

Treatment of Early Stage Non-small Cell Lung Cancer*

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Photodynamic therapy (PDT), brachytherapy, electrocautery, cryotherapy, and Nd-YAG laser therapy are therapeutic options available for management of endobronchial malignancies. All of these treatment modalities have been used for both palliation of late obstructing cancers, and more recently have been used as primary treatment of early radiographically occult cancers. We reviewed the evidence for the use of these treatment options in the management of early lung cancer. (CHEST 2003; 123:176S-180S)

Key words: carcinoma *in situ*; cryotherapy; interventional bronchoscopy; lasers; lung cancer; photodynamic therapy

Abbreviation: PDT = photodynamic therapy

The definition of an early stage cancer for discussion in this article will be as follows: a radiographically occult squamous cell carcinoma that is < 2 cm in surface area, appears superficial endoscopically, has clearly visible margins, and has no invasion beyond the bronchial cartilage assessed either by pathologic assessment or by available imaging including high-resolution CT.

MATERIALS AND METHODS

Published guidelines on lung cancer diagnosis and management were identified by a systematic review of the literature and evaluated by the Appraisal of Guidelines for Research and Evaluation method (see Section on Methods and Grading). Those guidelines including recommendations specific to the treatment of early stage lung cancer were identified for inclusion in this section. Supplemental material appropriate to this topic was obtained by literature search of a computerized database (MEDLINE) and review of the reference lists of relevant articles. Recommendations were developed by the section editor and writing committee, graded by a standardized method (see Section on Methods and Grading) and then reviewed by the entire guidelines panel, including the chair and the vice chair. The majority of the reported studies consisted of small-to-moderate case series. Clinical outcomes were defined as response to treatment and included complete, partial, or no response. Complete response is defined as no evidence of disease visually as well as on histology and cytology examination. Some studies also included time to tumor recurrence.

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REVIEW OF DATA

Roentgenographically occult lung cancers can be detected in high-risk patients with either sputum cytology or bronchoscopic inspection. Traditionally, the only treatment available for these cancers was surgical resection. Even though these cancers are small, 70% of cases require a lobectomy, and in the remaining 30%, either a bilobectomy or pneumonectomy is required.¹ There are patients with reduced cardiopulmonary reserve who are not candidates for any of these surgical options. Additionally, 1 to 4% of these patients will have a synchronous lung cancer.² Some studies report up to 15% of newly diagnosed early lung cancer cases have a synchronous lesion.³⁻⁵ The risk of acquiring a second lung cancer is 1 to 25% per year.⁶

Endobronchial therapies that preserve lung function have been developed and include photodynamic therapy (PDT),⁷ brachytherapy, electrocautery,⁸ cryotherapy,⁵ and Nd-YAG laser therapy.⁹ Most radiographically occult cancers, by chest radiograph and CT, are histopathologically squamous cell carcinoma and are located in relatively large central bronchi.¹⁰ The majority of these occult cancers invade the bronchial wall but are not metastatic.¹¹

Early stage squamous cell carcinomas have been defined as lesions that are roentgenographically occult with no evidence of invasion beyond the bronchial cartilage. Depth of intrabronchial invasion is a significant challenge, but bronchoscopic evaluation can provide valuable information regarding depth of invasion. Both the size of the lesion and its topographic appearance may determine the depth of penetration. Lesions < 10 mm in greatest dimension

with only superficial thickening of the epithelium have been reported to invade beyond the bronchial cartilage in < 5% of cases examined. Those with a nodular or polypoid appearance showed invasion in 18% and 27%, respectively.¹²

The time of assessment of complete response reported in published studies varied from 1 to 3 months. A significant proportion of those who had "complete response" acquired recurrent disease on longer follow-up. Therefore, the actual complete response rate is lower. Many trials that assessed the use of PDT in early stage lung cancer included stage I disease in addition to stage 0. These factors have to be taken into account when evaluating the results of published reports. Currently, there has been no good technique for early stage lung cancer detection, and thus there has been no consistent method of treatment.

