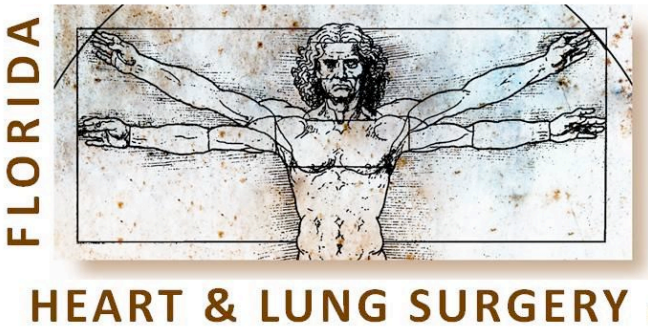
Review of Thoracic Surgical Oncology



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NSCLC metastasis

Metastasis following lung resection for NSCLC follows a predictable and orderly temporal pattern

*J Thorac Oncol. 2012 Apr;7(4):723-30. Recurrence dynamics for non-small-cell lung cancer: effect of surgery on the development of metastases. Demicheli R, Fornili M, Ambrogi F, Higgins K, Boyd JA, Biganzoli E, Kelsey CR. *Scientific Directorate,Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy †Medical Statistics and Biometry, Università di Milano, Milano, Italy ‡Radiation Oncology, Duke Cancer Institute, Durham, North Carolina §Radiation Oncology, University of Texas Southwestern, Dallas, Texas ||Medical Statistics and Biometry, Università di Milano e Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy ¶Radiation Oncology, Duke Cancer Institute, Durham, North Carolina. Abstract INTRODUCTION: We study event rates over time (event dynamics) in patients undergoing surgery for early-stage non-small-cell lung cancer (NSCLC). METHODS: : Using a database of patients undergoing initial surgery for NSCLC, the event dynamics, based on the hazard rate, were evaluated. Events evaluated included time to any treatment failure, local recurrence, distant metastasis (DM), and development of a second primary lung cancer. RESULTS: : Among 1506 patients, time to any treatment failure dynamics demonstrated an initial surge in the hazard rate 9 months after surgery, followed by two smaller peaks at the end of the second and fourth years, respectively. This pattern was dominated by DM events. Two distinguishable peaks were noted for local recurrence in the first and second years. In contrast, the hazard rate for second primary lung cancer exhibited a more uniform pattern over time. The DM dynamics was analyzed by sex and three peaks emerged for both sexes. The timing of the first peak was similar for both sexes, at 7 to 9 months after surgery. The second peak occurred earlier in men (18-20 months) than women (24-26 months). For both sexes the third peak appeared during the fourth year. CONCLUSIONS: : Recurrence dynamics of resected early-stage NSCLC displays a multipeak pattern, which supports the hypothesis of a metastasis growth model previously described for early-stage breast cancer. The model assumes both cellular and micrometastatic tumor dormancy and a transient phase of acceleration of metastatic growth following surgical excision of the primary tumor.*

Editor's commentary: This is a fascinating description of the temporal pattern of recurrence following lung resection for NSCLC. Clinicians have suspected for years that surgery for NSCLC may impact progression of latent metastatic disease, and in rare cases, actually induce rapid progression. This paper is the first that I am aware of that proves that recurrence following surgery follows a predictable temporal pattern: there is a dominant peak at 9 months, followed by two additional smaller peaks at 2 and 4 years. The authors note a similarity to breast cancer recurrence and also hypothesize a rationale for this dynamic. This data provides an excellent opportunity to understand the biology of recurrence better, and gives hope that adjuvant therapy may be tailored to the mechanisms that underlie this dynamic.

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Mesothelioma

Single institution comparison favors pleurectomy/ decortication over extrapleural pneumonectomy

