technical aspects of incorporating robotic assistance and the perioperative outcomes.

Methods

Patients with adequate cardiopulmonary reserve to tolerate lobectomy for clinical stage I NSCLC or other pathologic tumors that were peripheral and confined to the lung were considered eligible for VATS lobectomy. At our institution the procedure is performed using two 1 – 1.5 cm access incisions and a ≤ 4 cm non-rib-spreading utility incision with intrathoracic visualization achieved via thoracoscope exclusively. Initial thoracic exploration is conducted with conventional thoracoscopy in order to verify resectability and to establish the three standard VATS lobectomy access incisions. Once the incisions have been made, the da Vinci® robot is brought into position, the surgical instruments are introduced under direct thoracoscopic vision, and the operating surgeon moves to the surgeonís console. Robotic assistance is defined as use of the da Vinci® Surgical System during a VATS lobectomy for individual dissection, isolation, and ligation of the pulmonary hilar structures, as well as mediastinal lymph node dissection.

Informed consent for robotic assistance during VATS lobectomy was obtained. Data on patient characteristics, operative details and postoperative recovery were collected in a prospective database approved by the institutional review board and analyzed retrospectively. All complications were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE 3.0)(http://ctep.cancer.gov/reporting/ctc.html).

Results

Between November 2002 and May 2006 there were 63 consecutive patients who underwent attempted robotic-assisted VATS lobectomy employing the da Vinci® Surgical System. The patient characteristics are listed in the Table. Most of the lesions were located in the upper lobes (44/63, 70%) with right upper lobe tumors being the most common (28). The vast majority of our patients had NSCLC (60/63, 95%), two patients had typical carcinoid tumors, and one had a primary pulmonary lymphoma. Those with NSCLC all were clinical stage IA preoperatively. Eleven patients (17%) had no tissue diagnosis and underwent initial VATS and wedge resection in the same setting.

VATS lobectomy using robotic assistance was completed in 58 (92%) patients. Conversion to thoracotomy was required in 5 patients (8%). Three patients were converted for minor bleeding, two from cautery injuries to a segmental pulmonary artery in the course of dissection and one during isolation of the superior pulmonary vein. None of these patients required blood transfusion intraoperatively or postoperatively. One patient required conversion secondary to loss of single lung isolation and one underwent thoracotomy for excessive adhesions and inflammatory nodal disease. The Table shows the perioperative results. Median total operative time was 284 minutes (range 185 – 460). Median intrathoracic operative time was 210 minutes (range 143 – 350). Of note, the median total and intrathoracic operative time for the last 10 cases were 210 minutes (range 185 – 301) and 186 minutes (range 151 – 240), respectively. Every type of lobectomy was done, and mediastinal lymph node dissection was performed in each instance. The median number of lymph node stations dissected in patients undergoing successful robotic-assisted VATS lobectomy was 5.0 (range 2 – 7).

For the patients with NSCLC the overwhelming majority had adenocarcinoma, and 87% (52/60) had pathologic stage I disease. The median size of the lesions pathologically was 2.0 cm (0.8 – 5.0). Eight patients were pathologic stage II, and only 2 patients had unsuspected stage IIIA disease. All patients underwent R0 resection.

The median chest tube duration for the entire group was 3.0 days (range 2 – 19), and the median length of stay was 4.0 days (range 2 – 20). The complication rate for all patients was 24% (15/63). The most common complication was supraventricular tachycardia. The majority of complications were minor (CTCAE grade 2). One patient with a history of coagulopathy had postoperative hemorrhage requiring re-exploration with no clear source of bleeding identified. Two patients suffered postoperative myocardial infarctions: one underwent emergency cardiac catheterization and stent placement while the second had successful medical management. There were no in-hospital deaths, and the 30-day mortality rate was 0%.

Conclusions

Robotic-assistance for VATS lobectomy is feasible and safe. The primary utility of robotic-assistance for VATS lobectomy is in the superior articulation of the instruments. Increasing experience reduces operative times.

