Session E07: Treatment of Locally Advanced NSCLC

E07-01  Treatment of Locally Advanced NSCLC, Mon, Sept 3, 16:00 – 17:30

Combined modality therapy for locally advanced NSCLC

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There has certainly been a progression in the approach to locally advanced non-small cell lung cancer over the last two decades. Until the 1980s, radiation therapy alone had been the standard of care for locally advanced NSCLC despite the dismal survival data. During the early 1990s, results of multiple randomized phase III studies shifted the standard toward concurrent chemoradiation therapy. The mechanism of chemotherapeutic radiosensitization is thought to be direct inhibition of radiation-induced damage repair; elimination of radioresistant, chemosensitive clones; and/or suppression of inter-fraction tumor repopulation. Concurrent chemoradiation addresses both distant and locoregional disease simultaneously. The two modalities should act synergistically on tumor clonogens susceptible to both modality and in a complementary fashion on locoregional clonogens that are susceptible to only one of the modalities. A number of phase III randomized trials have shown a statistically significant improvement in clinical outcomes, including survival, with the concurrent approach. However, this innovative strategy has also led to an increase in the incidence and severity of treatment-related toxicities. These innovations in treatment now begin to cooperate with improvements in the imaging of cancers like PET scanning and with the improvements in computers and automation that are allowing us to deliver radiation in a more conformal fashion than before to reduce toxicity while improving tumor control. The implication of these new technologies in treating lung cancers is really quite profound. New treatment planning systems allow for the delivery of more targeted radiation with multiple, non-traditional field arrangements when needed to protect normal structures. Areas of atelectatic lung remain a challenge for the radiation oncologist to be able to adequately define the target volume. However, incorporation of the physiologic data provided by PET scanning may not only allow physicians to spare the collapsed lung but may allow them to deliver higher doses of radiation to more biologically active and presumably more aggressive areas of tumors as well. Advances in radiation therapy (RT) techniques, chemotherapeutic regimens, and different combined-modality approaches have yielded a modest impact on the prognosis of patients with advanced lung cancer. But the median survival for locally advanced NSCLC patients is only 18-24 months at best. There is clearly a need for additional strategies. Recent discoveries in molecular biology have identified a number of molecular determinants that may be responsible for resistance of cancer cells to radiation or other cytotoxic agents, and as such may serve as targets for augmentation of radio- or chemo-response. Among these determinants are epidermal growth factor receptor (EGFR), Anti Angiogenesis agents, mutated ras, angiogenic molecules, and various other molecules that regulate different steps in their signal transduction pathways. Incorporating newer biologic agents into chemoradiotherapy is critical to further improve outcomes in this setting. One strategy should improve therapeutic outcomes by blocking receptors and pathways that help tumor cells survive radiation and repair damage without increasing normal tissue toxicity. In this meeting we will review the current research challenges in incorporating these agents into radiotherapy and chemoradiotherapy and preliminary data in patients with locally advanced NSCLC.

E07-02  Treatment of Locally Advanced NSCLC, Mon, Sept 3, 16:00 – 17:30

The role of surgery in the treatment of locally advanced non-small cell lung cancer

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Since the TNM system has been applied to lung cancer, patients have been paradigmically subdivided into two subcategories, according to surgical possibilities. The surgical landmark was defined precisely between stages III A and B, since T3 and/or N2 tumors are worldwide considered as fit for resection, while T4 and/or N3 are generally unresectable [1]. Actually non-small cell lung cancers (NSCLC) should be subdivided in three subgroups: 1) patients who could be cured by surgery alone, some of them able to benefit from adjuvant strategy; 2) patients with so-called marginally resectable locally advanced tumors, in which surgical resection alone is generally unable to achieve a long-term survival; 3) patients with advanced disease, definitively not amenable to surgery [2].

