including cancer, in Asia. The detailed molecular mechanism underlying the anti-cancer effects of this plant and the anti-cancer action of the combinatorial treatment of S. tamariscina and doxorubicin have not yet been investigated. **AIM OF THE STUDY:** We evaluated the inhibitory activity of S. tamariscina extract (STE) and its major compound, amentoflavone, on human aldo-keto reductase family 1B10 (AKR1B10), which is a detoxification enzyme involved in drug resistance, to evaluate their anti-cancer effects and their potential as adjuvant agents for doxorubicin cancer chemotherapy. **MATERIALS AND METHODS:** We tested the AKR1B10 inhibitory activity of STE and amentoflavone via an in vitro biochemical assay using recombinant human AKR1B10. We tested the anti-proliferative activity in A549, NCI-H460, SKOV-3, and MCF-7 human cancer cells, which contain different expression levels of AKR1B10, and determined the combination index to evaluate whether the addition of STE and amentoflavone is synergistic or

antagonistic to the anti-cancer action of doxorubicin. We finally evaluated the in vivo anti-tumor effects of STE in a nude mouse xenograft model of A549 cells. **RESULTS:** STE and amentoflavone potently inhibited human AKR1B10 and synergistically increased the doxorubicin anti-proliferative effect in A549 and NCI-H460 human lung cancer cells that express a high level of AKR1B10 mRNA and protein. STE also significantly inhibited A549 tumor growth in animal experiments. **CONCLUSION:** Our results suggest that STE and amentoflavone could be potential anti-cancer agents that target AKR1B10 and might be candidate adjuvant agents to boost the anti-cancer effect of doxorubicin.

[Ulmus davidiana Nakai induces apoptosis and autophagy on Non-Small Cell Lung Cancer Cells.](#)

Hong SO1, Keun Choi I2, Jeong W3, Ryeon Lee S2, Jung Sung H2, Su Hong S3, Hong Seo J4. J Ethnopharmacol. 2017 Mar 8. pii: S0378-8741(16)32364-9. doi: 10.1016/j.jep.2017.03.009. [Epub ahead of print]

ETHNOPHARMACOLOGICAL RELEVANCE: *Ulmus davidiana Nakai* (UDN) is frequently used in the treatment of cancer in traditional oriental medicine. Although several reports indicate that UDN has inhibitory effects in some cancers, there has been no report on the inhibitory effects of UDN via both autophagy and apoptosis. **MATERIALS AND METHODS:** Cytotoxicity induced by UDN in human non-small cell lung cancer (NSCLC) H-1299 and H-460 cell lines was evaluated using the 2, 3-Bis (2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide inner salt (XTT) assay and trypan blue exclusion assay. Induction of apoptosis was also investigated using Hoechst staining and annexin-V binding assay and was confirmed with western blot analysis. Induction of autophagy was investigated through observation of autophagy vacuoles under inverted phase-contrast microscopy and was confirmed by observing the formation of autophagy vacuoles under a fluorescence microscope using monodansylcadaverine (MDC) staining and western blot analysis. The in vivo anti-tumorigenic effect of UDN was investigated in an athymic nude mouse xenograft model using H-1299 NSCLC cells.

RESULTS: UDN exhibited a marked inhibitory effect on cell growth in H-1299 and H-460 human NSCLC cell lines in a dose- and time-dependent manner in vitro and in vivo. It induced not only apoptosis, but also autophagy in both H-1299 and H-460 cells in a dose-dependent manner. UDN-mediated autophagy led to the accumulation of autophagosome, resulting in apoptosis induction and cell death. **CONCLUSIONS:** From our current knowledge, we are the first to demonstrate that UDN has the potential to induce both autophagy and apoptosis in H-1299 and H-460 human NSCLC cell lines. We suggest that UDN can be considered a potential candidate for lung cancer-specific chemotherapy with efficacy as a cytotoxic agent.

