



Caring Ambassadors Lung Cancer Program Literature Review, March 2016

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Preclinical Evaluation of 4-\[\(18\)F\]Fluoroglutamine PET to Assess ASCT2 Expression in Lung Cancer.](#) Hassanein M1,2, Hight MR3,4, Buck JR3,4, et al. Mol Imaging Biol. 2016 Feb;18(1):18-23. doi: 10.1007/s11307-015-0862-4.

PURPOSE: Alanine-serine-cysteine transporter 2 (ASCT2) expression has been demonstrated as a promising lung cancer biomarker. (2S,4R)-4-[(18)F]Fluoroglutamine (4-[(18)F]fluoro-Gln) positron emission tomography (PET) was evaluated in preclinical models of non-small cell lung cancer as a quantitative, non-invasive measure of ASCT2 expression. **PROCEDURES:** In vivo microPET studies of 4-[(18)F]fluoro-Gln uptake were undertaken in human cell line xenograft tumor-bearing mice of varying ASCT2 levels, followed by a genetically engineered mouse model of epidermal growth factor receptor (EGFR)-mutant lung cancer. The relationship between a tracer accumulation and ASCT2 levels in tumors was evaluated by IHC and immunoblotting. **RESULT:** 4-[(18)F]Fluoro-Gln uptake, but not 2-deoxy-2-[(18)F]fluoro-D-glucose, correlated with relative ASCT2 levels in xenograft tumors. In genetically engineered mice, 4-[(18)F]fluoro-Gln accumulation was significantly elevated in lung tumors, relative to normal lung and cardiac tissues. **CONCLUSIONS:** 4-[(18)F]Fluoro-Gln PET appears to provide a non-invasive measure of ASCT2 expression. Given the potential of ASCT2 as a lung cancer biomarker, this and other tracers reflecting ASCT2 levels could emerge as precision imaging diagnostics in this setting.

[Role of deltaNp63\(pos\) CD44v\(pos\) cells in the development of N-nitroso-tris-chloroethylurea-induced peripheral-type mouse lung squamous cell carcinomas.](#) Yamano S1, Gi M1, Tago Y1, et al. Cancer Sci. 2016 Feb;107(2):123-32. doi: 10.1111/cas.12855. Epub 2016 Feb 13.

The role of cells expressing stem cell markers deltaNp63 and CD44v has not yet been elucidated in peripheral-type lung squamous cell carcinoma (pLSCC) carcinogenesis. Female A/J mice were painted topically with N-nitroso-tris-chloroethylurea (NTCU) for induction of pLSCC, and the histopathological and molecular characteristics of NTCU-induced lung lesions were examined. Histopathologically, we found atypical bronchiolar hyperplasia, squamous metaplasia, squamous dysplasia, and pLSCCs in the treated mice. Furthermore, we identified deltaNp63(pos) CD44v(pos) CK5/6(pos) CC10(pos) clara cells as key constituents of early precancerous atypical bronchiolar hyperplasia. In addition, deltaNp63(pos)

CD44v(pos) cells existed throughout the atypical bronchiolar hyperplasias, squamous metaplasias, squamous dysplasias, and pLSCCs. Overall, our findings suggest that NTCU induces pLSCC through an atypical bronchiolar hyperplasia-metaplasia-dysplasia-SCC sequence in mouse lung bronchioles. Notably, Ki67-positive deltaNp63(pos) CD44v(pos) cancer cells, cancer cells overexpressing phosphorylated epidermal growth factor receptor and signal transducer and activator of transcription 3, and tumor-associated macrophages were all present in far greater numbers in the peripheral area of the pLSCCs compared with the central area. These findings suggest that deltaNp63(pos) CD44v(pos) clara cells in mouse lung bronchioles might be the origin of the NTCU-induced pLSCCs. Our findings also suggest that tumor-associated macrophages may contribute to creating a tumor microenvironment in the peripheral area of pLSCCs that allows deltaNp63(pos) CD44v(pos) cancer cell expansion through activation of epidermal growth factor receptor signaling, and that exerts an immunosuppressive effect through activation of signal transducer and activator of transcription 3 signaling.

[Investigating the Radioresistant Properties of Lung Cancer Stem Cells in the Context of the Tumor Microenvironment.](#) Chan R1, Sethi P1, Jyoti A1, McGarry R1, Upreti M1. *Radiat Res.* 2016 Feb;185(2):169-81. doi: 10.1667/RR14285.1. Epub 2016 Feb 2.

Lung cancer is the most common cause of cancer-related deaths worldwide and non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer. While recent research has shown that cancer stem cells (CSC) exhibit radioresistant and chemoresistant properties, current cancer therapy targets the bulk of the tumor burden without accounting for the CSC and the contribution of the tumor microenvironment. CSC interaction with the stroma enhances NSCLC survival, thus limiting the efficacy of treatment. The aim of this study was to elucidate the role of CSC and the microenvironment in conferring radio- or chemoresistance in an in vitro tumor model for NSCLC. The novel in vitro three-dimensional (3D) NSCLC model of color-coded tumor tissue analogs (TTA) that we have developed is comprised of human lung adenocarcinoma cells, fibroblasts, endothelial cells and NSCLC cancer stem cells maintained in low oxygen conditions (5% O₂) to recapitulate the physiologic conditions in tumors. Using this model, we demonstrate that a single 5 Gy radiation dose does not inhibit growth of TTA containing CSC and results in elevated expression of cytokines (TGF- α , RANTES, ENA-78) and factors (vimentin, MMP and TIMP), indicative of an invasive and aggressive phenotype. However, combined treatment of single dose or fractionated doses with cisplatin was found to either attenuate or decrease the proliferative effect that radiation exposure alone had on TTA containing CSC maintained in hypoxic conditions. In summary, we utilized a 3D NSCLC model, which had characteristics of the tumor microenvironment and tumor cell heterogeneity, to elucidate the multifactorial nature of radioresistance in tumors.

[Resveratrol analogue 4,4'-dihydroxy-trans-stilbene potently inhibits cancer invasion and metastasis.](#) Savio M1, Ferraro D1, Maccario C1, et al. *Sci Rep.* 2016 Feb 1;6:19973. doi: 10.1038/srep19973.

We investigated the preventive effects of resveratrol analogue 4,4'-dihydroxy-trans-stilbene (DHS) on cancer invasion and metastasis. Two different in vivo approaches of mouse and zebrafish lung cancer invasion models were employed in our study. The in vitro results showed that DHS displays potent inhibition on anchorage-dependent or -independent cell growth of LLC cells, leading to impairment of the cell cycle progression with reduction of cell numbers arresting at the G1 phase, an evident accumulation of pre-G1 events correlated with apoptotic behaviour. In addition, DHS induces a marked inhibition of LLC cell migration and matrigel invasion. In a murine lung cancer model, tumour volume, cell proliferation, and tumour angiogenesis were significantly inhibited by DHS. Importantly, liver metastatic lesions were significantly reduced in DHS-treated mice. Similarly, DHS significantly inhibits lung cancer cell dissemination, invasion and metastasis in a zebrafish tumour model. These findings demonstrate that DHS could potentially be developed as a novel therapeutic agent for treatment of cancer and metastasis.

ERK and AKT phosphorylation status in lung cancer and emphysema using nanocapillary isoelectric focusing.

Crosbie PA1, Crosbie EJ2, Aspinall-O'Dea M3, et al. *BMJ Open Respir Res.* 2016 Feb 17;3(1):e000114. doi: 10.1136/bmjresp-2015-000114. eCollection 2016.

BACKGROUND: Emphysema is an independent risk factor for the development of lung cancer in smokers. Activation of oncogenic signalling proteins AKT and ERK by phosphorylation has an established role in the development of lung cancer and has also been implicated in the pathogenesis of emphysema. The aim of this study was to compare the protein level and phosphorylation status of AKT and ERK in paired lung cancer and emphysema tissue using a highly sensitive phosphoprotein analysis approach. **METHODS:** An antibody-based, nanocapillary isoelectric focusing (cIEF) assay was used to determine the relative quantities and phosphorylation status of AKT and ERK in tumour and matched lung tissue from patients, with or without evidence of emphysema, undergoing curative resection for non-small cell lung cancer. **RESULTS:** 20 patients with adenocarcinoma (n=9) or squamous cell carcinoma (n=11) of the lung were included (mean age 67.3 years (SD 7.5, range 47-80 years)), 12 were men and all were current (n=10) or former smokers (n=10). Paired macroscopically normal lung tissue was either histologically normal (n=7) or showed emphysema (n=13). Total and phosphorylated AKT levels were fourfold (p=0.0001) and fivefold (p=0.001) higher in tumour compared with matched lung, respectively. There was no correlation with tumour histology, stage or differentiation; however, total AKT signal in tumour was significantly correlated with fluorodeoxyglucose avidity on positron emission tomography-CT scan (r=0.53, p=0.035). Total ERK was not differentially expressed, but doubly phosphorylated (activated) ERK was threefold higher in emphysema (23.5%, SD 9.2) than either matched tumour (8.8%, SD 8.6) or normal lung tissue (8.3%, SD 9.0) and correlated with the histological severity of emphysema (p=0.005). **CONCLUSIONS:** cIEF offers opportunities for quantifying subtle shifts in the phosphorylation status of oncoproteins in nanogram amounts of lung tissue. ERK activation is a feature of emphysema.

Genomic Alteration During Metastasis of Lung Adenocarcinoma. Tan Q1, Cui J, Huang J, et al. *Cell Physiol Biochem.* 2016;38(2):469-86. doi: 10.1159/000438644. Epub 2016 Feb 1.

