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

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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
range. It is therefore advantageous to use light to detect pre-invasive lung cancer and preneoplastic lesions that are usually very thin and small. When tissue is illuminated by light, the light can be absorbed, scattered, induce fluorescence or vibration changes. Significant differences in reflectance and autofluorescence properties have been observed between normal, pre-malignant and malignant tissues. These differences in optical properties have been exploited to enhance the detection rate of high-grade bronchial dysplasia and carcinoma in-situ. Current commercially available autofluorescence bronchoscopy devices make use of a combination of autofluorescence and reflectance. A blue or violet light is used to induce tissue autofluorescence. The fluorescence image is then combined with a blue, red and/or green reflectance image for display. In addition to multiple single center studies, there are 3 multi-center clinical trials and two randomized trials that showed improved detection rate with fluorescence bronchoscopy or with fluorescence-reflectance bronchoscopy compared to white-light bronchoscopy alone. Autofluorescence bronchoscopy has the advantage that a biopsy can be taken during the same examination for pathological confirmation. For cancer beyond the range of the bronchoscope, gene expression analysis of bronchial brush cells holds promise to differentiate between malignant versus benign peripheral lung nodules. Autofluorescence bronchoscopy has contributed to improved histopathological classification and molecular profiling of preneoplastic lesions. It has become an integral part of a standard bronchoscopic examination for lung cancer diagnosis. False-positive fluorescence can occur due to inflammation or conditions that increase vascularity of the bronchial mucosa. Optical coherence tomography (OCT) can overcome this problem by allowing visualization of the sup-epithelial layers. The principle of OCT is similar to ultrasound. Instead of using sound, infrared light is used. Back-scattered light from varying tissue depths can be used to delineate cellular and extra-cellular structures. Doppler OCT can add further information on vascular density and blood flow. Recent studies showed that high-grade dysplasia, carcinoma in-situ and invasive cancer can be distinguished from normal, hyperplastic or metaplastic epithelium. Interruption of the basement membrane would indicate the presence of invasive cancer. Areas of inflammation also show distinctive changes. Since small pre-neoplastic lesions can be removed by a biopsy procedure, OCT holds promise as a non-biopsy tool to study the natural history of preneoplastic lesions and the effect of chemoprevention. In the context of an early lung cancer detection program, approximately 18% of cancers - majority of which being Stage 0 cancers, are detected by fluorescence bronchoscopy alone with a negative spiral CT. Lung cancer risk assessment models using biometric data such as family history, presence or absence of chronic obstructive pulmonary disease, family history of lung cancer and body mass index in addition to age, smoking history and occupational exposure are being validated. These models have the potential to predict the risk of lung cancer development better than the Gail model for breast cancer. Prospective clinical trials need to be performed to validate the use of these lung cancer risk models to select individuals at highest risk of developing lung cancer for intensive screening utilizing both fluorescence-reflectance bronchoscopy and spiral CT to detect early cancer in both the central and peripheral airways that are amenable to curative therapies.

References

EBUS-TBNA: Real-time endobronchial ultrasound guided transbronchial needle aspiration
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Endobronchial ultrasound (EBUS) guided biopsy in respiratory disease is a promising new modality. The radial probe EBUS (20 MHz) has been used for the biopsy of peripheral lung lesions using the guide sheath. In addition, the radial probe EBUS guided TBNA has increased the yield of TBNA of mediastinal lymph nodes. However it is still not a real-time procedure with target visualization. To overcome these problems, a new convex probe endobronchial ultrasound (CP-EBUS, XBF-UC260F-OL8) with ability to perform real-time EBUS guided TBNA (EBUS-TBNA) was developed in collaboration with Olympus Optical Co. Tokyo, Japan 1,2. This CP-EBUS is a flexible bronchoscope with a linear curved array transducer on the tip with a frequency of 7.5 MHz that scans parallel to the insertion direction of the bronchoscope. Images can be obtained by directly contacting the probe or by attaching a balloon on the tip and inflating with saline. The outer diameter of the insertion tube of the flexible bronchoscope is 6.7 mm and that of the tip is 6.9 mm. A dedicated 22-gauge needle was developed to perform transbronchial aspiration. The needle can be visualized through the optics and on the ultrasound image. EBUS-TBNA was initially developed for lymph node staging of lung cancer. However from our experience, there are many other uses in clinical practice. The applications of EBUS-TBNA are (a) lymph node staging in lung cancer patients; (b) diagnosis of intrapulmonary tumors; (c) diagnosis of unknown hilar and/or mediastinal lymphadenopathy; and (d) diagnosis of mediastinal tumors. From our 5 year experience, we have not experienced any major complications. For lymph node assessment in lung cancer patients, EBUS-TBNA can be used for preoperative evaluation as well as post-chemotherapy and post-operative evaluation. To evaluate the usefulness of CP-EBUS in pre-operative lymph node staging of lung cancer, we performed EBUS-TBNA in 108 patients with lung cancer or suspected lung cancer having mediastinal lymph nodes suspected of malignancy. In 105 patients, EBUS-TBNA was successfully performed to obtain samples from 163 lymph nodes. With respect to the correct prediction of lymph node stage, EBUS-TBNA had a sensitivity of 94.6%, specificity of 100%, positive predictive value of 100%, negative predictive value of 89.5%, and diagnostic accuracy rate of 96.3%. In the 20 suspected lung cancer cases, mediastinal lymph node was used for tissue diagnosis of malignancy as well as staging. As a result of EBUS-TBNA, 29 mediastinoscopies, 8 thoracotomies, 4 thoracoscopies, and 9 CT-guided PCNB were avoided 3. In addition, a cost effectiveness study comparing EBUS-TBNA to other conventional tools used for mediastinal staging