MISCELLANEOUS WORKS

[Association of Smoking in the Home With Lung Cancer Worry, Perceived Risk, and Synergistic Risk.](#)

Butler KM1, Rayens MK1, Wiggins AT1, Rademacher KB1, Hahn EJ1. Oncol Nurs Forum. 2017 Mar 1;44(2):E55-E63. doi: 10.1188/17.ONF.E55-E63.

PURPOSE/OBJECTIVES: To examine the association of smoking in the home with lung cancer worry, perceived risk, and synergistic risk, controlling for sociodemographics, family history of lung cancer, and health-related self-concept. The hypothesis is that participants with smoking in the home would have higher scores for lung cancer worry, perceived risk, and synergistic risk. **DESIGN:** Cross-sectional baseline survey. **SETTING:** Participants recruited from an outpatient clinic and pharmacy at University of Kentucky HealthCare, an academic medical center. **SAMPLE:** 515 homeowners from a larger randomized, controlled trial aimed at reducing exposure to radon and secondhand smoke (SHS).

METHODS: Homeowners were selected via quota sampling so that about half would have a smoker or smokers in the home. **MAIN RESEARCH VARIABLES:** Lung cancer worry and perceived risk; perception of synergistic risk of radon and SHS exposure; demographics. **FINDINGS:** Participants with

smoking in the home had higher rates of lung cancer worry and perceived risk. In addition, those with less education and a family history of lung cancer and who were current smokers had higher lung cancer worry and perceived lung cancer risk scores. Predictors of perception of synergistic risk were marital status and health-related self-concept.^[P]^[SEP]**CONCLUSIONS:** Homeowners with smoking in the home, less education, and a family history of lung cancer had greater lung cancer worry and perceived lung cancer risk. Lung cancer risk reduction interventions with vulnerable populations are needed. **IMPLICATIONS FOR NURSING:** Nurses are in a unique position to target high-risk populations and identify opportunities to create teachable moments to reduce environmental risks of radon and tobacco smoke exposure.

Residence in Rural Areas of the United States and Lung Cancer Mortality, Disease Incidence, Treatment Disparities, and Stage-Specific Survival. Atkins GT1, Kim T2, Munson J1,3. *Ann Am Thorac Soc.* 2017 Mar;14(3):403-411. doi: 10.1513/AnnalsATS.201606-469OC.

RATIONALE: There is increased lung cancer mortality in rural areas of the United States. However, it remains unclear to what extent rural-urban differences in disease incidence, stage at diagnosis, or treatment explain this finding. **OBJECTIVES:** To explore the relationship between smoking rates, lung cancer incidence, and lung cancer mortality in populations across the rural-urban continuum and to determine whether survival is decreased in rural patients diagnosed with lung cancer and whether this is associated with rural-urban differences in stage at diagnosis or the treatment received. **METHODS:** We conducted a retrospective cohort study of 348,002 patients diagnosed with lung cancer between 2000 and 2006. Data from metropolitan, urban, suburban, and rural areas in the United States were obtained from the Surveillance, Epidemiology, and End Results program database. County-level population estimates for 2003 were obtained from the U.S. Census Bureau, and corresponding estimates of smoking prevalence were obtained from published literature. The exposure was rurality, defined by the rural-urban continuum code area linked to each cohort participant by county of residence. Outcomes included lung cancer incidence, mortality, diagnostic stage, and treatment received. **MEASUREMENTS AND MAIN RESULTS:** Lung cancer mortality increased with rurality in a dose-dependent fashion across the rural-urban continuum. The most rural areas had almost twice the smoking prevalence and lung cancer incidence of the largest metropolitan areas. Rural patients diagnosed with stage I non-small cell lung cancer underwent fewer surgeries (69% vs. 75%; $P < 0.001$) and had significantly reduced median survival (40 vs. 52 mo; $P = 0.0006$) compared with the most urban patients. Stage at diagnosis was similar across the rural-urban continuum, as was median survival for patients with stages II-IV lung cancer. **CONCLUSIONS:** Higher rural smoking rates drive increased disease incidence and per capita lung cancer mortality in rural areas of the United States. There were no rural-urban discrepancies in diagnostic stage, suggesting similar access to diagnostic services. Rural patients diagnosed with stage I non-small cell lung cancer had shorter survival, which may reflect disparities in access to surgical care. No survival difference for patients with advanced-stage lung cancer is attributed to lack of effective treatment during the time period of this study.