PDT

PDT is based on the interaction of tumor-selective photosensitizer and laser light. This interaction causes selective death of tumor cells. The majority of clinical data using PDT in early lung cancer has been for treatment of patients who were deemed nonsurgical candidates. The greatest experience has emerged from Japan in the last 2 decades.^{2,7,13-21} One hundred forty-five patients (191 cancers) with early non-small cell lung cancer have been treated with PDT since 1980. This includes 99 patients with stage 0 and 56 patients with stage IA disease. There were 141 men and 4 women. The majority of cases (98%) were squamous cell carcinoma. Complete response was achieved in 86% of lesions, with a recurrence rate of 13%, thereby resulting in a long-term response of 75%. When success of treatment was evaluated according to lesion size, lesions < 1.0 cm had a complete response of 95% and lesions \geq 2 cm had a complete response of only 46%. Treatment success was also related to whether the distal margin of the tumor could be clearly seen bronchoscopically. If the margin was visible, a complete response rate of 92% was achieved, compared to 67% if the margin was not visible. If the lesion was < 1.0 cm and the margin was visible, complete response was achieved in 98% of cases.^{18,19}

Imamura et al³ studied 29 patients (39 cancers) and achieved complete response in 64% of lesions. Recurrence occurred in 36%, giving a long-term response of 41%. On evaluation of lesion size, 72% of lesions that were < 3 cm² achieved a complete response.³ Ono et al²¹ studied 36 patients (39 cancers) and achieved a complete response rate of only 31%, with a recurrence in 33%. Therefore, the long-term response was only 21%.²¹ A number of

smaller studies from Europe and Canada have reported complete response rates of 62 to 91%.²²⁻²⁵ A multicenter investigator-initiated experience was collated and presented to the US Food and Drug Administration for approval of porfimer sodium in the treatment of early superficial squamous cell carcinoma.²⁶ A total of 102 patients with radiologically occult (stage 0, IA, and IB) squamous cell lung cancer were treated. An overall immediate complete response rate of 78% was achieved (95% confidence interval, 7 to 87). Forty-four percent of the patients had recurrent tumor on follow-up, giving a long-term response rate of 43%. The median time to tumor recurrence was 2.8 years (range 0.1 to 10 years). Analysis of the subgroup of the 24 inoperable patients revealed a complete response of 92% (95% confidence interval, 81 to 100%). A similar recurrence rate of 46%, a long-term response rate of 50%, and a median time to tumor recurrence of 2.7 years was observed.

The Mayo Clinic has reported treatment of 58 nonsurgical patients with early lung cancer.²⁷⁻³³ An 84% complete response rate was achieved after one treatment. Nineteen patients (39%) recurred and had a second PDT treatment. The median time to tumor recurrence after the first treatment was 4.1 years. Following the second treatment, 11 patients (22%) had recurrences. The long-term complete response rate was 66%.

PDT as an alternative to surgical resection was studied in 21 patients with small bronchial cancer.³¹ A 71% complete response (15 of 21 patients) was achieved, with 11 patients (52%) maintaining a complete response > 12 months. Patients who did not respond or had recurrence were offered surgery. Of the 10 patients who underwent surgery, 3 patients were found to have N1 disease. Two patients refused surgery. A total of nine patients (43%) were spared surgery.

In summary, PDT is affective in managing small superficial squamous cell carcinoma. The worldwide data showed that patients with early lung cancer treated with PDT achieve a complete response in approximately 75% of cases, with a recurrence rate of approximately 30%. Complete response rates as well as recurrence rates are best when lesions are small (< 1 cm in diameter) and superficial. Experience remains limited using PDT for patients who are surgical candidates.

Recommendations

1. For patients with early superficial squamous cell carcinoma who are not surgical candidates, PDT should be considered as a treatment option. Level of evidence, fair; benefit, moderate; grade of recommendation, B

2. For patients with early superficial squamous cell carcinoma who are surgical candidates, the use of PDT appears to be a promising treatment, but more experience is needed to compare PDT to surgical outcomes. Level of evidence, poor; benefit, none/negative; grade of recommendation, I

ELECTROCAUTERY

Electrocautery is the less expensive treatment for endobronchial tumors. Bronchoscopic electrocautery is the use of high-frequency electrical current that generates heat due to tissue resistance, resulting in destruction of tissue. A small study in early lung cancer of 13 patients (15 cancers) showed a complete response in 80% of lesions with no recurrence at 22 months of follow-up.⁸

Recommendation

3. In patients with early superficial squamous cell carcinoma, electrocautery may be an alternative to PDT for treatment. Level of evidence, poor; benefit, moderate; grade of recommendation, C