BACKGROUND/AIMS: Recurrent gene mutation has been identified by the analysis of exonic DNA from lung adenocarcinoma, but its progression has not been extensively profiled. The investigation of the mutational landscape of tumors provides new insights into cancer genome evolution and further discovers the interplay of somatic mutation, adaptation of clones to their environment and natural selection. Cancer development involves cycles of genomic damage, epigenetic deregulation, and increased cellular proliferation that eventually culminate in the carcinoma phenotype. **METHODS:** Comparative whole exome sequencing of both primary and metastatic tumor tissues from four patients of stage IV lung adenocarcinoma patients with chest wall metastasis was performed. Both primary and metastatic tumors were diagnosed through biopsy followed by surgical resection. All tumor specimens were cut into several pieces to assess potential heterogenic clones within the tumor tissue. Adjacent normal lung tissue was also obtained to provide germline mutation background. **RESULTS:** By modeling and analyzing progression of the cancer metastasis based on non-synonymous variants, we defined the extent of heterogeneity of cancer genomes and identified similar cancer evolution pattern in the four patients: metastasis was an early event occurring right after the primary cancer formation and evolution in the metastatic tumor was continuously and simultaneously in progression with that in the primary tumor. By characterizing the clonal hierarchy of genetic lesions, we further charted a pathway of oncogenic events along which genes may drive lung adenocarcinoma metastasis, such as *TAS2R31* and *UMODL1*, involving in G-protein coupled receptor protein signaling pathway. **CONCLUSION:** The candidate genes identified in this study may become targets for the treatment of lung adenocarcinoma metastasis.

[SULF2 Expression Is a Potential Diagnostic and Prognostic Marker in Lung Cancer.](#) Lui NS1, Yang YW1, van Zante A2, Buchanan P1, Jablons DM1, Lemjabbar-Alaoui H1. PLoS One. 2016 Feb 16;11(2):e0148911. doi: 10.1371/journal.pone.0148911. eCollection 2016.

AIMS: Lung cancer is one of the most deadly cancers; median survival from diagnosis is less than one year in those with advanced disease. Novel lung cancer biomarkers are desperately needed. In this study, we evaluated SULF2 expression by immunohistochemistry and its association with overall survival in a cohort of patients with non-small cell lung cancer (NSCLC). We also looked for the presence of SULF2 protein in plasma to evaluate its potential as an early detection biomarker for NSCLC. **METHODS:** We identified patients who underwent surgical resection for pulmonary adenocarcinoma or squamous cell carcinoma at our institution. A section from each paraffin-embedded specimen was stained with a SULF2 antibody. A pathologist determined the percentage and intensity of tumor cell staining. Survival analysis was performed using a multivariate Cox proportional hazards model. Using a novel SULF2 ELISA assay, we analyzed plasma levels of SULF2 in a small cohort of healthy donors and patients with early stage NSCLC. **RESULTS:** SULF2 staining was present in 82% of the lung cancer samples. Squamous cell carcinomas had a higher mean percentage of staining than adenocarcinomas (100% vs. 60%; $p < 0.0005$). After adjusting for age, sex, race, histologic type, stage, and neoadjuvant therapy, there was a non-significant (31%; $p = 0.65$) increase in the risk of death for patients with adenocarcinoma with SULF2 staining in tumor cells. In contrast, there was a significant decrease in the risk of death (89%; $p = 0.02$) for patients with squamous cell carcinoma with SULF2 staining in tumor cells. SULF2 protein was present in plasma of patients with early stage NSCLC, and soluble SULF2 levels increased with age. Finally, plasma SULF2 levels were significantly elevated in early stage NSCLC patients, compared to healthy controls. **CONCLUSIONS:** Tumor expression of SULF2 may affect prognosis in NSCLC, while blood SULF2 levels may have a significant role in the diagnosis of this fatal disease.

[Discovery and characterization of a high-affinity and high-specificity peptide ligand LXY30 for in vivo targeting of \$\alpha 3\$ integrin-expressing human tumors.](#) Xiao W1, Li T2,3,4, Bononi FC1, et al. EJNMMI Res. 2016 Dec;6(1):18. Epub 2016 Feb 27.

BACKGROUND: $\alpha 3\beta 1$ integrin is overexpressed in several types of human cancer and is associated with poor prognosis, metastasis, and resistance to cancer treatment. We previously identified a cyclic peptide ligand LXY1 that specifically binds to the $\alpha 3\beta 1$ integrin on human glioblastoma U-87MG cells. Here, we optimized LXY1 through one-bead one-compound combinatorial library screening and site-specific modifications to improve its in vivo binding property. **METHODS:** Three bead libraries were synthesized and whole-cell binding assays were performed. The binding capacity of individual peptide ligands against different tumor cells was determined by flow cytometry and confirmed by optical imaging. A complex joining biotinylated ligand with streptavidin-Cy5.5 was used for in vivo target imaging in both subcutaneous and orthotopic U-87MG xenograft mouse models. **RESULTS:** LXY30, a cyclic peptide with the sequence cdG-Phe(3,5-diF)-G-Hyp-NcR, emerged as the most potent and selective ligand for the $\alpha 3$ subunit of $\alpha 3\beta 1$ integrin with improved in vitro and in vivo tumor-targeting effects compared to LXY1 in U-87MG cells. LXY30 is considerably stable in plasma as demonstrated in an in vitro stability study in 90 % human plasma. LXY30 also binds to several other known $\alpha 3\beta 1$ integrin-expressing glioblastoma, lung, and breast cancer cell lines with various affinities. **CONCLUSIONS:** Our data support further investigating the role of LXY30 as a human tumor-targeting peptide ligand for systemic and intracranial delivery of imaging agents and cancer therapeutics.

[Experience With a CT Screening Program for Individuals at High Risk for Developing Lung](#)**[Cancer](#)**. McKee BJ1, Hashim JA2, French RJ2, et al. J Am Coll Radiol. 2016 Feb;13(2 Suppl):R8-R13. doi: 10.1016/j.jacr.2015.12.006.

PURPOSE: The aim of this study was to compare results of National Comprehensive Cancer Network (NCCN) high-risk group 2 with those of NCCN high-risk group 1 in a clinical CT lung screening program. **METHODS:** The results of consecutive clinical CT lung screening examinations performed from January 2012 through December 2013 were retrospectively reviewed. All examinations were interpreted by radiologists credentialed in structured CT lung screening reporting, following the NCCN Clinical Practice Guidelines in Oncology: Lung Cancer Screening (version 1.2012). Positive results required a solid nodule ≥ 4 mm, a ground-glass nodule ≥ 5 mm, or a mediastinal or hilar lymph node > 1 cm, not stable for > 2 years. Significant incidental findings and findings suspicious for pulmonary infection were also recorded. **RESULTS:** A total of 1,760 examinations were performed (464 in group 2, 1,296 in group 1); no clinical follow-up was available in 432 patients (28%). Positive results, clinically significant incidental findings, and suspected pulmonary infection were present in 25%, 6%, and 6% in group 2 and 28.2%, 6.2%, and 6.6% in group 1, respectively. Twenty-three cases of lung cancer were diagnosed (6 in group 2, 17 in group 1), for annualized rates of malignancy of 1.8% in group 2 and 1.6% in group 1. **CONCLUSION:** NCCN group 2 results were substantively similar to those for group 1 and closely resemble those reported in the National Lung Screening Trial. Similar rates of positivity and lung cancer diagnosis in both groups suggest that thousands of additional lives may be saved each year if screening eligibility is expanded to include this particular high-risk group.

[Negative EBUS-TBNA Predicts Very Low Prevalence of Mediastinal Disease in Staging of NSCLC](#)

Taverner J1, Cheang MY, Antippa P, See K, Irving LB, Steinfort DP. J Bronchology Interv Pulmonol. 2016 Feb 22. [Epub ahead of print]

BACKGROUND: Confirmation of mediastinal disease (N2/3) in non-small cell lung cancer (NSCLC) generally precludes curative surgical management. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become a routine first test in mediastinal staging of NSCLC; however, it remains unclear whether a negative EBUS-TBNA should be followed by mediastinoscopy before proceeding to surgery. Understanding the prevalence of metastases in lymph nodes with benign findings on EBUS-TBNA will inform decision making following negative EBUS-TBNA. **METHODS:** We examined a retrospective cohort of patients who underwent EBUS-TBNA before resection with mediastinal lymph node sampling for NSCLC between December 2009 and June 2014 in 3 hospitals in Melbourne, Australia. All patients had integrated positron emission tomography/computed tomography (PET/CT) before EBUS-TBNA. **RESULTS:** Eighty-two matched mediastinal lymph node stations were sampled in 57 patients by both EBUS-TBNA and surgical resection, 47 nodes in patients staged cN0/1 by PET/CT and 35 nodes in patients staged cN2/3. All patients had a negative EBUS-TBNA. Four malignant nodes were identified surgically (4.9% of lymph nodes). The mean size of malignant deposits was 5.5 mm. Per-node negative predictive value was $78/82=0.95$. All malignant nodes were located in patients with moderate-high risk disease (cN2/3), giving a disease prevalence in cN2/3 patients of 11%, and 0% in cN0/1. In patients staged cN2, per-node NVP was 0.89. **CONCLUSIONS:** The prevalence of mediastinal nodal disease following negative EBUS-TBNA is very low, at 4.9%. The per-node NVP of EBUS-TBNA is 0.95, decreasing to 0.89 in moderate-high risk patients. We suggest that a negative EBUS-TBNA of mediastinal nodes does not need to be confirmed by mediastinoscopy of those nodal stations, regardless of PET/CT findings.

[Volatile signature for the early diagnosis of lung cancer.](#) Gasparri R1, Santonico M, Valentini C, et al. J Breath Res. 2016 Feb 9;10(1):016007. doi: 10.1088/1752-7155/10/1/016007.

Exhaled breath contains hundreds of volatile organic compounds (VOCs). Several independent researchers point out that the breath of lung cancer patients shows a characteristic VOC-profile which can be considered as lung cancer signature and, thus, used for diagnosis. In this regard, the analysis of exhaled breath with gas sensor arrays is a potential non-invasive, relatively low-cost and easy technique for the early detection of lung cancer. This clinical study evaluated the gas sensor array response for the identification of the exhaled breath of lung cancer patients. This study involved 146 individuals: 70 with lung cancer confirmed by computerized tomography (CT) or positron emission tomography-(PET) imaging techniques and histology (biopsy) or with clinical suspect of lung cancer and 76 healthy controls. Their exhaled breath was measured with a gas sensor array composed of a matrix of eight quartz microbalances (QMBs), each functionalized with a different metalloporphyrin. The instrument produces, for each analyzed sample, a vector of signals encoding the breath (breathprint). Breathprints were analyzed with multivariate analysis in order to correlate the sensor signals to the disease. Breathprints of the lung cancer patients were differentiated from those of the healthy controls with a sensitivity of 81% and specificity of 91%. Similar values were obtained in patients with and without metabolic comorbidities, such as diabetes, obesity and dyslipidemia (sensitivity 85%, specificity 88% and sensitivity 76%, specificity 94%, respectively). The device showed a large sensitivity to lung cancer at stage I with respect to stage II/III/IV (92% and 58% respectively). The sensitivity for stage I did not change for patients with or without metabolic comorbidities (90%, 94%, respectively). Results show that this electronic nose can discriminate the exhaled breath of the lung cancer patients from those of the healthy controls. Moreover, the largest sensitivity is observed for the subgroup of patients with a lung cancer at stage I.