Table. Patient characteristics and perioperative results (n=63)

Median age	69.0 (12 - 85)
M:F	27:36
Tumor location	
RUL	28
LUL	16%
LLL	6
RLL	11
RML	2
Median tumor diameter	2.0 (0.8 - 5.0)
Tumor histology	
NSCLC	60
Typical carcinoid	2
MALT	1
Pathologic stage (NSCLC, n=60)	
T1N0M0 (IA)	42
T2N0M0 (IB)	10
T1N1M0 (IIA)	6
T2N1M0 (IIB)	2
T1-2N2M0 (IIIA)	2
Median total operative time (mins)	284 (185 - 460)
Median intrathoracic op time (mins)	284 (185 - 460)
Median chest tube duration (days)	3.0 (2 - 19)
Median length of stay (days)	4.0 (2 - 20)

MTP4-01 **Small Cell Lung Cancer Therapy, Mon, Sept 3, 07:00 - 08:00**

Small cell lung cancer

Murray, Nevin

British Columbia Cancer Agency, Vancouver, BC, Canada

Management of Small Cell Lung Cancer in 2007

Although small cell lung cancer (SCLC) makes up a smaller proportion of all lung cancers than it did 25 years ago, it remains a common cause of cancer mortality that requires more clinical and basic research than is currently underway. Progress in the management of small cell

lung cancer (SCLC)) has been slow and treatment paradigms have changed little over the past 20 years. The traditional reasons cited for lack of progress include a) utility of local therapies such as surgery and radiotherapy is limited by early development of systemic metastases, b) local relapses remain common despite initial radiotherapy responsiveness. c) Drug resistance remains problematic despite innovations in cytotoxic chemotherapy d) identification of new agents with novel therapeutic targets has been difficult.

Staging

Accurate staging determines the intent and structure of the treatment program. The principles of staging of SCLC are rooted in studies from another generation. The Veterans Administration Lung Group staging system that divides patients into either limited or extensive stages has been durable for SCLC because of its simplicity and reliable prognostic value. Limited-stage SCLC (LSCLC) is defined as tumor confined to one hemothorax and the regional lymph nodes, whereas extensive stage small cell lung cancer (ESCLC) is defined as disease beyond these bounds. The original operational definition of limited disease was tumor quantity and configuration that could be encompassed by a "reasonable" radiotherapy treatment volume. Because long-term survival is uncommon (5 to 7%) when chemotherapy alone is used to treat LSCLC, the "reasonable radiotherapy port" rule continues to be of practical importance in the assembly of combined-modality therapy programs that increase the long-term survival rate to over 20%. SCLC typically spreads early with 60% to 70% of patients having extensive stage disease (ESCLC) with metastases outside the limited-stage definition. Although patients with "regional" extensive stage disease such as pleural effusions and contralateral hilar and supraclavicular nodes may be given combined modality therapy with a small chance of cure, ESCLC is typically treated with palliative intent. In addition to limited stage, other pretreatment prognostic factors associated with a favorable outcome in Cox regression analyses include, good performance status, a low alkaline phosphatase level, a normal lactate dehydrogenase and female gender. Standard staging procedures include CT images of the chest and abdomen, CT/MRI of the brain and a radionuclide bone scan. Although widely used, the impact of PET scanning on staging and treatment has not yet been defined in large published data sets or practice guidelines.

Systemic Treatment

SCLC has been of particular interest to medical oncologists because this disease supposedly is "highly sensitive to chemotherapy treatment". Although response rates to chemotherapy are higher for SCLC than non-small cell lung cancer, the absolute survival statistics for patients with metastatic disease receiving cytotoxic drugs are similar for both conditions. Median survival times for patients receiving standard chemotherapy regimens for stages IIIB/IV NSCLC and extensive stage SCLC are both in the 8-10 month range and the proportion surviving 2-years is about 10-15%. Despite higher response rates, the median time required for chemotherapy resistant clones to cause a fatal outcome is similar for advanced SCLC and NSCLC.

Many permutations and variations of protocols containing five drugs (cyclophosphamide, doxorubicin, vincristine, etoposide, and cisplatin) or their analogues have been reported and a number of regimens have been used in phase III studies. Although a clearly superior combination never emerged, the power of chemotherapy was clearly improved with multi-agent chemotherapy. In 1975, Einhorn and colleagues combined cyclophosphamide, doxorubicin and vincristine (CAV) and produced not only high response rates but complete responses were observed in 20% of cases. Interest in the combination of etoposide and cisplatin (EP) was stimulated after it was shown to produce tumor regression in patients whose cancers had progressed following initial drug treatment with a cyclophosphamide-based regimen. The consistent performance of EP or carboplatin and etoposide in clinical trials plus the bonus of its compatibility with radiotherapy has made it a standard of such durability that it persists as the treatment of choice.[1]

Manipulations that intensify the delivery of chemotherapy with increased dose-intensity, increased number of agents and high dose chemotherapy with stem cell support have not worked. It has not been convincingly possible to demonstrate that delivery of more than four cycles of a platinum-etoposide regimen improves outcome.

