A number of protein targets in these pathways possess dysregulated kinase activity, as a result of oncogenic gene mutation or overexpression, and play a pivotal role in carcinogenesis. Receptor tyrosine kinases with roles in proliferation - insulin-like growth factor-I receptor, c-Met, and RET (rearranged during transfection); and cytoplasmic non-receptor kinases involved in proliferation and/or prevention of apoptosis - the serine/threonine kinases Raf, MEK, mTOR and Aurora kinases, and the tyrosine kinase Src. Met is a receptor tyrosine kinase widely expressed in epithelial and endothelial cells. Conversely, its cognate ligand HGF, is expressed by cells of the mesenchymal lineage, facilitating rigorous regulation of Met kinase activity. Activation and/or overexpression of Met have been widely documented as a frequent event in all major human tumor types Activating mutations of Met have been identified in hereditary and sporadic papillary renal carcinomas, in gastric, hepatocellular, head and neck, and ovarian carcinomas, and in small cell lung cancers and gliomas. Moreover, Met and/or HGF are commonly overexpressed in carcinomas and other solid tumors, and in their metastases. In clinical correlative studies, overexpression and/or dysregulation of Met and/or HGF is a negative prognostic indicator in patients with bladder, breast, cervical, gastric, head and neck, nasopharyngeal, thyroid, liver and lung carcinomas, and in patients with multiple myeloma and glioma. Twp inhibitors of MEK kinase, XL880 and ARQ197 as well as an antibody against HGF, AMG102 have completed phase I trials and will be discussed. IGF-1R is another attractive target with 4 monoclonal antibodies targetin this receptor, IMC-A12, AMG 479, CP-751,871 and R1507 in the clinic. MEK inhibitors and src kinase inhibitors will also be discussed.

References:

1. Molina JR, Adjei AA. The Ras/Raf/MAPK Pathway, Journal of Thoracic Oncology. 1 (1) :7-9, 2006
2. Adjei AA. The Role of Mitogen-Activated ERK-Kinase Inhibitors in Lung Cancer Therapy. Clin Lung Cancer.7(3):221-3, 2005.
3. Papadimitrakopoulou V and Adjei AA. The Akt/mTOR and mitogen-activated protein kinase pathways in lung cancer therapy. J Thoracic Oncol. 1(7):749-51, 2006.

MTP19-01 **Advanced Surgical Techniques, Thur, Sept 6, 07:00 - 08:00**

T4 N0/N1 nonsmall cell lung cancer can be cured as a first line treatment with an expected five year survival rate as high as 43% provided a radical resection is performed

Dartevelle, Philippe G.[1] Yildizeli, Bedrettin[2] Fadel, Elie[2] Mussot, Sacha[2]

[1] Paris Sud University, Paris, France; [2] Marie Lannelongue Hospital, Paris, France;

Objective: T4 non-small cell lung carcinoma (NSCLC) is a particular group of locally advanced cancers especially when non associated with mediastinal lymph node involvement. During the past two decades, surgical techniques for resecting locally advanced tumors [1-6] have been refined, allowing consideration for curative surgical therapy in patients who would not previously have been considered operative candidates. Surgery on patients after induction therapy poses special perioperative risks and technical challenges, however. Also, controversy exists in giving neoadjuvant treatment for the patients who have locally advanced disease without mediastinal lymph node involvement. Patients with T4 tumors with minimal nodal involvement (N0 or N1 disease) may benefit from surgery because these tumors are often more local-regionally than systemically aggressive. Survival rates of up to 30% to 40% have been reported for selected T4N0/N1 tumors.

The present report is aimed to assess operative mortality, morbidity, and long-term results of patients with surgically resected T4 NSCLC.

Methods: A retrospective analysis of survival characteristics in 271 patients who underwent resection for T4 tumors between 1981- 2006 was undertaken in a reference center for thoracic surgery. Patients were divided into four subgroups: 126 patients with superior sulcus tumors that were resected through anterior transclavicular approach, 92 with carinal involvement, 39 with massive superior vena cava (SVC) invasion requiring graft interposition and 14 with the tumor invading mediastinum, heart, and great vessels (aorta, and proximal main pulmonary vessels). There were 221 (81.5%) men and 50 women with a mean age of 56.3 years (range, 31-80 years). Only a total of 75 (27.6%) patients underwent induction therapy. Lung resection consisted of 115 right pneumonectomies (42.4 %), 19 left pneumonectomies, 111 lobectomies and 26 wedge resections. Among 126 patients with thoracic inlet tumors who had resection of lung, chest wall and subclavian vessels, 35 underwent a combined “en bloc” resection of the first thoracic vertebrae at three or four levels associated with spinal fixation. In the group of 39 SVC resections and prosthetic replacement, 17 patients required a combined right carinal pneumonectomy. Nine operations were performed under cardiopulmonary bypass (CPB). Resection was complete in 249 (92%) patients. The pathologic N statuses were N0 in 114, N1 in 94, N2 in 39, N3 in 17, and M1 in 7 patients. The histologic type was predominantly squamous cell carcinoma (n = 132; 48.7%). 139 (51.2%) patients received adjuvant therapy including radiation therapy in 109 cases. Follow-up was complete for all patients.