Stage IIIA

Theoretically resectable, stage IIIa disease actually includes a high proportion of non-resectable tumors, particularly because of nodal disease. These locally advanced lung cancers have a poor prognosis, related to their high potential for distant metastases. According to the hypothesis that the tumor debulking induced by neo-adjuvant treatments could render resectable some locally advanced NSCLC tumors in selected patients, chemotherapy, or chemoradiotherapy, was proposed as induction pre-operative strategy in stages IIIA patients. A large European randomized study comparing induction chemotherapy with primary surgery failed to demonstrate the superiority of neoadjuvant treatment in stage IIIA category [3]. Contrarily a retrospective study of more than 700 resected N2 non-small cell lung cancers showed that those preoperatively treated patients achieved a significantly better survival than patients who did not receive induction chemotherapy [4]. A North American Intergroup randomized study, attempted to assess the relevance of surgical resection after induction chemo-radiotherapy in stage IIIA NSCLC with N2 disease [5]. This trial explored the surgical question on a very homogeneous group of T1 to T3/N2 disease. Preliminary results of INT 0139 showed better survival (38% and 33% at 3 years in the surgical and non-surgical arms, respectively) than was observed in previous phase II trials (26% for N2 disease at 3 years in SWOG 8805[6]). Intriguingly, half of the patients (46%) were downstaged to N0, and for those patients, median survival was 37 months. These results emphasize the hypothesis that the absence of tumor in the mediastinal nodes at surgery is the strongest predictor of long-term survival, as it was previously reported in other studies [4,6,7,8]. A prospective approach for future clinical practice could suggest conducting surgery only on patients who respond at the mediastinal level after induction treatment. Another randomized trial in Europe compared surgical resection to radiotherapy after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer [9]. In this study surgical resection did not improve survival in comparison to radiotherapy. Nevertheless, an unplanned subgroup analysis performed in the surgery-arm showed that mediastinal clearance was a statistically significant factor.
Stage IIIA also includes lung cancers invading thoracic wall and superior pulmonary sulcus tumors. Pancoast’s tumors can be resected with overall 5-year survival rates around 30%, in the absence of vertebral invasion [10]. Lung cancers invading the thoracic wall (T3) are currently resected, by the means of an en bloc procedure in which parietal and pulmonary structures are removed together. In the absence of mediastinal lymph node involvement, 5-year survival rates of 50% were reported [11]. In these last categories of patients, the role of multimodality strategy, and particularly the place of radiotherapy, advocated by many groups remains to become clearer [12].

Stage IIIB

Currently stage IIib diseases are considered unresectable. Nevertheless, selected patients whose T4 tumor is not associated with a mediastinal N2 nodal involvement, can be proposed for extended resections, either as a primary treatment, of after induction.

The significance of surgical treatment for T4 lung cancer has been studied by numerous authors, particularly in Japan. For instance, Sakurada and his colleagues found 50% and 38% five-year survival rates after resection for lung cancer invading the left atrium and major vessels, respectively [13]. The only significant prognostic factor they identified was the completeness of resection (p<0.05). In the same way, Shirakusa and coll. reviewed their experience in extended operations for T4 lung carcinoma [14]. Interestingly the results were found far better in the last period of their study (from 1992 to 1997), with a 3-year survival rate of 25%, compared to the 7% observed in the former period (1978-1989), showing an increasing experience in the management of patient’s care. Regarding the T4 descriptors from the International Staging System separately, some of them, invading mediastinal organs, have been considered as potentially resectable by several groups.

Left atrium and great arteries

Proximal tumors from the lower lobe developed around the inferior pulmonary vein can extend until the atrial wall of the heart. Fukuse and coll. reported a series of 42 patients operated upon for lung cancer invading the left atrium or great vessels [15]. Overall 3-year survival was 17%. Great vessels invasions were found to be of better prognosis than atrial involvements (p=0.036).

Superior Vena Cava

Invasion of the superior vena cava by a T4 tumor coming from the right upper lobe led surgical teams to attempting lobectomies or pneumonectomies extended to the vena cava [16]. Actually direct extension to the vessel by the tumor mass itself is a rare situation. Usually a vena cava resection is needed by extension of a bulky disease, in which the nodal disease actually is the most component, and by consequence the tumor remains difficult to classify, between N2 or T4. A multicentric international review of prosthetic replacement after superior vena cava resection for non small cell lung cancer in 28 patients, in which N2 involvement was present in 50% of the cases, found an overall 5-year probability of survival of 15% [17].

Carina, trachea

A bronchial carcinoma from the right lung extended to the lower part of the thoracic trachea, and/or the tracheal carina can be resected in selected patients [18]. But the largest series in world shows a high rate of anastomotic complications (dehiscence or stenosis), who were found as predictor of operative mortality (p=0.04). Yatsuyanagi and coll. focused their study on anastomotic complications after bronchoplastic procedures [19]. Nodal involvement at postoperative pathological examination (pN0-1/N2) was the only clinical predictor of bronchial complications.

Vertebral body

Tumors involving the transverse process or the lateral part of the vertebral body could be resected through an enlarged posterolateral thoracotomy [20]. However, direct major invasion of the vertebral body remained an absolute contraindication to surgical repair until the first report in 1996 of a successful total vertebrectomy for en bloc resection of lung cancer invading the spine [21]. Among the factors who determine outcome in patients with superior sulcus tumors treated by multimodal approach at the University of Texas MD Anderson Cancer Center, surgical treatment was found as a significant predictor (p<0.01), while vertebral body involvement remained marginally significant (p=0.05) [22]. At the same institution a multidisciplinary team of neurosurgeons and thoracic surgeons attempted to achieve a locoregional control, i.e. a negative surgical margin of all areas including the involved vertebrae [23]. Preliminary results on 17 patients (median follow-up = 25 months) showed no postoperative lethality, consistent morbidity, tumor recurrences in half of the cases, and a 2-year survival rate of 80% for completely resected patients. In the same way, an en-bloc technique of resection was developed in Europe, in attempting to respect oncologic principles, by the means of a notouch resection attempt [24].