The cost-effectiveness of alectinib in anaplastic lymphoma kinase-positive (ALK+) advanced NSCLC previously treated with crizotinib. Carlson JJ1, Canestaro W1, Ravelo A2, Wong W2. *J Med Econ.* 2017 Mar 23:1-7. doi: 10.1080/13696998.2017.1302453. [Epub ahead of print]

INTRODUCTION: Anaplastic lymphoma kinase (ALK) targeting drugs provide an important option for advanced non-small cell lung cancer patients with this distinct tumor type; however, there is considerable uncertainty as to which drug provides the optimal value after crizotinib treatment. This study estimated the cost-utility of alectinib vs ceritinib from a US payer perspective. **METHODS:** A cost-utility model was developed using partition survival methods and three health states: progression-free (PF), post-progression (PP), and death. Survival data were derived from the key clinical trials (alectinib: NP28761 &

NP28673, ceritinib: ASCEND I and II). Costs included drugs, adverse events, and supportive care. Utilities were based on trial data and the literature. One-way and probabilistic sensitivity analyses (PSA) were performed to assess parameter uncertainty. **RESULTS:** Treatment with alectinib vs ceritinib resulted in increases of 2.55 months in the PF state, 0.44 quality adjusted life-years (QALYs), and \$13,868, yielding a mean cost/QALY of \$31,180. In the PSA, alectinib had a 96% probability of being cost-effective at a willingness-to-pay of \$100,000/QALY. Drivers of model results were drug costs and utilities in the PF health state. The ICER ranged from \$10,600-\$65,000 per QALY in scenario analyses, including a sub-group analysis limited to patients with prior chemotherapy and crizotinib treatment. **Conclusions:** Treatment with alectinib in ALK + crizotinib-treated patients increased time progression-free and QALYs vs ceritinib. The marginal cost increase was driven by longer treatment durations with alectinib. This model demonstrates that alectinib may be considered a cost-effective treatment after progression on crizotinib.

Cost and Survival Analysis Before and After Implementation of Dana-Farber Clinical Pathways for Patients With Stage IV Non-Small-Cell Lung Cancer. Jackman DM1, Zhang Y1, Dalby C1, et al. J

Oncol Pract. 2017 Mar 4;JOP2017021741. doi: 10.1200/JOP.2017.021741. [Epub ahead of print]

PURPOSE: Increasing costs and medical complexity are significant challenges in modern oncology. We explored the use of clinical pathways to support clinical decision making and manage resources prospectively across our network. **MATERIALS AND METHODS:** We created customized lung cancer pathways and partnered with a commercial vendor to provide a Web-based platform for real-time decision support and post-treatment data aggregation. Dana-Farber Cancer Institute (DFCI) Pathways for non-small cell lung cancer (NSCLC) were introduced in January 2014. We identified all DFCI patients who were diagnosed and treated for stage IV NSCLC in 2012 (before pathways) and 2014 (after pathways). Costs of care were determined for 1 year from the time of diagnosis. **RESULTS:** Pre- and postpathway cohorts included 160 and 210 patients with stage IV NSCLC, respectively. The prepathway group had more women but was otherwise similarly matched for demographic and tumor characteristics. The total 12-month cost of care (adjusted for age, sex, race, distance to DFCI, clinical trial enrollment, and EGFR and ALK status) demonstrated a \$15,013 savings after the implementation of pathways (\$67,050 before pathways v \$52,037 after pathways). Antineoplastics were the largest source of cost savings. Clinical outcomes were not compromised, with similar median overall survival times (10.7 months before v 11.2 months after pathways; P = .08). **CONCLUSION:** After introduction of a clinical pathway in metastatic NSCLC, cost of care decreased significantly, with no compromise in survival. In an era where comparative outcomes analysis and value assessment are increasingly important, the implementation of clinical pathways may provide a means to coalesce and disseminate institutional expertise and track and learn from care decisions.