Results: Overall thirty day mortality and morbidity rates were 4% and 35%, respectively. Postoperative death occurred in 6 patients (6.5%) with carinal resection, one (0.8 %) with superior sulcus tumors, three (7.6 %) with SVC invasion, and one with invasion of the mediastinum (7.1 %). In univariate and multivariate analyses, only right pneumonectomy (p=0.01) was associated with high rate of postoperative death. At follow-up, 185 patients are dead, whereas 86 patients are alive. Mean survival was 28 months. Overall 5-year survival rate was 38.4% (Figure 1). Survivals according to the four subgroups of T4 category were as follows: superior sulcus tumor, 36.6%; carinal involvement, 42.5%; SVC invasion, 29.7%; invasion of the mediastinum, 59.3%. Recurrences were observed in 138 patients of whom 29 were local and 15 were both local and systemic and 94 were systemic. By multivariate analysis, two factors significantly and independently influenced survival: nodal status (N0-N1 vs. N2-3M1; p=0.003; 43% vs. 17.7% at 5 years, respectively, figure 2), and complete resection (R0 vs. R1; p=0.01; 40.4% vs. 15, 9%, respectively, figure 3).

Conclusions: Improved surgical techniques have increased the feasibility and radicality of extended operations for patients with potentially resectable but locally invasive NSCLC. Advances in the perioperative management and postoperative care, along with a careful patient selection, will likely make the operative mortality and morbidity less prohibitive and a more favorable prognosis.

It has been well demonstrated that the prognosis after operations for T4 tumors mainly depends on the N stage and complete resection. Patients with N0 or minimal N1 disease and patients with complete resection do significantly better after radical resection, a finding that clearly justifies operative therapy in these patients. Presence of pN2 disease should be considered a potential contraindication to resection of T4 tumors. On the other hand, both the technical complexity of the operation and its rare occurrence therefore suggest centralization of the procedure to departments that express profound and continuous interest in such

problems and that at the same time have a high degree of experience with both general thoracic, cardiac, vascular and spinal procedures.

Our policy regarding locally advanced lung cancer patients is to perform surgery on first intention, whenever a complete resection is thought to be technically possible. Complete resection of T4 NSCLC results in 40.4% of 5-year survival rate. Patients with NSCLC who have carinal involvement, SVC invasion, superior sulcus tumor even with vertebral invasion or mediastinal invasion without mediastinal lymph node involvement should undergo radical surgery without any attempt of giving neoadjuvant chemotherapy.

The thoracic medical and surgical community should promote all efforts to extend the surgical indications for locally advanced NSCLC, making these operations available whenever possible to patients in whom radical resection can be achieved.

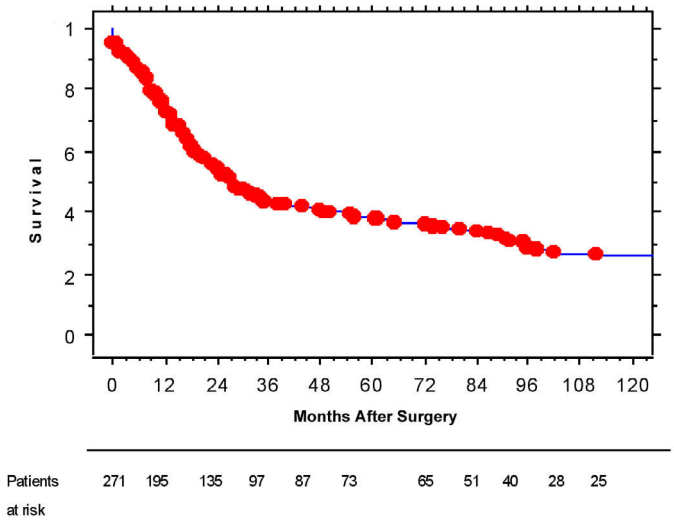

Figure 1. Actuarial survival for patients with T4 Non-small Cell Lung Cancer undergoing resection, including the operative deaths. The estimated 5-, and 10-year survivals were 38.4%, and 26%, respectively. A total of 73 patients were alive at 5 years, and 25 at 10 years.

