Long-Term Survival of Patients Treated With Photodynamic Therapy for Carcinoma In Situ and Early Non-Small-Cell Lung Carcinoma

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Purpose: The role of photodynamic therapy (PDT) in the treatment of small cancers has been established in several clinical studies. Here, we report on the efficacy of PDT for early inoperable or recurrent non-small-cell lung cancer (NSCLC).

Methods and Materials: From June 1989 to November 2004, 40 patients with 50 NSCLC were treated with PDT. Twelve cases were inoperable for medical reasons and were staged as T1N0M0, and 28 had recurrent in situ carcinoma. Patients with residual disease after PDT received definitive radiotherapy and/or brachytherapy. Follow-up ranged from 6 to 167 months (median 43.59). Twenty of the 40 patients received i.v. injections of hematoporphyrin derivative (5 mg/kg), the other 20 had injections of porfimer sodium (Photofrin, 2 mg/kg). An argon dye laser (630 nm wavelength, 200–300 J/cm²) was used for light irradiation in 24 of the 40 patients, a diode laser (Diomed, 630 nm wavelength, 100–200 J/cm²) in the other 16.

Results: PDT obtained a 72% complete response (CR) rate (36/50 treated lesions), that is 27 CR among the 37 Tis carcinomas and 9 among the 13 T1 cases. Kaplan–Meier curves showed a mean overall survival (OS) of 75.59 months (median 91.4 months). Two- and 5-year OS rates were 72.78% and 59.55%. The mean and median survival rates for patients with Tis stage were 86.5 and 120.4 months, respectively (standard error 9.50) and for patients with T1 disease they were 45.78 and 35.71 months, respectively; the difference was statistically significant (P = 0.03). No severe early or late PDT-related adverse events were recorded.


Key words: non-small-cell lung cancer; photodynamic therapy; hematoporphyrin derivative; photofrin

INTRODUCTION

Non-small-cell lung cancer (NSCLC) is a major cause of neoplasia-related death, with an estimated incidence of 100 new cases per 100,000 population a year [1]. Although surgery is considered the only curative measure, about half of all newly diagnosed cases are inoperable for medical or technical reasons [2]. Combined radio- and chemo-therapy is thought to offer a 10–30% 2-year survival and cure rates ranging between 2% and 10% [3–5].

Recurrent disease after surgery is treated mainly with radiotherapy and/or chemotherapy. Endoscopic surveillance of operated patients often reveals small recurrent tumors or even in situ carcinomas, sometimes amenable to conformal radiotherapy or endobronchial brachytherapy. Photodynamic therapy (PDT) is a promising alternative treatment option for small tumors of the genitourinary tract, lung or head–neck area [6,7].

The present retrospective study reports on a series of patients with early inoperable or recurrent NSCLC who were treated with PDT.

MATERIALS AND METHODS

The study included patients with early (T1N0M0) NSCLC who were inoperable for medical reasons and patients with recurrent carcinoma in situ after previous treatment with surgery, RT or Nd:YAG laser therapy, seen from June 1989 to November 2004.

The initial work-up consisted of a complete history and physical examination, chest X-ray, computed tomography (CT) scan and bronchoscopy, abdominal CT scan, ECG, and interview with the anesthesiologist. Autofluorescence bronchoscopy (ABF) with the SAFE system was introduced in 1999. Laboratory tests included blood cell counts and blood chemistry, including serum electrolytes, serum creatinine, AST, ALT, alkaline phosphatase, bilirubin, and urinalysis.

All patients were staged according to the lung cancer staging system of International Union Against Cancer (UICC).
Twenty-six patients (26/40) had previously undergone resection surgery for invasive lung cancer; most bronchoscopies were performed during post-operative follow-up and ABF (used from 1999 onwards) identified 28 recurrent in situ carcinomas.

Twelve of the 40 patients were inoperable for medical reasons, that is respiratory function impairment due either to chronic obstructive lung disease or to resection of their primary lung cancer.

Four of the 40 patients had previously been treated with the Nd:YAG laser, 4 had been given RT, and 4 had received no prior treatment.

The 40 patients had treatment for 50 lesions in all, 37 of which (in 28/40 patients) were staged as Tis and 13 (in 12/40 patients) as T1 carcinomas; tumor size was 0.5–1 cm in 48 lesions and 1–2 cm in 2.