[Planning and Implementation of Low-Dose Computed Tomography Lung Cancer Screening Programs in the United States.](#) Qiu R1, Copeland A2, Sercy E3, Porter NR3, McDonnell KK4, Eberth J3. Clin J Oncol Nurs. 2016 Feb 1;20(1):52-8. doi: 10.1188/16.CJON.52-58.

BACKGROUND: One of the largest, most expensive randomized, controlled trials, the National Lung Screening Trial, found that annual low-dose computed tomography (LDCT) scans led to a 20% reduction in lung cancer deaths. **OBJECTIVES:** This study describes the characteristics and program implementation barriers experienced by LDCT screening programs in the United States. **METHODS:** Using a mixed-methods approach, Lung Cancer Alliance Screening Centers of Excellence were surveyed and interviewed in 2013. Representatives from 65 centers completed an electronic questionnaire, followed by in-depth interviews with 13 physicians and nurse navigators regarding their institution's screening programs. **FINDINGS:** Participants cited low patient demand and few physician referrals as barriers, but few centers reported needing additional staff or equipment. Those interviewed discussed the importance of a multidisciplinary team and overcoming barriers related to insurance reimbursement, costs, and physician knowledge to improve program implementation.

[A robust prognostic gene expression signature for early stage lung adenocarcinoma.](#) Krzystanek M1, Moldvay J2, Sziuts D3, Szallasi Z4, Eklund AC1. Biomark Res. 2016 Feb 19;4:4. doi: 10.1186/s40364-016-0058-3. eCollection 2016.

BACKGROUND: Stage I lung adenocarcinoma is usually not treated with adjuvant chemotherapy; however, around half of these patients do not survive 5 years. Therefore, a reliable prognostic biomarker for early stage patients would be critical to identify those most likely to benefit from early additional treatments. Several studies have searched for gene expression prognostic biomarkers for lung adenocarcinoma, but these have not yielded a widely accepted prognosticator. **RESULTS:** We analyzed gene expression from seven published lung adenocarcinoma cohorts for which we included only stage I

and II patients who were not given adjuvant therapy. Seven genes consistently obtained statistical significance in Cox regression for overall survival. The combined signature has a weighted mean hazard ratio of 3.2 in all cohorts and 3.0 (C.I. 1.3-7.4, $p < 0.01$) in an independent validation cohort and is strongly correlated with previously published signatures of chromosomal instability and cell cycle progression. **CONCLUSIONS:** The new prognostic signature, if validated prospectively, may enable better stratification and treatment of early stage lung cancer patients.

[Community-Based Multidisciplinary Computed Tomography Screening Program Improves Lung Cancer Survival.](#)

Miller DL1, Mayfield WR2, Luu TD2, et al. Ann Thorac Surg. 2016 Feb 12. pii: S0003-4975(15)01840-8. doi: 10.1016/j.athoracsur.2015.11.001. [Epub ahead of print]

Helms GA2, Muster AR2, Beckler VJ2, Cann A2.

BACKGROUND: Lung cancer is the most common cause of cancer deaths in the United States. Overall survival is less than 20%, with the majority of patients presenting with advanced disease. The National Lung Screening Trial, performed mainly in academic medical centers, showed that cancer mortality can be reduced with computed tomography (CT) screening compared with chest radiography in high-risk patients. To determine whether this survival advantage can be duplicated in a community-based multidisciplinary thoracic oncology program, we initiated a CT scan screening program for lung cancer within an established health care system. **METHODS:** In 2008, we launched a lung cancer CT screening program within the WellStar Health System (WHS) consisting of five hospitals, three health parks, 140 outpatient medical offices, and 12 imaging centers that provide care in a five-county area of approximately 1.4 million people in Metro-Atlanta. Screening criteria incorporated were the International Early Lung Cancer Action Program (2008 to 2010) and National Comprehensive Cancer Network guidelines (2011 to 2013) for moderate- and high-risk patients. **RESULTS:** A total of 1,267 persons underwent CT lung cancer screening in WHS from 2008 through 2013; 53% were men, 87% were 50 years of age or older, and 83% were current or former smokers. Noncalcified indeterminate pulmonary nodules were found in 518 patients (41%). Thirty-six patients (2.8%) underwent a diagnostic procedure for positive findings on their CT scan; 30 proved to have cancer, 28 (2.2%) primary lung cancer and 2 metastatic cancer, and 6 had benign disease. Fourteen patients (50%) had their lung cancer discovered on their initial CT scan, 11 on subsequent scans associated with indeterminate pulmonary nodules growth and 3 patients who had a new indeterminate pulmonary nodules. Only 15 (54%) of these 28 patients would have qualified as a National Lung Screening Trial high-risk patient; 75% had stage I or II disease. Overall 5-year survival was 64% and 5-year cancer specific survival was 71% in the screened patients, whereas nonscreened lung cancer patients during that time in WHS had an overall survival of only 19% ($p < 0.001$). **CONCLUSIONS:** A community-based multidisciplinary lung cancer screening program can improve survival of patients with lung cancer outside of a large multicenter study. This survival advantage was caused by a significant stage shift to earlier disease. Lung cancer CT screening may also benefit patients not meeting the National Lung Screening Trial criteria who are at moderate or high risk for lung cancer.

[Programmed cell death-ligand 1 expression is associated with a favourable immune microenvironment and better overall survival in stage I pulmonary squamous cell carcinoma.](#)

Yang CY1, Lin MW2, Chang YL3, Wu CT4, Yang PC1. Eur J Cancer. 2016 Feb 19;57:91-103. doi: 10.1016/j.ejca.2015.12.033. [Epub ahead of print]

BACKGROUND: Programmed cell death-ligand 1 (PD-L1) is expressed in a subgroup of lung cancer that may benefit from immunotherapy. The interaction between PD-L1 expression and tumour infiltrating lymphocytes (TIL) remains poorly understood. This study investigated the expression of PD-L1 in surgically resected stage I pulmonary squamous cell carcinoma (SqCC) and correlated it with TILs in

tumour microenvironments, common driver mutations, and clinical outcomes. **MATERIALS AND METHODS:** One hundred and five patients with surgically resected stage I squamous cell carcinoma were examined. Paraffin-embedded tumour sections were stained with PD-L1 antibody. Tumours with moderate-to-strong membrane staining in $\geq 5\%$ of tumour cells were scored as positive for PD-L1 expression. The driver mutation epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), and v-raf murine sarcoma viral oncogene homolog B (BRAF) were examined by direct sequencing, while anaplastic lymphoma kinase (ALK), phosphoinositide 3-kinase catalytic alpha (PI3KCA), and fibroblast growth factor receptor 1 (FGFR1) were analysed by immunohistochemistry. The correlations of PD-L1 expression with each subtype of TIL, driver mutations, clinicopathologic parameters, and clinical outcomes were analysed. **RESULTS:** There was positive PD-L1 expression in 56.2% (59/105) of patients. PD-L1 expression was not associated with the common clinicopathologic features and mutations of EGFR, KRAS, BRAF, ALK, PI3KCA, and FGFR1. As regards TILs composition, tumour PD-L1 expression was significantly associated with increased tumour epithelial CD8+ T cells and stromal CD4+ T cells. Otherwise, PD-L1 (+) tumour cells were negatively correlated with PD-L1 (+) immune cells within tumour stroma. By multivariate analysis, tumour PD-L1 expression and increased CD4+ T cell infiltrations in the tumour stroma were independent predictors of better overall survival and had a trend of better disease-free survival. **CONCLUSIONS:** PD-L1 expression is associated with a favourable immune microenvironment in stage I pulmonary SqCC and correlates with better clinical outcome.

[The Impact of Electromagnetic Navigational Bronchoscopy on a Multidisciplinary Thoracic Oncology Program.](#) Brown C1, Ben-Or S1, Walker P1, Bowling M1. J Natl Compr Canc Netw. 2016 Feb;14(2):181-4.

BACKGROUND: The Leo W. Jenkins Cancer Clinic has adopted a programmatic, multidisciplinary approach to thoracic tumors, which has involved the implementation of new therapeutic and diagnostic approaches. In 2012 we began using electromagnetic navigational bronchoscopy (ENB) as a new diagnostic tool. ENB uses a guidance system that combines CT imaging with magnetic field-guided spatial information to allow tissue sampling or placement of fiducial markers to guide radiation therapy. **METHODS:** The numbers of early-stage (I and II) and late-stage (III and IV) lung cancers were compared before and after the introduction of ENB. We also examined the number of cases of fiducial marker placement using bronchoscopy versus interventional radiology before and after ENB was introduced. Fisher's exact test was used to compare the early- versus late-stage lung cancers found at diagnosis pre- and post-ENB introduction, fiducial marker placements using interventional radiology versus bronchoscopy pre- and post-ENB introduction, and pneumothorax rates. **RESULTS:** More early-stage cancers were diagnosed after ENB introduction (67 of 286 cases vs 116 of 290; $P < .0001$). Bronchoscopy was also used more frequently to place fiducial markers post-ENB (53 of 86 pre-ENB vs 105 of 117 post-ENB; $P < .0001$) and had a lower pneumothorax rate (4% vs 22%) than fiducial placement in interventional radiology ($P < .001$). **CONCLUSIONS:** The addition of ENB to a multidisciplinary thoracic oncology program may permit the diagnosis of lung cancer at an earlier stage and offers the ability to safely place fiducial markers for therapeutic purposes, such as radiation therapy, within the same procedure, potentially improving safety and decreasing time to treatment.