Multimodal approach in stage IIIB

Several reported studies have demonstrated the feasibility of surgical resection after induction chemoradiotherapy in patients with stage IIIB non-small cell lung cancer [6-8]. Stamatis and his colleagues reported a complete resection rate of 48% after bifractionated radiotherapy associated with chemotherapy given preoperatively in 56 patients with stage IIIB disease [25]. Those patients who could be completely resected survived at 5 years in 43% of the cases, while overall 5-year survival of the entire series was 26%. In our study, surgical resection after induction chemoradiotherapy achieved an encouraging 28% long-term survival for patients with stage IIIB disease in whom chemoradiotherapy alone failed to control disease [26].

In conclusion, the role of surgery in locally advanced non-small cell lung cancer remains under investigation. Clearly surgical resection is an efficient salvaging procedure for selected stage IIIB patients who are partial responders without mediastinal lymph node involvement at the time of surgery. Altogether, available data suggest that post-induction TN status is more accurate than pretreatment TN status to guide the indications of surgery for patients with locally advanced NSCLC.

Several questions remaining: What is the best preoperative strategy to increase the rate of mediastinal lymph node downstaging ? How can multimodality treatment-induced toxicity be lessened ? Faced with such toxicity, should surgery be performed in patients presenting a complete response and how can they be identified preoperatively?

In addition, the staging system for lung cancer must be adjusted in accordance to progress in surgical techniques, allowing extended resections in the context of multimodality treatments, and particularly taking into account the different concepts of documented versus unforeseen N2 involvements and potentially resectable versus definitively nonresectable advanced tumors.

References


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**E07-03** Treatment of Locally Advanced NSCLC, Mon, Sept 3, 16:00 – 17:30

**Treatment of locally advanced non-small cell lung cancer - neoadjuvant or adjuvant chemotherapy**

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Over recent years combined modality therapy has become firmly established as a standard in the treatment of patients with locoregionally advanced unresectable non-small cell lung cancer (NSCLC). In direct comparison, concomitant chemoradiotherapy was shown repeatedly to be superior to induction chemotherapy. A case can be made that concomitant chemoradiotherapy primarily addresses locoregional disease while induction chemotherapy might be better suited to eradicate distant micrometastatic foci. Therefore, continuing sequential and concomitant therapy might be beneficial and the addition of induction or adjuvant chemotherapy to the concomitant chemoradiotherapy standard have been investigated.

CALGB 39801 compared concomitant chemoradiotherapy using the carboplatin paclitaxel platform versus induction chemotherapy with carboplatin and paclitaxel for two cycles followed by identical chemoradiotherapy. While a numerical trend favored the induction chemotherapy arm, there was no significant advantage for overall survival. Similarly, the Hoosier Oncology Group evaluated the administration of concomitant chemoradiotherapy using the cisplatin etoposide platform with or without three additional cycles of consolidation chemotherapy with docetaxel. This study was based on promising pilot data generated by the Southwest Oncology Group. Again, the study showed no significant survival advantage from the addition of concomitant chemoradiotherapy. Therefore, at the present time, concomitant chemoradiotherapy should be regarded as the standard approach for most patients with unresectable non-small cell lung cancer.

Induction chemotherapy may have a role for patients with poor performance status who may not be candidates to undergo aggressive chemoradiotherapy. Certain targeted agents might be appropriate to investigate in the consolidation setting under carefully defined experimental conditions. This need is highlighted by the recent experience in SWOG 0023 in which the administration of gefitinib as maintenance therapy was found to decrease survival rates.

**Session E08: New Technology for Diagnosis**

**E08-01** New Technology for Diagnosis, Tue, Sept 4, 16:00 – 17:30

**Autofluorescence bronchoscopy and optical coherence tomography**

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The lung is an internal organ consisting of a complex branching system of airways leading to gas exchange units. Lung cancer consists of several cell types instead of a single cell type. Different cell types are preferentially located in different parts of the bronchial tree. There is no single method that can detect pre-invasive cancer in the entire bronchial epithelium and allow simultaneous tissue sampling for pathological diagnosis and molecular profiling. While computerized tomography, magnetic resonance imaging and ultrasound can detect objects in the sub-millimeter scale, photonic imaging can detect structural and functional changes in cells and tissues down to the micron and sub-micron scale.