Depth of invasion was assessed on the strength of the biopsy and the negativity of the CT scan. Lesions larger than 2 cm were excluded.

**PDT Protocol**

Eligibility criteria were as follows:

- Age 18–65 years.
- Sex M/F.
- Histology squamous cell carcinoma.
- Stage Tis and T1.
- Tumor size ≤2 cm.
- Single and multiple lesions.
- Prior chemo- or radio-therapy, or surgery.
- Inoperability for medical reasons.

The protocol was approved by the Hospital Ethical Committee on clinical studies and informed consent was obtained from all patients taking part.

**PDT**

Hematoporphyrin derivative (5 mg/kg) (20/40 patients) or Photofrin II (2 mg/kg) (20/40 patients) were administered by slow i.v. infusion 48 hours before the laser treatment. Patients were hospitalized in a room with windows equipped with special screens. The light sources used in this study were an argon dye laser (in 24/40 patients) to obtain a red wavelength of 630 nm and a power of 300–800 mW (median 500 mW) and a diode laser (in 16/40 patients) to obtain a red wavelength of 630 nm and a power of 400 mW/cm. The estimated energy dose delivered ranged from 100 to 300 J/cm² (output fluence rate measured in air) in most cases.

The light was aimed at the lesion through optical microlens fibers so that the lesions were uniformly illuminated by a circular spot. The distal tip of the fiber was kept between 1.0 and 1.5 cm away from the surface of the tumor.

Tumor necrosis and fibrin clots usually obstruct the bronchus after PDT, so patients underwent bronchial toileting 24 hours after PDT to prevent any obstructive pneumonia. The repetition of the treatment was planned but rarely implemented and only in the case of a partial reaction being observed in the 24–48 hours after the first treatment. Patients were allowed to return home and were strongly advised to avoid exposure to the sunlight for 30 days.

Endoscopy was repeated 40 days after PDT to assess response, enabling direct examination, and the collection of biopsies. Chest CT scan was also repeated.

**Tumor Response to PDT**

Tumor response to PDT was evaluated histologically and by flexible fibroscopy and CT scan. Response was judged as: complete (CR), where there was no evidence of the lesion at endoscopy or CT and histology was negative; partial (PR), showing a more than 50% shrinkage of the lesion at endoscopy, but persistent cancer at biopsy; or no response (NR), that is a less than 50% reduction in tumor size, or stable or progressive disease.

**Statistical Analysis**

The SAS system (SAS Institute, Inc., Cary, NC) was used for statistical analysis and to generate survival curves. Fisher's exact test was used to test the differences between categorical variables.

Survival curves were plotted using the Kaplan–Meier method. P-values of ≤0.05 were considered statistically significant.

The Log Rank-test was used to compare two survival curves and local relapse-free survival (LRFS) for the Tis and T1 lesions.

**Post-PDT/Follow-Up Protocol**

Patients with a CR (histologically confirmed) after 1 or 2 courses of PDT were monitored by endoscopy every 3 months for the first year and every 4 months thereafter, and were given no further treatment. They also had chest and upper abdomen CT scan, and full blood counts and biochemical tests every 4–6 months. If recurrent disease was identified by endoscopy, patients were treated with RT and/or brachytherapy (HDR-BT).

Previously non-irradiated patients with a PR or NR after 2 PDT applications received external beam radiotherapy (ERT) using a 6-MV linear accelerator. A total radiation dose of 44 Gy (standard fractionation 2 Gy/fraction, 5 fractions/week) was delivered to the tumor and mediastinum using three or four fields, depending on the results of computerized treatment planning. Booster fields were used to increase the radiation dose to 64 Gy at the tumor. Patients were monitored regularly by endoscopy and chest and upper abdomen CT scan (every 3 months for the first year and every 4 months thereafter).

High-dose rate brachytherapy (HDR-BT) was used for treatment after PDT in patients who relapsed or had residual disease. Endobronchial irradiation was performed using a 192Ir source projector. Patients received 6–7 fractions of 500 cGy at 10 mm from the center of the applicator, once a week.

Chemotherapy and/or palliative care were offered to previously irradiated patients and those with metastatic disease.
The follow-up period for the forty patients ranged from 6 to 167 months (median 43.59 months).

