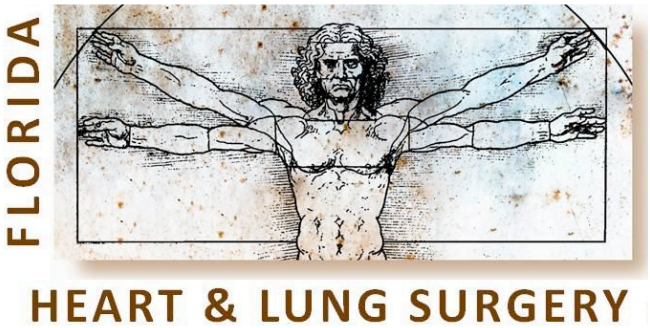
Review of Thoracic Surgical Oncology



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Mesothelioma

Randomized trial of extra-pleural pneumonectomy for mesothelioma raises questions of benefit or even harm

Lancet Oncol. 2011 Aug;12(8):763-72. Epub 2011 Jun 30. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study.Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, Snee M, O'Brien M, Thomas G, Senan S, O'Byrne K, Kilburn LS, Spicer J, Landau D, Edwards J, Coombes G, Darlison L, Peto J; MARS trialists.

BACKGROUND:The effects of extra-pleural pneumonectomy (EPP) on survival and quality of life in patients with malignant pleural mesothelioma have, to our knowledge, not been assessed in a randomised trial. We aimed to assess the clinical outcomes of patients who were randomly assigned to EPP or no EPP in the context of trimodal therapy in the Mesothelioma and Radical Surgery (MARS) feasibility study.

METHODS: MARS was a multicentre randomised controlled trial in 12 UK hospitals. Patients aged 18 years or older who had pathologically confirmed mesothelioma and were deemed fit enough to undergo trimodal therapy were included. In a prerandomisation registration phase, all patients underwent induction platinum-based chemotherapy followed by clinical review. After further consent, patients were randomly assigned (1:1) to EPP followed by postoperative hemithorax irradiation or to no EPP. Randomisation was done centrally with computer-generated permuted blocks stratified by surgical centre. The main endpoints were feasibility of randomly assigning 50 patients in 1 year (results detailed in another report), proportion randomised who received treatment, proportion eligible (registered) who proceeded to randomisation, perioperative mortality, and quality of life. Patients and investigators were not masked to treatment allocation. This is the principal report of the MARS study; all patients have been recruited. Analyses were by intention to treat. This trial is registered, number ISRCTN95583524.FINDINGS:Between Oct 1, 2005, and Nov 3, 2008, 112 patients were registered and 50 were subsequently randomly assigned: 24 to EPP and 26 to no EPP. The main reasons for not proceeding to randomization were disease progression (33 patients), inoperability (five patients), and patient choice (19 patients). EPP was completed satisfactorily in 16 of 24 patients assigned to EPP; in five patients EPP was not started and in three patients it was abandoned. Two patients in the EPP group died within 30 days and a further patient died without leaving hospital. One patient in the no EPP group died perioperatively after receiving EPP off trial in a non-MARS centre. The hazard ratio [HR] for overall survival between the EPP and no EPP groups was 1·90 (95% CI 0·92-3·93; exact p=0·082), and after adjustment for sex, histological subtype, stage, and age at randomization the HR was 2·75 (1·21-6·26; p=0·016). Median survival was 14·4 months (5·3-18·7) for the EPP group and 19·5 months (13·4 to time not yet reached) for the no EPP group. Of the 49 randomly assigned patients who consented to quality of life assessment (EPP n=23; no EPP n=26), 12 patients in the EPP group and 19 in the no EPP group completed the quality of life questionnaires. Although median quality of life scores were lower in the EPP group than the no EPP group, no significant differences between groups were reported in the quality of life analyses. There were ten serious adverse events reported in the EPP group and two in the no EPP group.INTERPRETATION: In view of the high morbidity associated with EPP in this trial and in other non-randomised studies a larger study is not feasible. These data, although limited, suggest that radical surgery in the form of EPP within trimodal therapy offers no benefit and possibly harms patients.

Editor's commentary: This trial organized and led by Dr. Tom Treasure continues his courageous campaign to examine the benefit of EPP in trimodality protocols in the world outside of Boston and Houston. Not unexpectedly, this trial raises the question of whether EPP offers **any** benefit to these patients. In my experience, patients with non-sarcomatous mesothelioma, no invasion outside the pleura, and without lymph node metastasis stand to do the best with EPP. One needs to be very selective in recommending surgery for these very unfortunate patients.