[A propensity score matching analysis of survival following segmentectomy or wedge resection in early-stage lung invasive adenocarcinoma or squamous cell carcinoma.](#) Zhang Y1,2, Sun Y1,2, Chen H1,2,3,4. *Oncotarget*. 2016 Feb 9. doi: 10.18632/oncotarget.7284. [Epub ahead of print]

PURPOSE: To compare the survival outcomes following segmentectomy or wedge resection in early-stage lung cancer. **METHODS:** A total of 5880 patients with invasive lung adenocarcinoma or squamous cell carcinoma from the Surveillance, Epidemiology, and End Results (SEER) database were included in this study, of which 1156 received segmentectomy. Baseline characteristics were balanced using propensity score methods. Cox regression analysis was used to compare overall survival (OS) and lung cancer-specific survival (LCSS) following segmentectomy or wedge resection after matching patients based on propensity scores. **RESULTS:** Overall, patients undergoing segmentectomy and wedge resection had no significant different OS and LCSS both in the invasive adenocarcinoma group and the squamous cell carcinoma group. Segmentectomy was associated with improved OS (hazard ratio = 0.626, 95% confidence interval: 0.457-0.858, P = 0.004) and LCSS (hazard ratio = 0.643, 95% CI: 0.440-0.939, P = 0.022) in invasive adenocarcinoma patients \leq 65 years old. In patients with \leq 2 cm invasive adenocarcinoma, segmentectomy was associated with significantly better OS (hazard ratio = 0.811, 95% confidence interval: 0.666-0.988, P = 0.038). **CONCLUSION:** Survival following segmentectomy or wedge resection was generally equivalent in lung invasive adenocarcinoma and squamous cell carcinoma. However, invasive adenocarcinoma patients who were \leq 65 years or had tumors \leq 2 cm in size may have improved survival outcomes after segmentectomy.

[One Hundred Planned Robotic Segmentectomies: Early Results, Technical Details, and Preferred Port Placement.](#) Cerfolio RJ1, Watson C2, Minnich DJ2, Calloway S2, Wei B2. *Ann Thorac Surg*. 2016 Mar;101(3):1089-96. doi: 10.1016/j.athoracsur.2015.08.092. Epub 2016 Feb 2.

BACKGROUND: Both robotic pulmonary operations and anatomic segmentectomy are being increasingly performed. The largest published series of anatomic robotic segmentectomy comprises 35 patients, and the specific details of port placement are poorly understood. **METHODS:** This is a review of a consecutive series of patients from a single surgeon's prospective database. All patients in the study were scheduled to undergo robotic anatomic segmentectomy. **RESULTS:** Between February 2010 and December 2014, 100 patients went to the operating room for a planned pulmonary segmentectomy. A robotic approach was chosen for all. Seven patients underwent conversion to robotic lobectomy, and the remaining 93 patients had an anatomic robotic segmentectomy. There were no conversions to thoracotomy. Indications for resection were lung cancer in 79 patients, metastatic lesions in 10 patients, fungal infections in 4 patients, and other conditions in 7 patients. The median age was 69 years, and 50 patients were men. The median blood loss was 20 mL (range, 10-120 mL), the median number of lymph nodes removed was 19, the median operative time was 1.28 hours (88 minutes), the median length of stay was 3 days, and major morbidity occurred in 2 patients (pneumonia in both). All had undergone R0 resection. There were no 30- or 90-day mortalities. Of the 79 patients with lung cancer, the median follow-up was 30 months, and 3 patients (3.4%) had recurrence in the operated lobe. Overall survival was 95% at 30 months. **CONCLUSIONS:** Completely portal robotic anatomic segmentectomy is safe and effective and offers outstanding intraoperative 30-day and 90-day results. The recurrence rate is approximately 3% at 2.5 years.

[Circulating Tumor Cells Identify Early Recurrence in Patients with Non-Small Cell Lung Cancer Undergoing Radical Resection.](#) Bayarri-Lara C1, Ortega FG2, Cueto Ladrón de Guevara A1, Puche JL2,3, et al. PLoS One. 2016 Feb 25;11(2):e0148659. doi: 10.1371/journal.pone.0148659. eCollection 2016.

BACKGROUND: Surgery is the treatment of choice for patients with non-small cell lung cancer (NSCLC) stages I-IIIa. However, more than 20% of these patients develop recurrence and die due to their disease. The release of tumor cells into peripheral blood (CTCs) is one of the main causes of recurrence of cancer. The objectives of this study are to identify the prognostic value of the presence and characterization of CTCs in peripheral blood in patients undergoing radical resection for NSCLC.

PATIENTS AND METHODS: 56 patients who underwent radical surgery for previously untreated NSCLC were enrolled in this prospective study. Peripheral blood samples for CTC analysis were obtained before and one month after surgery. In addition CTCs were phenotypically characterized by epidermal growth factor receptor (EGFR) expression. **RESULTS:** 51.8% of the patients evaluated were positive with the presence of CTCs at baseline. A decrease in the detection rate of CTCs was observed in these patients one month after surgery (32.1%) ($p = 0.035$). The mean number of CTCs was 3.16 per 10 ml (range 0-84) preoperatively and 0.66 (range 0-3) in postoperative determination. EGFR expression was found in 89.7% of the patients at baseline and in 38.9% patients one month after surgery. The presence of CTCs after surgery was significantly associated with early recurrence ($p = 0.018$) and a shorter disease free survival (DFS) ($p = .008$). In multivariate analysis CTC presence after surgery (HR = 5.750, 95% CI: 1.50-21.946, $p = 0.010$) and N status (HR = 0.296, 95% CI: 0.091-0.961, $p = 0.043$) were independent prognostic factors for DFS. **CONCLUSION:** CTCs can be detected and characterized in patients undergoing radical resection for non-small cell lung cancer. Their presence might be used to identify patients with increased risk of early recurrence.

[Long-term impact of developing a postoperative pulmonary complication after lung surgery.](#)

Lugg ST1, Agostini PJ2, Tikka T3, et al. Thorax. 2016 Feb;71(2):171-6. doi: 10.1136/thoraxjnl-2015-207697.

INTRODUCTION: Postoperative pulmonary complications (PPC) such as atelectasis and pneumonia are common following lung resection. PPCs have a significant clinical impact on postoperative morbidity and mortality. We studied the long-term effects of PPCs and sought to identify independent risk factors.

METHODS: A prospective observational study involved all patients following lung resection in a regional thoracic centre over 4 years. PPCs were assessed daily in hospital using the Melbourne group scale based on chest X-ray, white cell count, fever, purulent sputum, microbiology, oxygen saturations, physician diagnosis and intensive therapy unit (ITU)/high-dependency unit readmission. Follow-up included hospital length of stay (LOS), 30-day readmissions, and mortality. **RESULTS:** 86 of 670 patients (13%) who had undergone a lung resection developed a PPC. Those patients had a significantly longer hospital LOS in days (13, 95% CI 10.5-14.9 vs 6.3, 95% CI 5.9 to 6.7; $p < 0.001$) and higher rates of ITU admissions (28% vs 1.9%; $p < 0.001$) and 30-day hospital readmissions (20.7% vs 11.9%; $p < 0.05$). Significant independent risk factors for development of PPCs were COPD and smoking ($p < 0.05$), not age. Excluding early postoperative deaths, developing a PPC resulted in a significantly reduced overall survival in months (40, 95% CI 34 to 44 vs 46, 95% CI 44 to 47; $p = 0.006$). Those who developed a PPC had a higher rate of non-cancer-related deaths (11% vs 5%; $p = 0.020$). PPC is a significant independent risk factor for late deaths in non-small cell lung cancer patients (HR 2.0, 95% CI 1.9 to 3.2; $p = 0.006$).

CONCLUSIONS: Developing a PPC after thoracic surgery is common and is associated with a poorer long-term outcome.

[Sleeve Lobectomy Versus Standard Lobectomy for Lung Cancer: Functional and Oncologic](#)

[Evaluation](#). D'Andrilli A1, Maurizi G2, Andreotti C2, et al. *Ann Thorac Surg*. 2016 Feb 22. pii: S0003-4975(15)01965-7. doi: 10.1016/j.athoracsur.2015.11.057. [Epub ahead of print]

BACKGROUND: The purpose of this study was to compare functional and oncologic outcome of sleeve lobectomy (SL) with that of standard lobectomy (STL) in patients with non-small cell lung cancer.

METHODS: Between January 2009 and April 2013, 44 consecutive patients undergoing upper SL (29 right side, 15 left side) were prospectively enrolled to be compared with 44 patients with the same side distribution who were randomly selected from patients undergoing upper STL during the study period. Functional and oncologic results of the two groups were compared. **RESULTS:** Pathologic tumor stage ranged between I and IIIa with similar patient distribution between the two groups. Postoperative complication rates were 20.5% in the SL group and 16% in the STL group. There was no postoperative mortality in either group. Mean postoperative decrease in forced expiratory volume in 1 second at 3 months postoperatively was $17.5\% \pm 6.2\%$ in the SL group and $19\% \pm 14.8\%$ in the STL group ($p = 0.52$). There also was no significant difference ($p = 0.15$) in mean postoperative decrease in 6-minute walk test (64.3 ± 2.5 m versus 69.1 ± 21.4 m) between the two groups. Evaluation of postoperative changes in quality of life at 3 and 6 months based on a standardized questionnaire (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire) did not show significant differences between the SL group and the STL group ($p > 0.05$) in terms of global health status, physical functioning, and fatigue. Actuarial survival rates at 3 and 5 years, respectively, were 85.3% and 60.1% in the SL group and 88.7% and 58.2% in the STL group, without significant difference ($p = 0.68$). **CONCLUSIONS:** Functional and oncologic results of SL are comparable to those of STL in patients with non-small cell lung cancer.

NSCLC - CHEMOTHERAPY

[Navigating the Challenges of Adjuvant Chemotherapy in Older Patients with Early-Stage Non-Small-Cell Lung Cancer](#)

Poudel A1, Sinha S1, Gajra A2. *Drugs Aging*. 2016 Feb 25. [Epub ahead of print]

Lung cancer is a disease of older adults. In the US and worldwide, more than 60 % of patients being diagnosed are over the age of 65 years. The preferred treatment of stage I-II non-small-cell lung cancer (NSCLC) is surgical resection. Adjuvant chemotherapy with a platinum-based combination is the standard of care for patients with early-stage NSCLC after surgery. However, there have been no large prospective studies to test the efficacy of adjuvant chemotherapy in the elderly, the population most affected by lung cancer. The available evidence is limited to retrospective reviews of large population databases or post hoc analyses of prospective studies in age-unselected populations. This review aims to address the knowledge gap pertaining to the use of adjuvant chemotherapy in older patients with resected NSCLC. There are many barriers to use of adjuvant chemotherapy in older adults with NSCLC. The utilization of adjuvant chemotherapy amongst older adults has been slow but is improving. While the elderly may tolerate a lower dose intensity of chemotherapy compared with younger patients, they do garner benefit from adjuvant chemotherapy. There is a lack of a standardized tool to risk-stratify older patients for adjuvant chemotherapy after resection. Geriatric assessment may help guide decision making in the clinical practice setting. The principles of geriatric assessment and commonly employed tools for such assessment will be reviewed. Further, the emerging therapies in adjuvant treatment of lung cancer based on genetic mutations will be discussed.