With respect to the introduction of new chemotherapy agents, a phase III trial from Japan[2] was stopped early when the combination or irinotecan and cisplatin demonstrated survival superiority to the EP combination in ESCLC. Median survival was typical in the EP arm at 9.4 months versus 12.8 months for the irinotecan-treated arm (P = 0.002). At 2 years, the percentage of patients surviving was 19.5% versus 5.2%. However, a phase III trial of a different schedule (day 1,8) of irinotecan and cisplatin generated identical outcomes compared to the EP regimen.[3] A confirmatory phase III trial by the Southwest Oncology Group (S0124) is designed to reproduce the clinical data of the Japanese trial in a larger population (620 patients) and also investigate pharmacogenomic endpoints predictive of toxicity or efficacy of irinotecan and cisplatin. A pall of pessimism exists that combinations including topoisomerase inhibitors are capable of displacing EP as standard therapy for ESCLC.

Other new drugs such as pemetrexed and amrubicin are active and undergoing testing in combination with a platinum agent in ESCLC. However, like advanced NSCLC, it is increasingly unlikely that the plateau in the power of treatment for SCLC will be changed with the introduction of an analogue of a folate antagonist or another anthracycline. The two drug combination of etoposide and cisplatin is likely to remain the standard of care for cytotoxic therapy.

With respect to targeted therapy for SCLC, at the moment, the most interest exists for drugs that target angiogenesis. Pujol et al. have reported survival extension with maintenance thalidomide in a randomized trial.[4] Confirmatory trials are underway and thalidomide analogues are under investigation. At the 12th World Conference in Korea, data will be presented on phase II studies that have added bevacuzimab to combination chemotherapy for SCLC.

Combined Modality Therapy for Limited Stage SCLC

Although investigation of thoracic irradiation timing is reported in 7 randomized trials of varying structure, size and vintage, sequence and timing continues to generate controversy. Recently, a meta-analysis performed according to the Cochrane Collaboration Guidelines examined randomized controlled clinical trials comparing different timing of chest radiotherapy in patients with LSCLC.[5] Early chest irradiation was defined as beginning within 30 days after the start of chemotherapy. Seven randomized trials were eligible. A weighted estimate of the typical treatment effect across studies was computed for 2-year survival data as well as the 5-year survival data, local control and toxicities. The odds ratio (OR) was used as the effect measure. Taking all seven studies into account, the overall survival at 2 years or at 5 years was not significantly different between early or late chest radiotherapy (OR for 2 years 0.84, 95% CI 0.56-1.28, OR at 5-years 0.80, 95% CI 0.47-1.38). When the one trial that delivered non-platinum chemotherapy concurrently with chest radiation[6] was excluded, the OR was

significantly in favor of early chest radiotherapy at 5 years (OR: 0.64, 95% CI 0.44-0.92, P=0.02). Considering studies with an overall treatment time of chest radiation of less than 30 days, the 5-year survival was even better (OR:0.56, 95%CI: 0.37-0.85; P = 0.006). As expected, esophageal, pulmonary and pulmonary toxicity was worse with initial concurrent chemoradiation but severe leukopenia was more frequent in patients receiving late chest radiotherapy (P = 0.0004).

Although a conclusion in favor of early concurrent chemoradiation for LSCLC is not definitive, analysis of relevant subsets of the data is rational. Exclusion of non-platinum chemotherapy is supported by a meta-analysis showing superiority of SCLC regimens containing cisplatin and a conclusive phase III trial showing better survival of the EP regimen compared to a cyclophosphamide/anthracycline-based regimen.[7] Early thoracic irradiation cannot be expected to perform well unless it is coupled with a chemotherapy regimen compatible with concurrent radiotherapy and efficacious enough to improve control of micro-metastases outside the thoracic irradiation volume.

By evidence, the standard dose and treatment for LSCLC is 45 Gy delivered in three weeks in 30 fractions of 1.5 Gy, administered concurrently with cisplatin plus etoposide.[8] In Canada, 40 Gy in three weeks is still widely used.[9] We really do not know that longer treatments or higher doses are better for local control or survival, but we are now able to deliver doses up to 70 Gy in 7 weeks without a clear signal that higher doses are superior.

Prophylactic Cranial Irradiation

Patients with cancer control outside the brain have a 60% actuarial risk of developing brain metastases within 2 to 3 years after starting treatment. In a meta-analysis of 7 randomized trials evaluating the value of prophylactic cranial irradiation, the risk of developing central nervous system metastases was reduced by >50%.[10] Additionally, 3-year overall survival of complete responders (predominately LSCLC) was 20.7% with PCI versus 15.3% in the control group.

The selection of an optimal dose for PCI that would lead to further decreases in brain metastasis incidence with minimal toxicity is the subject of an ongoing international trial addressing the question of the optimal PCI dose for the prevention of metastases. A standard dose of 25 Gy in 10 fractions is being compared to 36 Gy in 18 fractions or 36 Gy in 24 twice daily fractions. PCI should not be given with systemic chemotherapy because of increased toxicity.

