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Early central airways lung cancer

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Abstract Early central airways lung cancer accounts for very small percentage of all lung cancers. Given this fact, it is much difficult to carry out a prospective randomized comparative clinical trial. Even retrospective studies can offer important information. Early central airways lung cancer is usually detected by sputum cytology. If sputum cytology shows atypical epithelial cells implying malignancy, the next thing we have to do is bronchoscopy. Both autofluorescence bronchoscopy and white light bronchoscopy were superior to white light bronchoscopy alone in detecting this type of lung cancer. Natural history of this cancer showed about the two-thirds of the patients die from original disease within 10 years. If the tumor length is 10 mm or less, photodynamic therapy is a first-line modality. After photodynamic therapy, a 5-year overall survival of about 80 % and a 10-year overall survival of 70 % can be expected. If a cancer does not meet the criteria for photodynamic therapy, surgical resection is recommended, and 5-year overall survival of about 80 % can be expected. Segmentectomy should be considered because of pulmonary function preservation if a tumor is located at segmental bronchi or beyond it. The frequency of multicentricity is high. Treatment strategy for subsequent primary lung cancer is an important key for the prognosis of patients with treated early central airways lung cancer. Surgical resection is still the most reliable treatment of subsequent primary lung cancer, except for in situ or microinvasive carcinoma located centrally, which could be cured by photodynamic therapy.

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Introduction

Early central airways lung cancer always has no abnormality on chest X-ray and computed tomography, and is usually detected by sputum cytology. It has superficial change of bronchial epithelia on bronchoscopic findings, and its histology is squamous cell carcinoma in most cases. Here we reviewed the literatures on diagnosis and treatment for early central airways lung cancer, placing the focus on autofluorescence bronchoscopy, narrow band imaging, and photodynamic therapy.

Natural history

Understanding the natural history of lung cancer is crucial for making appropriate therapeutic decisions. However, very few studies have described the natural history of stage I lung cancer, and we previously reported the only study about the natural history of early central airways lung cancer [1]. In this article, a total of 251 early central airways lung cancer patients were retrospectively reviewed, 44 of who declined cancer treatment, i.e. natural history group and 207 of who were treated with resection. The survival rate due to primary lung cancer death in the natural history group was 53.2 % at 5 years and 33.5 % at 10 years. On the other hand, the survival rate of treated group was 96.7 % at 5 years and 94.9 % at 10 years. Since about the two-thirds of the patients with early central airways lung cancer die from lung cancer within 10 years

if untreated, those should undergo appropriate tumor treatment.

Diagnosis

Autofluorescence bronchoscopy (AFB)

If sputum cytology shows atypical epithelial cells implying malignancy, the next thing we need to do is bronchoscopy. At first, white light bronchoscopy (WLB) is performed. WLB reveals the shape of tumor. But sometimes, only AFB can detect slight superficial change of bronchial epithelia. We previously reported detection rate of its superficial change by AFB comparing with WLB [2]. The sensitivity by WLB alone was 85.3 %, whereas that of AFB with WLB was 94.1 %.

A multicenter prospective trial was conducted [3], where there were 115 men and 55 women. Seven hundred seventy-six biopsy specimens were included, and seventy-six were classified as positive (moderate dysplasia or worse) by pathology. The relative sensitivity on a per-lesion basis of WLB + AFB versus WLB was 1.5. The relative sensitivity on a per-patient basis was 1.33. The relative sensitivity to detect intraepithelial neoplasia was 4.29 and 3.5 on a per-lesion and per-patient basis, respectively. They concluded that AFB + WLB improves the detection and localization of intraepithelial neoplasia when compared with WLB alone.

Sun and colleagues [4] conducted a meta-analysis of 21 studies to evaluate the value of AFB combined with WLB compared with WLB alone in the diagnosis of intraepithelial neoplasia and invasive cancer. They reported that the pool relative sensitivity on a per-lesion basis of AFB + WLB versus WLB alone to detect intraepithelial neoplasia and invasive cancer was 2.04 (95 % CI 1.72–2.42) and 1.15 (95 % CI 1.05–1.26), respectively. The pool relative specificity on a per-lesion basis of AFB + WLB versus WLB alone was 0.65 (95 % CI 0.59–0.73). They concluded that AFB + WLB seemed to significantly improve the sensitivity to detect intraepithelial neoplasia, but this advantage seemed much less in detecting invasive cancer.