[Maintenance therapy with pemetrexed and bevacizumab versus pemetrexed monotherapy after induction therapy with carboplatin, pemetrexed, and bevacizumab in patients with advanced non-squamous non small cell lung cancer.](#) Karayama M1, Inui N2, Fujisawa T3, et al. Eur J Cancer. 2016 Feb 25;58:30-37. doi: 10.1016/j.ejca.2016.01.013. [Epub ahead of print]

OBJECTIVES: Single agent maintenance therapy is widely accepted for advanced non-squamous non small cell lung cancer (NSCLC). However, there is no consensus on the initial and maintenance phase regimens, and the clinical benefit of adding bevacizumab to cytotoxic drugs in the maintenance phase remains unclear. **METHODS:** Chemotherapy-naïve patients with non-squamous NSCLC were randomly assigned to maintenance therapy with pemetrexed and bevacizumab or pemetrexed alone, after achieving disease control after four cycles of induction therapy with carboplatin (area under the curve = 6), pemetrexed (500 mg/m²), and bevacizumab (15 mg/kg). The primary end-point was 1-year progression-free survival (PFS) rate. **RESULTS:** One hundred ten patients were enrolled in the study, with 55 patients assigned to the two groups. The mean 1-year PFS rate was 43.9% (95% confidence interval [CI]: 29.6-59.2%) in the combination maintenance group and 35.2% (95% CI: 22.1-51.0%) in the pemetrexed maintenance group, and the difference was not significant (p = 0.433). Median PFS measured from enrolment was 11.5 months (95% CI: 7.1-19.0) in the combination maintenance group and 7.3 months (95% CI: 5.7-14.1, hazard ratio: 0.73, 95% CI: 0.44-1.19, log-rank p = 0.198) in the pemetrexed maintenance group. Nasal haemorrhage, hypertension, and proteinuria were significantly more frequent in the combination maintenance group, but they were mild and tolerable. **CONCLUSION:** Both maintenance therapy with pemetrexed alone and pemetrexed and bevacizumab in combination were feasible in patients with non-squamous NSCLC who have achieved disease control after induction therapy with carboplatin, pemetrexed, and bevacizumab. According to the selection design, differences in the superiority between these maintenance therapies were not demonstrated.

[Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study.](#) Antonia S1, Goldberg SB2, Balmanoukian A3, et al. Lancet Oncol. 2016 Feb 5. pii: S1470-2045(15)00544-6. doi: 10.1016/S1470-2045(15)00544-6. [Epub ahead of print]

BACKGROUND: PD-L1 and CTLA-4 immune checkpoints inhibit antitumour T-cell activity. Combination treatment with the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab might provide greater antitumour activity than either drug alone. We aimed to assess durvalumab plus tremelimumab in patients with advanced squamous or non-squamous non-small cell lung cancer (NSCLC). **METHODS:** We did a multicentre, non-randomised, open-label, phase 1b study at five cancer centres in the USA. We enrolled immunotherapy-naïve patients aged 18 years or older with confirmed locally advanced or metastatic NSCLC. We gave patients durvalumab in doses of 3 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg every 4 weeks, or 10 mg/kg every 2 weeks, and tremelimumab in doses of 1 mg/kg, 3 mg/kg, or 10 mg/kg every 4 weeks for six doses then every 12 weeks for three doses. The primary endpoint of the dose-escalation phase was safety. Safety analyses were based on the as-treated population. The dose-expansion phase of the study is ongoing. This study is registered with ClinicalTrials.gov, number NCT02000947. **FINDINGS:** Between Oct 28, 2013, and April 1, 2015, 102 patients were enrolled into the dose-escalation phase and received treatment. At the time of this analysis (June 1, 2015), median follow-up was 18·8 weeks (IQR 11-33). The maximum tolerated dose was exceeded in the cohort receiving durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg, with two (30%) of six patients having a dose-limiting toxicity (one grade 3 increased aspartate aminotransferase and alanine aminotransferase and one grade 4 increased lipase). The most frequent treatment-related grade 3 and 4 adverse events were diarrhoea (11 [11%]), colitis (nine [9%]), and increased lipase (eight [8%]). Discontinuations attributable to treatment-related adverse events occurred in 29 (28%) of 102 patients. Treatment-related serious adverse events occurred in 37 (36%) of 102 patients. 22 patients died during the study, and three deaths were related to treatment. The treatment-related deaths

were due to complications arising from myasthenia gravis (durvalumab 10 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), pericardial effusion (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), and neuromuscular disorder (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg). Evidence of clinical activity was noted both in patients with PD-L1-positive tumours and in those with PD-L1-negative tumours. Investigator-reported confirmed objective responses were achieved by six (23%, 95% CI 9-44) of 26 patients in the combined tremelimumab 1 mg/kg cohort, comprising two (22%, 95% CI 3-60) of nine patients with PD-L1-positive tumours and four (29%, 95% CI 8-58) of 14 patients with PD-L1-negative tumours, including those with no PD-L1 staining (four [40%, 95% CI 12-74] of ten patients). **INTERPRETATION:** Durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg showed a manageable tolerability profile, with antitumour activity irrespective of PD-L1 status, and was selected as the dose for phase 3 studies, which are ongoing.

[East Asian Subgroup Analysis of a Randomized, Double-Blind, Phase 3 Study of Docetaxel and Ramucirumab Versus Docetaxel and Placebo in the Treatment of Stage IV Non-Small-Cell Lung Cancer Following Disease Progression After One Prior Platinum-Based Therapy \(REVEL\).](#)

Park K1, Kim JH2, Cho EK3, et al. *Cancer Res Treat.* 2016 Feb 22. doi:10.4143/crt.2015.401. [Epub ahead of print]

PURPOSE: REVEL demonstrated improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) with docetaxel + ramucirumab vs. docetaxel + placebo in 1253 intent-to-treat (ITT) stage IV non-small-cell lung cancer (NSCLC) patients with disease progression following platinum-based chemotherapy. Results from the East Asian subgroup analysis are reported.

MATERIALS AND METHODS: Subgroup analyses were performed in the East Asian ITT population (n=89). Kaplan-Meier analysis and Cox proportional hazards regression were performed for OS and PFS, and the Cochran-Mantel-Haenszel test was performed for response rate. **RESULTS:** In docetaxel + ramucirumab (n=43) vs. docetaxel + placebo (n=46), median OS was 15.44 months vs. 10.17 months (hazard ratio [HR]: 0.762, 95% confidence interval [CI]: 0.444-1.307), median PFS was 4.88 months vs. 2.79 months (HR: 0.658, 95% CI: 0.408-1.060), and ORR was 25.6% (95% CI: 13.5-41.2) vs. 8.7% (95% CI: 2.4-20.8). Due to increased incidence of neutropenia and febrile neutropenia in East Asian patients, starting dose of docetaxel was reduced for newly enrolled East Asian patients (75 to 60 mg/m², n=24). In docetaxel + ramucirumab vs. docetaxel + placebo, incidence of neutropenia was 84.4% vs. 72.7% (75 mg/m²) and 54.5% vs. 38.5% (60 mg/m²). Incidence of febrile neutropenia was 43.8% vs. 12.1% (75 mg/m²) and 0 vs. 7.7% (60 mg/m²). **CONCLUSIONS:** Results of this subgroup analysis showed a trend favoring ramucirumab + docetaxel for median OS, PFS, and improved ORR in East Asian patients, consistent with ITT population results. Reduction of starting dose of docetaxel in East Asian patients was associated with improved safety.

[Efficacy and safety of afatinib in Chinese patients with EGFR-mutated metastatic non-small-cell lung cancer \(NSCLC\) previously responsive to first-generation tyrosine-kinase inhibitors \(TKI\) and chemotherapy: comparison with historical cohort using erlotinib.](#)

Lee VH1, Leung DK2, Choy TS3, Lam KO4, Lam PM5, Leung TW6, Kwong DL7. *BMC Cancer.* 2016 Feb 24;16(1):147. doi: 10.1186/s12885-016-2201-9.

BACKGROUND: Afatinib has shown anti-tumor activity against metastatic EGFR-mutated NSCLC after prior failure to first generation EGFR-TKI and chemotherapy. We prospectively evaluated the efficacy and safety of afatinib in Chinese patients who previously failed first-generation TKI and chemotherapy under a compassionate use program (CUP) and compared to the erlotinib cohort.

METHODS: Patients who suffered from metastatic EGFR-mutated NSCLC previously responsive to first-generation TKI and chemotherapy received afatinib until progression, loss of clinical benefits or intolerable toxicity. Treatment response, survival and safety were evaluated and compared to the erlotinib

cohort. **RESULTS:** Twenty-five and 28 patients received afatinib and erlotinib respectively. More patients in the afatinib group had worse performance status (ECOG 2) than the erlotinib group ($p = 0.008$). After a median follow-up of 12.1 months, afatinib demonstrated comparable objective response rate (ORR) (20.0 % vs. 7.1 %, $p = 0.17$) but significantly higher disease control rate (DCR) (68.0 % vs. 39.3 %, $p = 0.04$) compared to erlotinib. Median progression-free survival (PFS) (4.1 months [95 % CI, 2.7-5.5 months] vs. 3.3 months [95 % CI, 2.2-4.3 months], $p = 0.97$) and overall survival (OS) were not different between the two groups (10.3 months [95 % CI, 7.5-13.0 months] vs. 10.8 months [95 % CI, 7.4-14.2 months], $p = 0.51$). Multivariate analyses revealed that age ≤ 70 years and time to progression (TTP) ≥ 18 months for the 1(st) TKI therapy were prognostic of PFS ($p = 0.006$ and $p = 0.008$ respectively). Afatinib caused less rash (60.0 % vs. 67.9 %, $p = 0.04$) but more diarrhea (60.0 % vs. 10.7 %, $p = 0.002$) compared to erlotinib. **CONCLUSION:** Afatinib produced encouraging clinical efficacy as 2(nd) TKI therapy with manageable safety profiles in our Chinese patients after failure to another TKI and systemic chemotherapy.