Conclusion

Although small cell lung cancer (SCLC) makes up a smaller proportion of all lung cancers than it did 25 years ago, it remains a common cause of cancer mortality that requires more clinical and basic research than is currently underway. Trials of newer chemotherapy variations have failed to produce a regimen that is clearly superior to the two drug combination of etoposide and cisplatin, which remains the standard of care for both limited and extensive stage SCLC. Paradoxically advances in this systemic disease have come from radiotherapy innovations for limited SCLC including addition of thoracic irradiation to systemic chemotherapy, more intense thoracic irradiation, early integration of thoracic irradiation with systemic chemotherapy and prophylactic cranial irradiation.[11]

1. Spira, A. and D.S. Ettinger, Multidisciplinary Management of Lung Cancer. N Engl J Med, 2004. 350(4): p. 379-392.
2. Noda, K., et al., Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. New England Journal of Medicine., 2002. 346(2): p. 85-91.
3. Hanna, N.H., et al., Randomized, phase III trial comparing irinotecan/cisplatin (IP) with etoposide/cisplatin (EP) in patients (pts) with previously untreated, extensive-stage (ES) small cell lung cancer (SCLC). J Clin Oncol (Meeting Abstracts), 2005. 23(16_suppl): p. LBA7004-.
4. Pujol, J.L., et al., A prospective randomized phase III, double-blind, placebo-controlled study of thalidomide in extended-disease (ED) SCLC patients after response to chemotherapy (CT): An intergroup study FNCLCC Cleo04 - IFCT 00-01. J Clin Oncol (Meeting Abstracts), 2006. 24(18_suppl): p. 7057-.
5. Pijls, M., et al., Early versus late chest radiotherapy for limited stage small cell lung cancer: a systematic review and meta-analysis. Lung Cancer, 2005. 49(Supplement 2): p. S101.
6. Perry, M.C., et al., Chemotherapy with or without radiation therapy in limited small-cell carcinoma of the lung. New England Journal of Medicine, 1987. 316(15): p. 912-8.
7. Sundstrom, S., et al., Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up.[comment]. Journal of Clinical Oncology., 2002. 20(24): p. 4665-72.
8. Turrisi, A.T., 3rd, et al., Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. New England Journal of Medicine., 1999. 340(4): p. 265-71.
9. Murray, N., et al., Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. Journal of Clinical Oncology, 1993. 11(2): p. 336-44.
10. Auperin, A., et al., Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. New England Journal of Medicine., 1999. 341(7): p. 476-84.
11. Murray, N. and A.T. Turrisi, 3rd, A review of first-line treatment for small-cell lung cancer. J Thorac Oncol, 2006. 1(3): p. 270-8.

MTP5-01 Clinical Trial Methodology for Targeted Agents, Mon, Sept 3, 07:00 - 08:00

Clinical trials methodology for targeted agents

Paesmans, Marianne

Institut Jules Bordet, Brussels, Belgium

In oncological patients with solid tumor, treatment is most often guided by histology and staging which are also the main eligibility criteria for clinical trials. However, it is known for decades that there might be considerable heterogeneity within the same histological type and that this heterogeneity leads to variations for response to treatment and survival with sensitivity to a given therapy being restricted to a subgroup of patients. If this heterogeneity is unknown and disregarded in the design of a clinical trial, it can have harmful consequences on the power of a trial to detect a benefit for the investigational treatment, the loss of power depending on the differential treatment effect in sensitive and in non sensitive patients as well as on the true proportion of sensitive patients, sensitive patients who are not necessarily accurately represented in phase II trials (1). Tumor biology might be responsible for the heterogeneity and progress in the knowledge of tumor biology did allow the development of molecularly targeted agents. This complicates drug development and, in particular, the design of randomised phase III clinical trials.

In some situations, at the time of initiating a phase III trial, we may be lacking from reliable and/or quick assays to select sensitive patients and, consequently, traditional trials with broad eligibility criteria are still used despite the fact that a true treatment effect on the sensitive patients only may be diluted by the absence of effect (or worse by a deleterious effect) in non sensitive patients. At the end of the trial, a stratified analysis can be done for the sensitivity status although a stratified randomisation for the sensitivity status might be wished to avoid random differences in the proportion of sensitive patients in both arms. Freidlin and Simon (2) proposed an attractive adaptive design combining in the same time the development of a classifier and the conduct of a clinical trial for testing an overall effect of the investigational treatment and a specific effect in a subgroup of sensitive patients,