Chen and colleagues [5] reported another meta-analysis. They pooled 14 studies to evaluate the diagnostic efficacy of AFB for identification of lung cancer and preneoplastic lesions. The pooled sensitivity and specificity of AFB were 0.9 (95 %CI 0.84–0.93) and 0.56 (95 % CI 0.45–0.66), respectively, and those of WLB were 0.66 (95 %CI 0.58–0.73) and 0.69 (95 % CI 0.57–0.79), respectively. They concluded that AFB was superior to WLB in detecting lung cancer and preneoplastic lesions.

All these studies including two meta-analyses indicated both AFB and WLB were superior to WLB alone in detecting lung cancer, especially intraepithelial neoplasia.

Narrow band imaging (NBI)

Narrow band imaging is a diagnostic tool in pulmonary endoscopy other than AFB and WLB. Vincent and colleagues [6] reported a pilot study of NBI compared with WLB. They performed bronchoscopy on 22 patients with known or suspected bronchial dysplasia or malignancy. There were one malignant and four dysplastic lesions detected by NBI after WLB findings were considered normal. They concluded that the addition of NBI to WLB significantly improved detection of bronchial dysplasia compared to WLB alone.

Herth and colleagues [7] reported the diagnostic yields of NBI individually and in combination with AFB and WLB. Fifty-seven patients who were at high risk for lung cancer without known diagnosis were analyzed. There were 17 patients with either CIS or high-grade dysplasia. In detecting CIS or high-grade dysplasia, the sensitivity of WLB was 0.18 (95 %CI −0.78) and the specificity was 0.88 (95 %CI 0.76–1). The relative sensitivities (compared with WLB) of AFB and NBI were 3.7 and 3.0, respectively. The relative specificities of AFB and NBI were 0.5 and 1.0, respectively. Combining the findings of WLB to either AFB or NBI did not change the relative sensitivity. Combined AFB and NBI showed no statistically significant improvement of relative sensitivity compared with either AFB alone or NBI alone. They concluded that NBI was an alternative to AFB in the detection of early central airways lung cancer.

In brief, many reports about AFB for diagnosis of early central airways lung cancer have been published so far and their results have been consistent: AFB and WLB are superior to WLB alone in diagnostic yields. NBI may have similar ability to AFB in diagnosis of early central airways lung cancer, but to date, there have been fewer reports about NBI than those about AFB. Therefore, at present, AFB and WLB are considered to be the gold standard to diagnose early central airways lung cancer.

Treatment

Surgical resection

Before photodynamic therapy (PDT) showed up in the clinical practice, surgical resection was the first choice of the treatment for early central airways lung cancer [8, 9]. Its outcome was excellent as reported previously [10]: 5-year overall survival rate was 80 % and 5-year disease

specific survival rate was 94 %. Limited surgery with curative intent was examined because those patients usually had poor pulmonary function reserve due to smoking habit [11]. Segmentectomy showed similar outcome to lobectomy; 5-year overall and disease specific survival rate was 83 and 92 %, respectively[12]. Accordingly, at present, early central airways lung cancer, which does not meet the criteria for PDT stated below, is the candidate for segmentectomy with curative intent.

Moreover, subsequent primary lung cancer was another key for the prognosis of early central airways lung cancer. The frequency of multicentricity in cases of resected early central airways lung cancer was reported to be high [8, 9, 13, 14]. We analyzed a total of 127 patients with resected early central airways lung cancer, and reported the cumulative rate and the incidence of subsequent primary lung cancer were 11 % at 5 years after initial operation and 2.2 % per patient-year, respectively [14]. Furthermore, the cumulative rate and the incidence of third primary lung cancer were 47 % at 5 years and 11 % per patient-year, respectively. This is about three times higher than the rate of second primary tumor in patients with initial cancer. Among all 13 patients having subsequent primary lung cancer, only 6 patients underwent surgical resection of subsequent tumor. Recurrence was observed in one of the 6 patients undergoing resection and in two of the 4 patients treated with laser and/or radiation therapy. Surgical resection is still the most reliable treatment of subsequent primary lung cancer, except for in situ or microinvasive carcinoma located centrally, which could be cured by PDT.