NSCLC - RADIOTHERAPY

[Lung stereotactic ablative radiotherapy \(SABR\): dosimetric considerations for chest wall toxicity.](#)

Murray L1, Karakaya E1, Hinsley S2, et al. Br J Radiol. 2016 Feb;89(1058):20150628. doi: 10.1259/bjr.20150628.

OBJECTIVE: To investigate chest wall pain in patients with peripheral early stage lung cancer treated with stereotactic ablative radiotherapy (SABR), and to identify factors predictive of Common Terminology Criteria of Adverse Events Grade 2 + chest wall pain. **METHODS:** Patients who received 55 Gy in five fractions were included. A chest wall structure was retrospectively defined on planning scans, and chest wall dosimetry and tumour-related factors recorded. Logistic regression was performed to identify factors predictive of \geq Grade 2 chest wall pain. **RESULTS:** 182 patients and 187 tumours were included. There were 20 (10.9%) episodes of \geq Grade 2 chest wall pain. Multivariate logistic regression demonstrated that the maximum dose received by 1 cm³ of chest wall (Dmax1 cm³) and tumour size were significant predictors of \geq Grade 2 chest wall pain [Dmax1 cm³ odds ratio : 1.104, 95% confidence interval : 1.012-1.204, $p = 0.025$; tumour size (mm) odds ratio : 1.080, 95% confidence interval : 1.026-1.136, $p = 0.003$]. This model was an adequate fit to the data (Hosmer and Lemeshow test non-significant) and a fair discriminator for chest wall pain (area under receiver-operating characteristic curve: 0.74). Using the multivariate logistic regression model, parameters for Dmax1 cm³ are provided, which predict <10% and <20% risks of \geq Grade 2 chest wall pain for different tumour sizes. **CONCLUSION:** Grade 2+ chest wall pain is an uncommon side effect of lung SABR. Larger tumour size and increasing Dmax1 cm³ are significant predictors of \geq Grade 2 chest wall pain. When planning lung SABR, it is prudent to try to avoid hot volumes in the chest wall, particularly for larger tumours. **ADVANCES IN KNOWLEDGE:** This article demonstrates that Grade 2 or greater chest wall pain following lung SABR is more common when the tumour is larger in size and the Dmax1 cm³ of the chest wall is higher. When planning lung SABR, the risk of chest wall pain may be reduced if maximum doses are minimized, particularly for larger tumours.

[Stereotactic body radiotherapy \(SBRT\) for high-risk central pulmonary metastases.](#)

Lischalk JW1, Malik RM2, Collins SP3, Collins BT4, Matus IA5, Anderson ED6. Radiat Oncol. 2016 Feb 27;11(1):28.

BACKGROUND AND PURPOSE: Radiotherapy of central lung tumors carries a higher risk of treatment-related toxicity and local failure. In the era of aggressive oligometastatic management the exploration of the proper dose-fractionation for metastatic central lung tumors is essential. **MATERIALS AND METHODS:** Patients diagnosed with high-risk metastatic lesions of the central pulmonary tree comprised this single-institutional retrospective analysis. "High-risk" central pulmonary lesions were

defined as those with abutment and/or invasion of the mainstem bronchus. All patients were treated using the CyberKnife SBRT system in 5 fractions to a total dose of 35 or 40 Gy. **RESULTS:** Twenty patients were treated from 2008 to 2011 at Georgetown University Hospital. At a median follow up of 19 months, 1-year Kaplan-Meier local control and overall survival was 70 and 75 %, respectively. Late grade 2 or higher atelectasis was the most common treatment-related toxicity and was significantly associated with maximum dose to the mainstem bronchus. Gross endobronchial involvement was associated with significantly lower overall survival. **CONCLUSIONS:** Five-fraction SBRT to a total dose of 35 or 40 Gy appears to be a safe and effective management strategy for high-risk central pulmonary metastatic lesions, though care should be taken to limit the maximum point dose to the mainstem bronchus.

Prognostic Value of Semiautomatic CT Volumetry in Patients With Stage I Non-Small Cell Lung Cancer Treated With Stereotactic Body Radiation Therapy. Satoh Y1, Motosugi U, Nambu A, Saito A, Onishi H. J Comput Assist Tomogr. 2016 Feb 6. [Epub ahead of print]

OBJECTIVE: The aim of this study was to examine the prognostic value of semiautomated 3-dimensional image analysis-based parameters from pretreatment computed tomography (CT) in patients with non-small cell lung cancer treated with stereotactic body radiation therapy. **METHODS:** We evaluated 91 patients. We defined 2 parameters: (1) VOL, extracted tumor volume with a threshold ≥ -400 HU; and (2) ATN, the mean CT attenuation value. The maximum standardized uptake value (SUVmax) was recorded as F-fluorodeoxyglucose positron emission tomography/CT parameter. The prognostic values were assessed using the Kaplan-Meier and a Cox proportional hazards analysis. **RESULTS:** Overall survival and progression-free survival were significantly worse in patients with larger VOL, higher ATN, and higher SUVmax. VOL was an independent indicator of overall survival, whereas ATN was an indicator of progression-free survival, lymph node recurrence, and distant metastasis. However, SUVmax was not an independent prognostic factor for either outcome. **CONCLUSIONS:** VOL and ATN from 3-dimensional image analysis of CT scans have prognostic values for non-small cell lung cancer patients treated with stereotactic body radiation therapy.

Stereotactic Body Radiation Therapy (SBRT) for Recurrent Non-small Cell Lung Cancer (NSCLC). Janssen S1, Käsmann L2, Rudat V3, Rades D4. Anticancer Res. 2016 Feb;36(2):825-8.

AIM: For local recurrence of non-small cell lung cancer (NSCLC), stereotactic body radiation therapy (SBRT) has become increasingly popular. Many patients with recurrent NSCLC are unable to receive high-dose SBRT [biologically effective dose (BED) >100 Gy] due to poor performance status and potential normal tissue damage. **PATIENTS AND METHODS:** Thirty-one patients receiving lower-dose SBRT with a BED of 57.6 to 96.0 Gy, were analyzed for local control, freedom from distant progression and survival. **RESULTS:** In the entire series, local control rates were 96% at 1, 2 and 3 years. Freedom from distant progression rates were 74%, 65% and 65%, respectively, and survival rates were 87%, 65% and 65%, respectively. On multivariate analysis, freedom from distant progression was significantly associated with absence of distant metastases ($p=0.009$), and survival with BED >75 Gy ($p=0.039$). **CONCLUSION:** SBRT with BED <100 Gy provided very promising outcomes when administered for recurrent NSCLC. A BED >75 Gy is recommended, which was superior to lower doses.

Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab. Walraven I1, van den Heuvel M2, van Diessen J1, et al. Radiother Oncol. 2016 Feb 15. pii: S0167-8140(16)00069-4. doi: 10.1016/j.radonc.2016.02.011. [Epub ahead of print]

BACKGROUND AND PURPOSE: Radiation dose escalation using hypofractionation might improve overall survival (OS). We investigated OS in a phase II multicenter study in locally advanced non-small cell lung cancer (LA-NSCLC) patients treated with hypofractionated concurrent chemoradiotherapy.

MATERIALS AND METHODS: A 2-armed phase II, multi-center study (NTR2230) was performed with the aim to assess the effect of cetuximab to concurrent chemoradiotherapy in LA-NSCLC patients (stage II/IIIA/B). Arm A received high dose radiotherapy (24×2.75Gy) and concurrent daily low-dose cisplatin (6mg/m²). Arm B received an identical treatment regimen with additional weekly cetuximab. Kaplan-Meier survival curves and 1-, 2- and 5-year OS proportions were calculated. **RESULTS:** Between February 2009 and May 2011, 102 patients were randomly allocated in two arms. Median OS was 31.5months (range 12.8-52.3), not significantly different between arms A and B; 33.0 (range 17.0-57.0) and 30.0 (11.0-52.0) months. 1-, 2- and 5-year OS rates were 74.5%, 59.4% and 37.3%, respectively. In multivariate analyses, worse performance score, V35 of the esophagus and the existence of comorbidities were significantly (P-value<0.05) associated with a shorter OS. **DISCUSSION:** In this phase II trial, the median OS for the entire group was remarkably high; 31.5months. Furthermore, 5-year OS was still 37.3%. Hypofractionation might contribute to improved OS in LA-NSCLC patients.

SMALL CELL LUNG CANCER - SCLC

[Genetic and Functional Analysis of Polymorphisms in the Human Dopamine Receptor and Transporter Genes in Small Cell Lung Cancer.](#)

Cherubini E1, Di Napoli A1, Noto A2,3, et al. J Cell Physiol. 2016 Feb;231(2):345-56. doi: 10.1002/jcp.25079.

The regulatory role of dopamine (DA) in endocrine, cardiovascular and renal functions has been extensively studied and used for clinical purposes. More recently DA has been indicated as a regulatory molecule for immune cells and malignant cell proliferation. We assessed the expression and the functional role DA, DA receptors, and transporters in primary small cell lung cancer (SCLC). By HPLC DA plasma levels were more elevated in SCLC patients in comparison with NSCLC patients and healthy controls. SCLC cell expressed DA D1- and D2-like receptors and membrane and vesicular transporters at protein and mRNA levels. We also investigated the effects of independent D1- or D2-like receptor stimulation on SCLC cell cultures. DA D1 receptor agonist SKF38393 induced the increase of cAMP levels and DARPP-32 protein expression without affecting SCLC growth rate. Cell treatment with the DA D1 receptor antagonist SCH23390 inhibited SKF38393 effects. In contrast, the DA D2 receptor agonist quinpirole (10 µM) counteracted, in a dose and time dependent way, SCLC cell proliferation, it did not affect cAMP levels and decreased phosphorylated AKT that was induced by DA D2 receptor antagonist sulpiride. However, in only one SCLC line, stimulation of DA D2 receptor failed to inhibit cell proliferation in vitro. This effect was associated to the existence of rs6275 and rs6277 polymorphisms in the D2 gene. These results gave more insight into DA control of lung cancer cell behavior and suggested the existence of different SCLC phenotypes.