Group	N	Mortality n (%)	5 year survival (%)	N0/1	N2+	P
Superior Sulcus Tumor	126	1 (0.8%)	36.6	38.5	10.1	0.002
Carinal Invasion	92	6 (6.5%)	42.5	49.8	17.1	0.002
SVC Invasion*	39	3 (7.6%)	29.7	37.5	19.6	0.002
Mediastinal Invasion	14	1 (7.1%)	59.3	55.6	7.5	0.002
TOTAL	271	11 (4.05%)	38.4	43	17.7	0.002

References

1. de Perrot M, Fadel E, Mercier O, Mussot S, Chapelier A, Dartevelle P. Long-term results after carinal resection for carcinoma: does the benefit warrant the risk? J Thorac Cardiovasc Surg. 2006 Jan; 131(1):81-9.
2. de Perrot M, Fadel E, Mussot S, de Palma A, Chapelier A, Dartevelle P. Resection of locally advanced (T4) non-small cell lung cancer with cardiopulmonary bypass. Ann Thorac Surg. 2005 May; 79(5):1691-6; discussion 1697.
3. Fadel E, Missenard G, Chapelier A, Mussot S, Leroy-Ladurie F, Cerrina J, Dartevelle P. En bloc resection of non-small cell lung cancer invading the thoracic inlet and intervertebral foramina. J Thorac Cardiovasc Surg. 2002 Apr; 123(4):676-85.
4. Dartevelle P, Macchiarini P. Surgical management of superior sulcus tumors. Oncologist. 1999; 4(5):398-407.
5. Dartevelle P, Macchiarini P. Techniques of pneumonectomy. Sleeve pneumonectomy. Chest Surg Clin N Am. 1999 May; 9(2):407-17.
6. Dartevelle P. Herbert Sloan Lecture. Extended operations for the treatment of lung cancer. Ann Thorac Surg 1997;63:12-9.

MTP20-01 **Image-Guided Radiation Therapy, Thur, Sept 6, 07:00 - 08:00**

Image guided radiation therapy: the path to protons

Cox, James D.

UT M. D. Anderson Cancer Center, Houston, TX, USA

The goal of Image Guided Radiation Therapy (IGRT) is the delivery of higher doses to tumors without delivering as high doses to normal tissues or, conversely delivering the desired dose to the tumor and reducing the dose to normal tissues. IGRT is a term that has evolved over that last decade. This is exemplified by the activities of the IGRT Committee of the Radiation Therapy Oncology Group which was established around that time. The first focus was on 3-dimensional radiation therapy (3D CRT), a development that was fostered by grants from the National Cancer Institute in the 1980's. These grants led to new tools that permitted 3-dimensional reconstructions of axial images from computed tomography and development of 3-dimensional radiation dose distributions including heterogeneity corrections. Treatment planning systems (TPS) were developed in research institutions that stimulated industry to develop TPS: these became available between 1993 and 1995. A grant from NCI led to creation of a reference and archival center at Washington University in St. Louis to which images could be sent and stored. This centered on 3D CRT for cancer of the prostate, but eventually expanded to other disease sites. Other reference centers developed and eventually coalesced into the Advanced Technology Consortium (ATC) that serves as a resource for many forms of advanced radiation treatment technologies today.

Physicists, engineers and equipment manufacturers developed the ability to plan and deliver intensity modulated radiation therapy (IMRT) whereby beamlets could be delivered with different intensities to shape radiation dose distributions even more precisely, giving higher doses to tumors and lesser doses to surrounding normal tissues. 3D CRT was adopted very quickly in the radiation oncology community whereas IMRT was greeted more skeptically. Reports of the successes of 3D CRT compared with traditional 2D treatments confirmed the benefit first demonstrated in comparative treatment planning studies. Randomized trials showed improved outcomes both in higher tumor control probabilities and lower normal tissue effects. Single institution trials with IMRT have shown it possible to increase total doses even to higher levels than with 3D CRT with very low complication rates. Recent results (non randomized) have demonstrated decreased pulmonary toxicity using IMRT for cancer of the lung compared with 3D CRT.

IGRT now encompasses advanced techniques of patient immobilization and verification (orthogonal images prior to treatment each day compared with images from treatment planning). Means of imaging tumors after patients are positioned have been developed with ultrasound and CT. Methods of coping with tumor motion between and during treatments have been implemented including 4d CT (capturing the images of the tumor while breathing, for example), respiratory gating, and fluoroscopic tracking of fiducial markers near the tumor as the most sophisticated form of gating.

The lessons learned from improved tumor control and normal tissue avoidance with 3D CRT and IMRT support the continued evolution of