PDT

Photodynamic therapy is based on the interaction of a photosensitizer with light of narrow bandwidth. At present, two kinds of photosensitizer (porfimer sodium and talaporfin sodium) are available. Each photosensitizer has specific absorption band, i.e. 630 nm for porfimer sodium and 664 nm for talaporfin sodium. Tumor death occurs by direct singlet oxygen injury, cell cycle apoptosis, and so on. Photodynamic therapy is considered a useful and minimally invasive modality for early central airways lung cancer. From the results of a prospective phase II study [15], PDT with using porfimer sodium is considered a first-line modality for nonsurgical patients with early central airways lung cancer with a longitudinal extent of equal to or less than 10 mm. In this phase II study, a total of 59 lesions were assessed, and complete response rate was 85 %. Univariate analysis showed that the length of longitudinal tumor extent (97.8 % <10 mm vs. 43 % >10 mm, $p = 0.0001$) was the most significantly variable related to complete response. Multivariate analysis showed the length of longitudinal tumor extent was the only independent indicator for complete response.

Furukawa and colleagues [16] reported outcome of PDT with porfimer sodium for 114 lesions. The complete response and 5-year survival rates of patients with lesions less than 10 mm were 92.8 and 57.9 %, respectively. On the other hand, those of patients with lesions more than 10 mm were 58.1 and 59.3 %, respectively. PDT for patients with lesion less than 10 mm showed significantly higher complete response rate.

Moreover, we recently reported results of long-term follow-up of PDT for patients with early central airways lung cancer who were medically operable [17]. A total of 48 patients with early central airways lung cancer with longitudinal extension less than 10 mm underwent PDT with using porfimer sodium. The complete response rate was 94 %, and local recurrence rate after complete response was 20 %. About 89 % of patients having recurrent disease were alive at the last follow-up. The 5- and 10-year overall survival rates were 81 and 71 %, respectively. The 5-year survival rates of patients with and without local recurrence were 100 and 76 %, respectively, indicating no statistically significant difference (log-rank test $p = 0.62$). The Cox proportional hazards model showed that only metachronous multiple primary lung cancer was an independent poor prognostic factor. Therefore, we concluded that PDT was considered to be a first-line modality for patients with early central airways lung cancer having less than 10 mm longitudinal extension, even if the tumor was medically operable, and that multiple primary lung cancer subsequent to PDT was an important issue from the viewpoint of survival. Most local recurrence can be cured by salvage therapy such as surgery, radiotherapy, or second PDT.

Kato and colleagues [18] conducted phase II study of PDT with using talaporfin sodium as a photosensitizer for early central airways lung cancer with longitudinal extension less than 20 mm. Thirty-five patients with 39 lesions were eligible for efficacy evaluation. Complete response was seen in 84.6 % of lesions (82.9 % of patients). Their complete response rate seemed to be slight lower than that of PDT using porfimer sodium. This must be because about 27 % of lesions had longitudinal extension more than 10 mm.

Usuda and colleagues [19, 20] also reported outcome of PDT for early central airways lung cancer. They also used talaporfin sodium. Seventy lesions equal to or less than 10 mm in diameter and 21 lesions more than 10 mm in diameter were identified, and the complete response rates was 94 and 90 %, respectively. Although they did not show survival after PDT, their complete response rate of lesion equal to or less than 1 cm in diameter was comparable to ours.

In summary, at present, two kinds of photosensitizer of PDT are available, and its efficacy seems similar: complete response rate for early central airways lung cancer with 10 mm or less in longitudinal extension is around 95 %. PDT should be considered to be a first-line modality for any patients with early central airways lung cancer having 10 mm or less in longitudinal extension. PDT for those with more than 10 mm in longitudinal extension is still controversial, although its complete response rate is 90 % or lower. For those with more than 10 mm in longitudinal extension, we should compare with other modalities including surgery, brachytherapy, and so on, from the viewpoint of survival and quality of life.

Conclusion

Early central airways lung cancer is detected by sputum cytology at first, and then should be precisely diagnosed and evaluated by WLB and AFB. If it is longitudinal length is 10 mm or less, PDT is a first-line modality. After PDT, a 5-year overall survival of about 80 % and a 10-year overall survival of 70 % can be expected. Most local recurrence can be cured by salvage therapy including surgery, radiotherapy, laser therapy, or PDT. Subsequent primary lung cancer after PDT is the most important issue from the viewpoint of survival.

If an early central airways lung cancer does not meet the criteria for PDT, surgical resection is recommended as the first-line treatment, and 5-year overall survival of about 80 % can be expected. Segmentectomy should be considered because of pulmonary function preservation if a tumor is located at segmental bronchi or beyond it. The frequency of multicentricity in cases of resected early central airways lung cancer is high. And surgical resection is still the most reliable treatment of subsequent primary lung cancer.

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