[Effective growth-suppressive activity of maternal embryonic leucine-zipper kinase \(MELK\) inhibitor against small cell lung cancer.](#)

Inoue H1, Kato T1, Olugbile S1, et al. Oncotarget. 2016 Feb 10. doi: 10.18632/oncotarget.7297. [Epub ahead of print]

Maternal embryonic leucine zipper kinase (MELK), that plays a critical role in maintenance of cancer stem cells (CSCs), is predominantly expressed in various types of human cancer including small cell lung cancer (SCLC). SCLC usually acquires resistance to anti-cancer drugs and portends dismal prognosis. We have delineated roles of MELK in development/progression of SCLC and examined anti-tumor efficacy of OTS167, a highly potent MELK inhibitor, against SCLC. MELK expression was highly upregulated in both SCLC cell lines and primary tumors. siRNA-mediated MELK knockdown induced significant growth inhibition in SCLC cell lines. Concordantly, treatment with OTS167 exhibited strong cytotoxicity against eleven SCLC cell lines with IC₅₀ of < 10 nM. As similar to siRNA knockdown, OTS167 treatment induced cytokinetic defects with intercellular bridges, and in some cell lines we observed formation of neuronal protrusions accompanied with increase of a neuronal differentiation marker

(CD56), indicating that the compound induced differentiation of cancer cells to neuron-like cells. Furthermore, the MELK inhibition decreased its downstream FOXM1 activity and Akt expression in SCLC cells, and led to apoptotic cell death. OTS167 appeared to be more effective to CSCs as measured by the sphere formation assay, thus MELK inhibition might become a promising treatment modality for SCLC.

[The Highest Metabolic Activity on FDG PET Is Associated With Overall Survival in Limited-Stage Small-Cell Lung Cancer.](#) Kwon SH1, Hyun SH, Yoon JK, An YS, Oh YT, Choi JH, Park KJ, Lee SJ. *Medicine (Baltimore)*. 2016 Feb;95(5):e2772. doi: 10.1097/MD.0000000000002772.

We evaluated the prognostic value of F-fluorodeoxyglucose positron emission tomography (FDG PET) parameters for limited-stage small-cell lung cancer (LS-SCLC). We retrospectively enrolled 59 LS-SCLC patients who underwent pretreatment FDG PET/CT. Various PET parameters were measured in all malignant lesions, and we recorded the highest maximum standardized uptake value (SUVmax), and sum of metabolic tumor volume (MTVsum) and total lesion glycolysis (TLGsum). The relationship between the highest SUVmax and volumetric PET parameters was evaluated. The prognostic significances of PET parameters and clinical variables were assessed using Cox's proportional hazard regression analysis. Overall survival (OS) and progression-free survival (PFS) were assessed by the Kaplan-Meier method. The SUVmax of the highest metabolic lesion had a significant positive correlation with MTVsum and TLGsum ($P < 0.001$). Upon multivariate analysis, the highest SUVmax was an independent predictor of OS (1 unit increase, hazard ratio [HR]: 1.133, $P = 0.003$) and MTVsum was a significant prognostic factor of PFS (10-cm increase, HR: 1.027, $P = 0.034$) after adjusting for age, sex, performance status, tumor stage, and treatment modality. The highest SUVmax was a prognostic factor for PFS with marginal significance (1 unit increase, HR: 1.078, $P = 0.053$). Patients with higher SUVmax (≥ 11) were also characterized by a significantly shorter median OS ($P < 0.001$) and PFS ($P = 0.002$) compared with patients with lower SUVmax. The highest SUVmax is an independent prognostic factor for survival in LS-SCLC patients. Therefore, the highest SUVmax might be a possible imaging biomarker for risk stratification in LS-SCLC. A further study in a large cohort is needed to validate the prognostic significance of the parameter.

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Karnosky Performance Score and Radiation Dose Predict Survival of Patients Re-irradiated for a Locoregional Recurrence of Small Cell Lung Cancer. Käsmann L1, Janssen S2, Schild SE3, Rades D4. *Anticancer Res.* 2016 Feb;36(2):803-5.

AIM: When patients with small cell lung cancer (SCLC) experience locoregional recurrence, surgery is often not employed as salvage therapy. Systemic chemotherapy and radiotherapy are often used. Many radiation oncologists are reluctant to deliver a second course of radiotherapy. However, select patients may benefit from re-irradiation. This study aimed to identify these patients. **PATIENTS AND ETHODS:** In patients receiving re-irradiation for a locoregional recurrence of SCLC, 11 potential prognostic factors were analyzed for survival. **RESULTS:** Survival was positively associated with a Karnofsky performance score ≥ 80 ($p=0.003$) and a cumulative dose >90 Gy ($p=0.026$). A trend was observed for younger age, longer interval between first course of radiotherapy and re-irradiation, a greater dose of re-irradiation and for concurrent chemotherapy. **CONCLUSION:** Significant predictors of survival in patients re-irradiated for a locoregional recurrence of SCLC were identified. Patients with a good performance status can benefit from re-irradiation if administered in sufficient doses.

PALLIATIVE AND SUPPORTIVE CARE

Implementation of a Lung Cancer Nurse Navigator Enhances Patient Care and Delivery of Systemic Therapy at the British Columbia Cancer Agency, Vancouver. Zibrik K1, Laskin J1, Ho C2. *J Oncol Pract.* 2016 Feb 16. pii: JOPR008813. [Epub ahead of print]

PURPOSE: A nurse navigator (NN) pilot project for patients with lung cancer was implemented in British Columbia, a publicly funded health-care system. The purpose was to improve referral practices, timelines, and availability of molecular testing for patients with advanced non-small-cell lung cancer (NSCLC). **METHODS:** Patients with stage IIIB/IV NSCLC referred to the BC Cancer Agency, Vancouver, in 2011 and 2014, pre- and post-implementation of an NN, were included. Referral patterns, systemic therapy, radiotherapy (XRT) timelines, and molecular testing practices were compared. **RESULTS:** The study included 408 patients: 212 in 2011 and 196 in 2014. Medical oncology (MO) end points comparing 2011 data with 2014 findings revealed that referral rates remained stable, and the proportion of patients who received systemic therapy increased from 57% to 69% ($P = .05$). Time from referral to MO consult was 18 days in 2011 versus 15.5 days in 2014 ($P = .11$); referral to systemic treatment was reduced from 48 to 38 days ($P = .016$). Comparison of molecular testing showed time between referral and the epidermal growth factor (EGFR) result was reduced from 34 days in 2011 to 20 days in 2014 ($P < .001$); rates of testing increased from 62% to 91%, respectively ($P < .001$); and EGFR mutation-positive rates were 19% versus 26%, respectively ($P = .26$). The radiation oncology (RO) end point results were as follows: 87% of patients were referred for RO consults in 2011 versus 80% in 2014 ($P = .05$), and the same proportion of patients received XRT (91% v 87%, respectively). Time from referral to RO consult decreased from 10 days in 2011 to 8 days in 2014 ($P = .005$); and referral to XRT in 2011 and 2014 was 18 days versus 11.5 days, respectively ($P < .001$). **CONCLUSION:** Implementation of an NN was associated with reduced wait times and increased molecular testing, improving appropriate delivery of first-line targeted therapy. NN involvement facilitates correct allocation of physician and clinical resources.

[The unmet supportive care needs-what advanced lung cancer patients' caregivers need and related factors.](#) Chen SC1,2, Chiou SC3, Yu CJ4, et al. Support Care Cancer. 2016 Feb 13. [Epub ahead of print] **PURPOSE:** To identify the unmet supportive care needs and related factors in caregivers of patients with advanced lung cancer. **METHODS:** A cross-sectional study of 166 lung cancer patient-caregivers dyads was recruited at a medical center. The supportive care needs, fatigue, and sleep disturbance of caregivers were collected. Patients were assessed for symptom severity, anxiety, and depression. Logistic regression was used to reveal the related factors of unmet supportive care needs. **RESULTS:** Of the 166 dyads surveyed, the top unmet needs were information needs, health care professional/health care service needs, and daily living needs. Patients' anxiety was positively correlated to overall caregiving needs, health care professional/health care service needs, interpersonal communication needs, and psychological/emotional needs of caregivers. The information needs and health care professional/health care service needs were related to the caregivers' fatigue. The sleep disturbance of caregivers was associated with their overall caregiving needs, daily living needs, and psychological/emotional needs. **CONCLUSIONS:** Future interventions to meet the needs of caregivers should include specific needs assessment and continuing education in caregiving.

[125I brachytherapy in the palliation of painful bone metastases from lung cancer after failure or rejection of conventional treatments.](#) Xiang Z1, Mo Z1, Li G1, Gilani S2, Zhong Z1, Zhang T1, Zhang F1, Gao F1. Oncotarget. 2016 Feb 23. doi: 10.18632/oncotarget.7584. [Epub ahead of print] **PURPOSE:** This study sought to assess the safety and effect of 125I seed implantation for palliation of painful bone metastases from lung cancer after failure or rejection of conventional treatments. **MATERIALS AND METHODS:** 89 patients with painful bone metastases secondary to lung cancer were consented and enrolled in this study from June 2013 to May 2015. All patients had failed or refused conventional treatments underwent percutaneous CT-guided 125I seed implantation. The Brief Pain Inventory (BPI) was used to measure pain intensity prior to treatment (T0), 2, 4, 6, 8 and 12 weeks (T2, T4, T6, T8 and T12) after treatment in a 24-hour period. Analgesic, quality of life (QOL) scores and complications were also recorded. Four patients were excluded as they were lost to follow-up or had incomplete data. **RESULTS:** 85 patients with 126 bone metastases from lung cancer were treated. There were significantly lower scores after treatment in the visual analog scale (VAS) and analgesic. The VAS scores for worst pain was 6.3 ± 1.8 at T0. At T2, T4, T6, T8 and T12, the score in a 24-hour period decreased to 4.9 ± 1.2 ($P < 0.01$), 3.7 ± 1.3 ($P < 0.01$), 3.4 ± 1.2 ($P < 0.01$), 2.6 ± 0.9 ($P < 0.01$), and 1.4 ± 0.8 ($P < 0.01$) respectively. Comparison of QOL scores showed improvements including sleep, appetite, spiritual state, and fatigue at T2, T4, T6, T8 and T12 when compared to T0. No serious complications or massive bleeding were observed. **CONCLUSIONS:** 125I brachytherapy is a safe and effective method for palliation of painful bone metastases from lung cancer after failure or rejection of conventional treatments.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Inhibitory effect of traditional oriental medicine-derived monoamine oxidase B inhibitor on radioresistance of non-small cell lung cancer.](#) Son B1, Jun SY2, Seo H1, et al. Sci Rep. 2016 Feb 24;6:21986. doi: 10.1038/srep21986.