*J Thorac Oncol. 2012 Apr;7(4):737-43. Pleurectomy/Decortication is Superior to Extrapleural Pneumonectomy in the Multimodality Management of Patients with Malignant Pleural Mesothelioma. Lang-Lazdunski L, Bille A, Lal R, Cane P, McLean E, Landau D, Steele J, Spicer J. *Department of Thoracic Surgery, London and Division of Cancer Studies, King's College London, London, United Kingdom †Department of Oncology and Haematology, London and Division of Cancer Studies, King's College London, London, United Kingdom ‡Department of Pathology,Guy's & St Thomas' Hospital NHS Foundation Trust, London and Division of Cancer Studies, King's College London, London, United Kingdom §Department of Medical Oncology, Barts and the London NHS Trust, London, United Kingdom. Abstract INTRODUCTION: : To compare the outcomes of two different multimodality regimens involving neoadjuvant chemotherapy, extrapleural pneumonectomy (EPP) and adjuvant radiotherapy versus pleurectomy/decortication (P/D), hyperthermic pleural lavage with povidone-iodine, and adjuvant chemotherapy in patients with malignant pleural mesothelioma. METHODS: : Nonrandomized prospective study of patients treated by multimodality therapy and operated on between January 2004 and June 2011. Second-line treatments were administered when appropriate. Survival and prognostic factors were analyzed by the Kaplan Meier method, log rank test, and Cox regression analysis. RESULTS: : Twenty-five consecutive patients received neoadjuvant chemotherapy, 22 underwent EPP, and 17 received adjuvant radiotherapy. Over the same period, 54 consecutive patients underwent P/D and hyperthermic pleural lavage and received prophylactic radiotherapy and adjuvant chemotherapy. The 30-day mortality rate was 4.5%in the EPP group and nil in the P/D group. Fifteen patients (68%) in the EPP group and 15 (27.7%) in the P/D group experienced complications. There were no differences between the EPP and P/D groups for age, sex, histology, pathologic stage, and nodal status. Trimodality therapy was completed by 68%of the patients in the EPP group and 100%in the P/D group. Survival was significantly better in the P/D group: median survival was 23 months versus 12.8 months, 2-year survival was 49%versus 18.2 %, and 5-year survival was 30.1%versus 9%, respectively (p = 0.004). At multivariate analysis, epithelioid histology, P/D, and completeness of resection were independent prognostic factors. CONCLUSIONS:: In our experience, P/D, hyperthermic pleural lavage with povidone-iodine, and adjuvant chemotherapy were superior to neoadjuvant chemotherapy, EPP, and adjuvant radiotherapy.*

Editor's commentary: This article extends the results of the recently reported MARS trial which suggested that extrapleural pneumonectomy (EPP) be abandoned for mesothelioma because of unpredictable and unfavorable results. This report describes results from a single institution, all by the same surgeon, and demonstrates superior results with pleurectomy/ decortication (P/D). In my experience, EPP is a formidable surgical undertaking for both the patient and the surgeon. I will be re-considering P/D as primary therapy for these patients in the future based on these reports.

NSCLC

Recurrance of NSCLC after complete surgical resection can benefit by local therapy

Ann Thorac Surg. 2012 Apr;93(4):1061-8. Results of long-term follow-up of patients with completely resected non-small cell lung cancer. Endo C, Sakurada A, Notsuda H, Noda M, Hoshikawa Y, Okada Y, Kondo T. Department of Thoracic Surgery, Tohoku University Hospital, Sendai, Japan. Abstract BACKGROUND: In patients with completely resected non-small cell lung cancer, recurrence-free survival, postrecurrence survival, and metachronous primary lung cancer have not been well studied at the same time. METHODS: A total of 315 patients with non-small cell lung cancer who underwent complete resection between 2001 and 2005 were examined. Patients were routinely assessed with computed tomography of the chest and physical checkups every 4 months for the first 2 years and every 6 months from the third to the fifth year. After that, they were examined annually. RESULTS: The overall 5-year survival was 70%. Of all 315 patients, 107 had recurrent disease. The median recurrence-free survival was 15.7 months. Multivariate analysis showed that pathologic stage and pleural invasion were associated with decreased recurrence-free survival. The median postrecurrence survival was 18.7 months. Multivariate analysis indicated that male sex, pleural invasion, extrathoracic recurrence, and supportive care for recurrence were associated with decreased postrecurrence survival. The cumulative rate of metachronous primary lung cancer at 5 years was 3.7%, and it developed even 8 years after the initial operation. CONCLUSIONS: Only pleural invasion of the original lung cancer was related to both recurrence-free survival and postrecurrence survival. Moreover, postrecurrence survival was related to both site and treatment of the initial recurrence. The incidence of metachronous primary lung cancer was stable over time after the initial operation.

Editor's commentary: This paper describes detailed information of outcomes of patients who undergo full surgical resection. Interestingly, long term survival can be achieved in a subset of patients who recur locally and are treated with surgery or radiation. Pleural involvement is a negative risk factor in patients with recurrence (as it is in patients upon presentation). As already detailed in multiple reports, there is a steady and increased risk of metachronous NSCLC in survivors of NSCLC cured by surgery. Also of note, the stage of the initial tumor was not correlated to post-recurrence survival; in my mind, this implies that full surgical resection "resets" the survival clock so to speak, so that characteristics of the **recurrent tumor** (and not the primary) determine subsequent survival.

Serum biomarkers for NSCLC

Panel of serum biomarkers improve accuracy of CT scan screening for NSCLC

J Thorac Oncol. 2012 Apr;7(4):698-708. A Multiplexed Serum Biomarker Immunoassay Panel Discriminates Clinical Lung Cancer Patients from High-Risk Individuals Found to be Cancer-Free by CT Screening. Bigbee WL, Gopalakrishnan V, Weissfeld JL, Wilson DO, Dacic S, Lokshin AE, Siegfried JM.