Adenocarcinoma of the lung

New IASLC/ATS/ERS adeno classification system coorelates survival differences based on histology

J Thorac Oncol. 2011 Sep;6(9):1496-504. Does lung adenocarcinoma subtype predict patient survival?: A clinicopathologic study based on the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary lung adenocarcinoma classification.Russell PA, Wainer Z, Wright GM, Daniels M, Conron M, Williams RA. Department of Anatomical Pathology, St. Vincent's Hospital, University of Melbourne, Victoria, Australia. prue.russell@svhm.org.au

INTRODUCTION: Lung adenocarcinoma is a heterogeneous group of tumors with a highly variable prognosis, not well predicted by the current pathologic classification system. The 2004 World Health Organization classification results in virtually all tumors encountered in clinical practice being allocated to the adenocarcinoma of mixed subtype category. A new classification developed by an international multidisciplinary expert panel sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society, is based on histomorphologic subtype and has recently been validated in a North American series of 514 stage I lung adenocarcinomas. We investigated the relationship between the new classification and patient survival in a series of Australian patients with stages I, II, and III lung adenocarcinoma.METHODS:We identified 210 patients from a surgical database who underwent resection of lung adenocarcinoma from 1996 to 2009. Two pathologists, blinded to patient outcome, independently performed histopathologic subtyping according to the new classification. Kaplan-Meier curves were used to calculate 5-year survival for each separate histopathologic subtype/variant. Univariate and multivariate analyses were undertaken to control for validated prognostic factors.RESULTS:We confirmed that the new subtypes of adenocarcinoma in situ, minimally invasive adenocarcinoma and lepidic-predominant adenocarcinoma had a 5-year survival approaching 100%, whereas micropapillary-predominant and solid with mucin-predominant adenocarcinomas were associated with particularly poor survival. Papillary-predominant and acinar-predominant adenocarcinomas had an intermediate prognosis. This effect persisted after controlling for stage.CONCLUSIONS:Classification of lung adenocarcinoma according to the new International Association for the Study of Lung Cancer/American Thoracic Society/ European Respiratory Society classification correlated with 5-year survival. These relationships persisted after controlling for known prognostic patient and tumor characteristics. The new classification has advantages not only for individual patient care but also for better selection and stratification for clinical trials and molecular studies.

Editor's commentary: This new classification system was presented last year and has not yet been widely adopted. The purpose was to clarify the many different histology presentations of adenocarcinoma of the lung. This paper is the first to show that the new histologic classification scheme correlates with prognosis which is a remarkable achievement. Hopefully, evidence such as this paper will spur adoption of the new system.

Lung resection following induction therapy

Review from Memorial confirms low operative mortality following induction therapy

J Thorac Oncol. 2011 Sep;6(9):1530-6.Contemporary Results of Surgical Resection of Non-small Cell Lung Cancer After Induction Therapy: A Review of 549 Consecutive Cases. Barnett SA, Rusch VW, Zheng J, Park BJ, Rizk NP, Plourde G, Bains MS, Downey RJ, Shen R, Kris MG. Thoracic Service, Department of Surgery, †the Department of Epidemiology and Biostatistics, and ‡the Thoracic Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York City, New York.OBJECTIVE: We previously reported a high mortality after induction therapy and pneumonectomy for non-small cell lung cancer. Recent reports suggest that operative mortality in these patients is declining. We analyzed our contemporary results to define operative mortality and factors determining surgical risk.METHODS: Eligible patients were identified from our prospective surgical database. Complications were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 3.0. Uni- and multivariate logistic regression models assessed the association of preoperative tests and clinical characteristics with outcome. Receiver operating characteristic curves and area under the receiver operating characteristic curve (AUC) statistics were calculated in a leave-one-out crossvalidation scheme to evaluate the predictive value of various models.RESULTS: From January 2000 to December 2006, 549 patients underwent surgery after induction therapy. Median patient age was 64 years (range: 30-86), and 54% were women (298/549). All received chemotherapy, and 17% also had radiation. Lobectomy (388/549, 71%) and pneumonectomy (70/549, 13%) were the most common procedures. Complications occurred in 250 patients (46%), with grade 3 or higher in 23% (126/549). Inhospital mortality was 1.8% (10/549), with only one death after right pneumonectomy (1/30, 3%). Multivariate analysis showed that predicted postoperative (PPO) pulmonary function was associated with postoperative morbidity. By receiver operating characteristic curves, PPO product (AUC = 0.75, $p < 0.001$), PPO diffusion capacity (AUC = 0.70, $p < 0.001$), and preoperative % predicted PPO diffusion capacity (AUC = 0.66, $p < 0.001$) predicted mortality.CONCLUSION: Our current experience shows that resection of non-small cell lung cancer after induction therapy, including pneumonectomy, is associated with low mortality. PPO pulmonary function is the strongest predictor of operative risk and should be used to select patients for surgery.

Editor's commentary: This is a review of a prospectively enrolled series of surgical patients who underwent lung resection following induction chemotherapy, and in a minority of patients, XRT. It is fascinating to see that this group specifically designed this trial to refute their own bad results for right pneumonectomy reported several years ago. In that report, right pneumonectomy mortality was 23.9%, but this was down to 3% in the current report. I guess this report proves that even the surgeons at Memorial can learn new tricks.