Increased survival of cancer cells mediated by high levels of ionizing radiation (IR) reduces the effectiveness of radiation therapy for non-small cell lung cancer (NSCLC). In the present study, danshensu which is a selected component of traditional oriental medicine (TOM) compound was found to reduce the radioresistance of NSCLC by inhibiting the nuclear factor- κ B (NF- κ B) pathway. Of the various TOM compounds reported to inhibit the IR activation of NF- κ B, danshensu was chosen as a final candidate based on the results of structural comparisons with human metabolites and monoamine oxidase

B (MAOB) was identified as the putative target enzyme. Danshensu decreased the activation of NF- κ B by inhibiting MAOB activity in A549 and NCI-H1299 NSCLC cells. Moreover, it suppressed IR-induced epithelial-to-mesenchymal transition, expressions of NF- κ B-regulated prosurvival and proinflammatory genes, and in vivo radioresistance of mouse xenograft models. Taken together, this study shows that danshensu significantly reduces MAOB activity and attenuates NF- κ B signaling to elicit the radiosensitization of NSCLC.

MISCELLANEOUS WORKS

[Cancer Incidence in Appalachia, 2004-2011.](#) Wilson RJ1, Ryerson AB2, Singh SD2, King JB2. *Cancer Epidemiol Biomarkers Prev.* 2016 Feb;25(2):250-8. doi: 10.1158/1055-9965.EPI-15-0946. Epub 2016 Jan 27.

BACKGROUND: Limited literature is available about cancer in the Appalachian Region. This is the only known analysis of all cancers for Appalachia and non-Appalachia covering 100% of the US population. Appalachian cancer incidence and trends were evaluated by state, sex, and race and compared with those found in non-Appalachian regions. **METHODS:** US counties were identified as Appalachian or non-Appalachian. Age-adjusted cancer incidence rates, standard errors, and confidence intervals were calculated using the most recent data from the United States Cancer Statistics for 2004 to 2011.

RESULTS: Generally, Appalachia carries a higher cancer burden compared with non-Appalachia, particularly for tobacco-related cancers. For all cancer sites combined, Appalachia has higher rates regardless of sex, race, or region. The Appalachia and non-Appalachia cancer incidence gap has narrowed, with the exception of oral cavity and pharynx, larynx, lung and bronchus, and thyroid cancers. **CONCLUSIONS:** Higher cancer incidence continues in Appalachia and appears at least in part to reflect high tobacco use and potential differences in socioeconomic status, other risk factors, patient health care utilization, or provider practices. It is important to continue to evaluate this population to monitor results from screening and early detection programs, understand behavioral risk factors related to cancer incidence, increase efforts to reduce tobacco use and increase cancer screening, and identify other areas where effective interventions may mediate disparities. **IMPACT:** Surveillance and evaluation of special populations provide means to monitor screening and early detection programs, understand behavioral risk factors, and increase efforts to reduce tobacco use to mediate disparities.

[Differences in Active and Passive Smoking Exposures and Lung Cancer Incidence Between Veterans and Non-Veterans in the Women's Health Initiative.](#) Bastian LA1, Gray KE2, DeRycke E3, et al. *Gerontologist.* 2016 Feb;56 Suppl 1:S102-11. doi: 10.1093/geront/gnv664.

INTRODUCTION: Women Veterans may have higher rates of both active and passive tobacco exposure than their civilian counterparts, thereby increasing their risk for lung cancer. **PURPOSE OF THE STUDY:** To compare differences in active and passive smoking exposure and lung cancer incidence among women Veterans and non-Veterans using prospective data from the Women's Health Initiative (WHI). **DESIGN AND METHODS:** We used data from the WHI, which collected longitudinal demographic, clinical, and laboratory data on 161,808 postmenopausal women. We employed linear and multinomial regression and generalized linear models to compare active and passive smoking exposure between Veterans and non-Veterans and Cox proportional hazards models to estimate differences in lung cancer incidence rates. **RESULTS:** After adjustment, Veterans had 2.54 additional pack years of smoking compared with non-Veterans (95% confidence interval [CI] 1.68, 3.40). Veterans also had a 1% increase in risk of any passive smoking exposure (95% CI 1.00, 1.02) and a 9% increase in risk of any workplace exposure (95% CI 1.07, 1.11) compared with non-Veterans. After adjustment for age and smoking exposures, Veterans did not have a higher risk of lung cancer compared with non-Veterans (relative risk = 1.06 95% CI 0.86, 1.30). **IMPLICATIONS:** Women Veterans had higher rates of tobacco use and

exposure to passive smoking, which were associated with a higher risk for lung cancer compared with non-Veterans. Clinicians who care for Veterans need to be aware that older women Veterans have more exposures to risk factors for lung cancer.

[Pairing smoking-cessation services with lung cancer screening: A clinical guideline from the Association for the Treatment of Tobacco Use and Dependence and the Society for Research on Nicotine and Tobacco.](#) Fucito LM1,2,3, Czabafy S4, Hendricks PS5, et al. *Cancer*. 2016 Feb 24. doi: 10.1002/cncr.29926. [Epub ahead of print]

Smoking cessation is crucial for reducing cancer risk and premature mortality. The US Preventive Services Task Force (USPSTF) has recommended annual lung cancer screening with low-dose computed tomography (LDCT), and the Center for Medicare and Medicaid Services recently approved lung screening as a benefit for patients ages 55 to 77 years who have a 30 pack-year history. The Society for Research on Nicotine and Tobacco (SRNT) and the Association for the Treatment of Tobacco Use and Dependence (ATTUD) developed the guideline described in this commentary based on an illustrative literature review to present the evidence for smoking-cessation health benefits in this high-risk group and to provide clinical recommendations for integrating evidence-based smoking-cessation treatment with lung cancer screening. Unfortunately, extant data on lung cancer screening participants were scarce at the time this guideline was written. However, in this review, the authors summarize the sufficient evidence on the benefits of smoking cessation and the efficacy of smoking-cessation interventions for smokers ages 55 to 77 years to provide smoking-cessation interventions for smokers who seek lung cancer screening. It is concluded that smokers who present for lung cancer screening should be encouraged to quit smoking at each visit. Access to evidence-based smoking-cessation interventions should be provided to all smokers regardless of scan results, and motivation to quit should not be a necessary precondition for treatment. Follow-up contacts to support smoking-cessation efforts should be arranged for smokers. Evidence-based behavioral strategies should be used at each visit to motivate smokers who are unwilling to try quitting/reducing smoking or to try evidence-based treatments that may lead to eventual cessation.

[Smokers are less likely than non-smokers to seek help for a lung cancer 'alarm' symptom.](#)

Friedemann Smith C1, Whitaker KL2, Winstanley K1, Wardle J1. *Thorax*. 2016 Feb 24. pii: thoraxjnl-2015-208063. doi: 10.1136/thoraxjnl-2015-208063. [Epub ahead of print]

BACKGROUND: The majority (>85%) of lung cancer cases are linked with smoking, and prognosis is poor because it is often diagnosed at a late stage. One contributor to late-stage diagnosis could be patient delay in help-seeking. We investigated the help-seeking behaviour of smokers and non-smokers for a recent lung cancer alarm symptom. **METHODS:** A health survey was sent to 4913 men and women aged >50 years through through General Practice. It included questions on symptoms experienced in the past 3 months (from a checklist), help-seeking (Yes/No) for each symptom and demographic characteristics including smoking status. Univariable and multivariable binary logistic regression analyses were used to assess the association between smoking status and help-seeking for a cough or hoarseness. **RESULTS:** Among 2042 participants (42% response rate), 280 (14%) reported 'cough or hoarseness' in the past 3 months; of whom 22% were current smokers. Being a smoker was associated with reduced likelihood of help-seeking (OR 0.44; 95% CI 0.23 to 0.83), even after adjusting for demographic factors (OR 0.46; 95% CI 0.21 to 1.00). **CONCLUSIONS:** Delay in help-seeking in smokers for a symptom that is potentially indicative of lung cancer is a cause for concern. Future research could usefully address the psychological mechanisms through which help-seeking in smokers is hindered.

Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities.

DeSantis CE1, Siegel RL2, Sauer AG3, Miller KD3, Fedewa SA4, Alcaraz KI5, Jemal A6. CA Cancer J Clin. 2016 Feb 22. doi: 10.3322/caac.21340. [Epub ahead of print]

In this article, the American Cancer Society provides the estimated number of new cancer cases and deaths for blacks in the United States and the most recent data on cancer incidence, mortality, survival, screening, and risk factors for cancer. Incidence data are from the National Cancer Institute, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries, and mortality data are from the National Center for Health Statistics. Approximately 189,910 new cases of cancer and 69,410 cancer deaths will occur among blacks in 2016. Although blacks continue to have higher cancer death rates than whites, the disparity has narrowed for all cancers combined in men and women and for lung and prostate cancers in men. In contrast, the racial gap in death rates has widened for breast cancer in women and remained level for colorectal cancer in men. The reduction in overall cancer death rates since the early 1990s translates to the avoidance of more than 300,000 deaths among blacks. In men, incidence rates from 2003 to 2012 decreased for all cancers combined (by 2.0% per year) as well as for the top 3 cancer sites (prostate, lung, and colorectal). In women, overall rates during the corresponding time period remained unchanged, reflecting increasing trends in breast cancer combined with decreasing trends in lung and colorectal cancer rates. Five-year relative survival is lower for blacks than whites for most cancers at each stage of diagnosis. The extent to which these disparities reflect unequal access to health care versus other factors remains an active area of research. Progress in reducing cancer death rates could be accelerated by ensuring equitable access to prevention, early detection, and high-quality treatment.