**Mass Spectrometry Platform, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania †Lung and Thoracic Malignancies Program, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania ‡Cancer Epidemiology, Prevention, and Control Program, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania §Department of Pathology, Graduate School of Public Health, Pittsburgh, Pennsylvania ‖ Department of Computational Biology, Graduate School of Public Health, Pittsburgh, Pennsylvania ¶Department of Epidemiology, Graduate School of Public Health, Pittsburgh, Pennsylvania #Department of Pulmonary Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania **Luminex Platform, Cancer Biomarkers Facility, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania ††Department of Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania ‡‡Department of Biomedical Informatics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.* *Abstract INTRODUCTION: Clinical decision making in the setting of computed tomography (CT) screening could benefit from accessible biomarkers that help predict the level of lung cancer risk in high-risk individuals with indeterminate pulmonary nodules. METHODS: To identify candidate serum biomarkers, we measured 70 cancer-related proteins by Luminex xMAP (Luminex Corporation) multiplexed immunoassays in a training set of sera from 56 patients with biopsy-proven primary non-small-cell lung cancer and 56 age-, sex-, and smoking-matched CT-screened controls. RESULTS: We identified a panel of 10 serum biomarkers-prolactin, transthyretin, thrombospondin-1, E-selectin, C-C motif chemokine 5, macrophage migration inhibitory factor, plasminogen activator inhibitor, receptor tyrosine-protein kinase, erbb-2, cytokeratin fragment 21.1, and serum amyloid A-that distinguished lung cancer patients from controls with an estimated balanced accuracy (average of sensitivity and specificity) of 76.0 ± 3.8% from 20-fold internal cross-validation. We then iteratively evaluated this model in an independent test and verification case/control studies confirming the initial classification performance of the panel. The classification performance of the 10-biomarker panel was also analytically validated using enzyme-linked immunosorbent assays in a second independent case/control population, further validating the robustness of the panel. CONCLUSIONS: The performance of this 10-biomarker panel-based model was 77.1% sensitivity/76.2% specificity in cross-validation in the expanded training set, 73.3% sensitivity/93.3% specificity (balanced accuracy 83.3%) in the blinded verification set with the best discriminative performance in stage I/II cases: 85% sensitivity (balanced accuracy 89.2%). Importantly, the rate of misclassification of CT-screened controls was not different in most control subgroups with or without airflow obstruction or emphysema or pulmonary nodules. These biomarkers have potential to aid in the early detection of lung cancer and more accurate interpretation of indeterminate pulmonary nodules detected by CT screening.*

Editor's commentary: Adding a panel of serum biomarkers improved the accuracy of CT scan screening in this NIH sponsored study. Reducing false positives in large scale CT screening for NSCLC is an important goal to make screening safer and more cost effective.

NSCLC

Surgical resection of bilateral synchronous primary tumors can lead to long term survival

Ann Thorac Surg. 2012 Apr;93(4):1055-60. Epub 2012 Mar 3. Outcomes after surgical management of synchronous bilateral primary lung cancers. Shah AA, Barfield ME, Kelsey CR, Onaitis MW, Tong B, Harpole D, D'Amico TA, Berry MF. Division of Cardiovascular and Thoracic Surgery, Duke University Medical Center, Durham, North Carolina. Abstract BACKGROUND: Distinguishing between synchronous primary lung cancers and metastatic disease in patients with bilateral lung masses is often difficult. The objective of this study is to examine outcomes associated with a strategy of performing staged bilateral resections in patients without N2 disease based on invasive mediastinal staging and without distant metastases. METHODS: Patients undergoing resections of bilateral synchronous primary lung cancer at our institution between 1997 and 2010 were reviewed. Perioperative complications were graded according to National Cancer Institute guidelines. Survival was estimated using the Kaplan-Meier method and compared using a log-rank test. End points included overall survival, disease-free survival, operative death, cancer recurrence, and postoperative complications. RESULTS: Resections of bilateral synchronous primary lung cancers were performed in 47 patients. Forty-five patients (96%) had at least a unilateral thoracoscopic approach; 28 (60%) had bilateral thoracoscopic approaches. The median postresection length of stay was 3 days. Thirteen patients (28%) had a postoperative complication; only 3 (6%) were grade 3 or higher. There was 1 perioperative death (2%). Eleven patients received adjuvant therapy; only 3 patients in whom adjuvant therapy was indicated did not receive the recommended treatment. The overall 3-year survival was 35%. Survival of patients whose bilateral tumors had identical histology did not differ from patients whose histology was different (p = 0.57). Three-year disease-free survival was 24%. CONCLUSIONS: Aggressive surgical treatment of apparent synchronous bilateral primary lung cancer can be performed with low morbidity. Most patients tolerate the bilateral surgeries and adjuvant therapy. Overall survival is sufficiently high to support this aggressive approach.

Editor's commentary: We reported our experience with multiple NSCLC primaries from Moffitt two years ago (J Thorac Oncol. 2010 Jul;5(7):1018-24). Our results were better than described in this experience from Duke, but both reports point out that good long term survival is possible in patients with multiple NSCLC primaries treated with resection.

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