Lung cancer pathology

Visceral pleural and lymphovascular invasion confirmed as negative prognostic findings in lung cancer

Eur J Cardiothorac Surg. 2011 Sep;40(3):664-70. Epub 2011 Feb 21.Clinical impact of visceral pleural, lymphovascular and perineural invasion in completely resected non-small cell lung cancer.Yilmaz A, Duyar SS, Cakir E, Aydin E, Demirag F, Karakaya J, Yazici U, Erdogan Y. Department of Pulmonology, Atatürk Chest Diseases and Thoracic Surgery Research and Education Hospital, Keçiören, Ankara, Turkey. OBJECTIVES: This study is conducted to show the relationship between visceral pleural, lymphovascular, and perineural invasion, and other clinicopathologic characteristics and their significance as prognostic factors. METHODS: The clinicopathologic characteristics of 289 patients who underwent a potentially curative surgical resection between 2000 and 2009 in our clinic were reviewed retrospectively. The prognostic factors were then evaluated by univariate and multivariate analysis. The patients who were given neoadjuvant-adjuvant chemotherapy and/or radiotherapy and who died due to postoperative mortality were excluded. Data from 188 patients were analyzed. RESULTS: Out of the 188 patients (108 diagnosed as adenocarcinoma and 80 squamous cell carcinoma), 66 patients had lymphovascular invasion, 53 patients had perineural invasion, and 92 patients had visceral pleural invasion. Visceral pleural invasion was related with T factor, tumor histology, dimension, stage, and differentiation. Lymphovascular invasion was related with N status and stage. Perineural invasion was observed more frequently in tumors with moderate/poor differentiation. Visceral pleural and lymphovascular invasion were found to be poor prognostic factors but we could not show statistically meaningful effect of perineural invasion on survival. CONCLUSION: The presence of visceral pleural or lymphovascular invasion can show higher risk of mortality whereas perineural invasion has no effect on prognosis.

Editor's commentary: If one reads pathology reports carefully, it is surprising, in my opinion, how often pathologists identify lymphovascular invasion, even in early stage tumors. When considering adjuvant postoperative treatment, this may be an important factor weighing in favor of treatment for early tumors.

Segmentectomy for lung cancer

Anatomic segmentectomy found to provide equivalent lymph node sampling compared to lobectomy

Does anatomical segmentectomy allow an adequate lymph node staging for cT1a non-small cell lung cancer? Jour Thor Oncology 6:1537. *Mattioli S, Ruffato A, Puma F, Daddi N, Aramini B, D'ovidio F. Division of Thoracic Surgery, GVM Care and Research, Maria Cecilia Hospital Cotignola (Ra), Alma Mater Studiorum-University of Bologna, Bologna, Italy. sandro.mattioli@unibo.it INTRODUCTION: Anatomical segmentectomy is again under evaluation for the cure of T1a N0 non-small cell lung cancer and carcinoid tumors. Whether anatomical segmentectomy does permit or not, an adequate resection of nodal stations for staging or cure is still pending. METHODS: A case-matched study was ruled on patients with peripheral cT1a N0 M0 tumors that underwent anatomical segmentectomy or lobectomy. Dissection of lymph node stations 4, 5, 6, and 7 was identical in anatomical segmentectomy and lobectomy; stations 10, 11, 12, and 13 were also dissected carefully during anatomical segmentectomy. RESULTS: We individually matched 46 (69% men) anatomical segmentectomy with 46 (71% men) lobectomy for age, anatomical segment, and size of the tumor. The median (interquartile range) size of the resected lesions was 1.7 cm (1.35-1.95 cm) in anatomical segmentectomy and 1.6 cm (1.3-1.9 cm) ($p = 0.96$) in lobectomy. The anatomical segmentectomy and lobectomy resection margins were free of cancer. The median number (interquartile range) of total dissected lymph nodes was 12 (8-5-14) in anatomical segmentectomy compared with 13 (12-14.5) in lobectomy ($p = 0.68$), with a number of N1 nodes being 6 (4-7.5) and 7 (4.5-9.5) ($p = 0.43$), respectively, and N2 nodes 5.5 (4-7.7) and 5 (4-6.5) ($p = 0.88$). Only 1 patient of 46 (2%) anatomical segmentectomy was N1, whereas in lobectomy, 4% had N1 (2 patients). Freedom from recurrence at 36 months was 100% for anatomical segmentectomy and 93.5% for lobectomy ($p = 0.33$). CONCLUSIONS: Anatomical segmentectomy for cT1a tumors compared with lobectomy procures an adequate number of N1 and N2 nodes for pathological examination. Cancer-specific survival was equivalent at 36 months.*

Editor's commentary: This has always been one of the most attractive features of anatomic segmentectomy in my opinion: it allows for an anatomic dissection of the hilar structures and procures the relevant lymph nodes draining the resected segment. I believe that in many patients it provides a resection comparable to lobectomy.

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