CRYOTHERAPY

Cryotherapy is a technique where tissue is destroyed by freezing and is the least expensive for treatment. A recent report included 35 patients (41 cancers) with early stage lung cancer. A complete response was obtained 91% of the patients with a recurrence rate of 28% within 4 years. A long-term response of 63% was achieved, similar to that of PDT.⁵

Recommendation

4. In patients with early superficial squamous cell carcinoma, cryotherapy may be an alternative to PDT for treatment. Level of evidence, poor; benefit, moderate; grade of recommendation, C

BRACHYTHERAPY

Brachytherapy refers to the placement of a radioactive source within or near an endobronchial malignancy to deliver local irradiation. This requires the insertion of an afterloading polyurethane catheter into the airway adjacent to the tumor during fiberoptic bronchoscopy. Iridium 192 is generally used. In two small studies, the use of high-dose brachytherapy in three to six sessions reported response rates similar to PDT.^{34,35} Marsiglia et al³⁴ reported

34 patients with early stage lung cancer with a complete response of 85% seen over 2 years of follow-up. Perol et al³⁵ reported 19 patients with early stage lung cancer with a complete response rate of 83%, which fell to 75% at 1-year follow-up.

Recommendation

5. In patients with early superficial squamous cell carcinoma, brachytherapy may be an alternative to PDT for treatment. Level of evidence, poor; benefit, moderate; grade of recommendation, C

ND-YAG LASER THERAPY

Nd-YAG laser therapy is used for direct thermal ablation of tissue in endobronchial malignancy. It has been used extensively as a palliative measure to relieve airway obstruction. The use of laser treatment for early lung cancer has not been widely studied. A study by Cavaliere et al⁹ showed a complete response rate of 100% in 22 patients with small bronchial cancers. The long-term outcome of these patients was not reported. Yttrium-aluminum-garnet laser therapy is not indicated for tumors that are located in the bronchial wall parallel to the bronchoscope or for tumors involving smaller bronchial branches because of the risk of perforation³⁶ that would occur due to heat sink effect and absorption of heat by the tissue.

Recommendation

6. In patients with early superficial squamous cell carcinoma, Nd-YAG laser therapy is not indicated for treatment. The risk of perforation is very high. Level of evidence, poor; benefit, none/negative; grade of recommendation, I

FOLLOW-UP/SURVEILLANCE

Following treatment, patients should be closely monitored for recurrent disease and development of metachronous lesions. These patients should undergo bronchoscopic examination every 3 to 6 months with both white light and fluorescence bronchoscopy if available. Please refer to the chapter of Follow-up/Surveillance in this guideline publication.

CONCLUSION

PDT is the most extensively studied endobronchial treatment for early lung cancer for patients who are not candidates for surgical resection. Suitable

lesions (< 1 cm) require careful assessment bronchoscopically and radiographically. The data for use of PDT for patients who are surgical candidates appears encouraging. Other endobronchial treatments such as electrocautery, cryotherapy, and brachytherapy are not as well studied, but appear to have similar response rates to PDT. The best response is seen in highly selected patients with small lesions and visible margins.

SUMMARY OF RECOMMENDATIONS

1. For patients with early superficial squamous cell carcinoma who are not surgical candidates, PDT should be considered as a treatment option. Level of evidence, fair; benefit, moderate; grade of recommendation, B
2. For patients with early superficial squamous cell carcinoma who are surgical candidates, the use of PDT appears to be a promising treatment, but more experience is needed to compare PDT to surgical outcomes. Level of evidence, poor; benefit, none/negative; grade of recommendation, I
3. In patients with early superficial squamous cell carcinoma, electrocautery may be an alternative to PDT for treatment. Level of evidence, poor; benefit, moderate; grade of recommendation, C
4. In patients with early superficial squamous cell carcinoma, cryotherapy may be an alternative to PDT for treatment. Level of evidence, poor; benefit, moderate; grade of recommendation, C
5. In patients with early superficial squamous cell carcinoma, brachytherapy may be an alternative to PDT for treatment. Level of evidence, poor; benefit, moderate; grade of recommendation, C
6. In patients with early superficial squamous cell carcinoma, Nd-YAG laser therapy is not indicated for treatment. The risk of perforation is very high. Level of evidence, poor; benefit, none/negative; grade of recommendation, I

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