RESULTS

The characteristics of the eligible patients are listed in Table 1.

Table 2 shows the tumor responses to PDT, stratified by stage and type of recurrence.

Of the 50 carcinomas treated, 36 (72%) had a CR, 10 (20%) had a PR, 3 had NR (6%) after initial PDT, and 1 was inaccessible (lost to follow-up).

Of the 36 CR, 27 were stage Tis, and 9 were T1. There was no statistically significant difference in the response to PDT in relation to the stage of disease ($P = 0.91$ with the Chi-square test; $P = 0.90$ with the Fisher’s exact test).

Of the 36 carcinomas achieving a CR, 13 (36%) recurred locally from 3 to 108 months after initial PDT Figure 5. Among the 10 carcinomas (in 7 patients) achieving a PR, there were 5 cases of disease progression after initial PDT.

CR was achieved in 27/37 lesions treated in the 28 patients in stage Tis, but 11 of these relapsed (in 10 patients); 17 of the 28 patients are alive, 11 have died.

CR was achieved in 9/13 lesions treated in the 12 patients in stage T1, but 2 patients suffered a relapse; 4 of the 12 T1 patients are alive, while 8 have died.

The 12 patients (13 cancers) with recurrent disease were treated as follows (Table 3):

- 1 repeated PDT obtaining a CR, then relapsed again after 5 months and underwent HDR-BT and is alive;
- 1 repeated PDT then had ERT and is alive;
- 1 repeated PDT, then died of disease progression and a second head and neck cancer;
- 1 was lost to follow-up;
- 1 underwent upper left lobectomy and is alive;
- 1 died of systemic cerebral and hepatic disease progression;
- 1 was treated with Nd:YAG laser and ERT, obtaining a CR, then relapsed again and died;
- 1 was treated with HDR-BT and died of a second gastrointestinal cancer;
- 1 was treated with HDR-BT then died of interstitial lung disease (without cancer);
- 2 were treated with HDR-BT and are alive and in CR;
- 1 was negative for disease at the next follow-up.

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- 1 underwent upper left lobectomy and is alive;
- 1 died of systemic cerebral and hepatic disease progression;
- 1 was treated with Nd:YAG laser and ERT, obtaining a CR, then relapsed again and died;
- 1 was treated with HDR-BT and died of a second gastrointestinal cancer;
- 1 was treated with HDR-BT then died of interstitial lung disease (without cancer);
- 2 were treated with HDR-BT and are alive and in CR;
- 1 was negative for disease at the next follow-up.

### Table 1. Characteristics of Patients and Their Disease

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Sex (male/female)</th>
<th>Number of carcinomas</th>
<th>Histology, squamous cell</th>
<th>Stage of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>65</td>
<td>39/1</td>
<td>50</td>
<td>50</td>
<td>TisN0M0 37 (28 patients)</td>
</tr>
<tr>
<td></td>
<td>50–78</td>
<td></td>
<td></td>
<td></td>
<td>T1N0M0 13 (12* patients)</td>
</tr>
<tr>
<td>Location of tumor</td>
<td>Trachea</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carina</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stump</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Main bronchus</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other bronchus</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous therapy</td>
<td>Lobectomy/pneumonectomy</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT ± other</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yag laser ± other</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*Inoperable for medical reasons.

### Table 2. Response to Initial PDT

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of carcinomas</th>
<th>CR (72%)</th>
<th>PR (20%)</th>
<th>NR (6%)</th>
<th>NV (2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>40</td>
<td>50 (100%)</td>
<td>36</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Photofrin II</td>
<td>20</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HpD</td>
<td>20</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tis* (28 patients)</td>
<td>28</td>
<td>37</td>
<td>27*</td>
<td>7*</td>
<td>2</td>
</tr>
<tr>
<td>T1 (12 patients)</td>
<td>12</td>
<td>13</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Light source</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argon dye laser</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diode laser</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression of disease</td>
<td></td>
<td>2</td>
<td>5*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*2 Relapses.
\*11 Relapses.
Seven patients achieved 10 PR after initial PDT and were subsequently treated as follows (Table 4):

- 2 had ERT, obtaining a CR, and both are alive and disease-free;
- 1 had HDR-BT, obtaining a CR and is alive;
- 1 repeated PDT, then had Nd:YAG laser, but died of disease progression;
- 1 repeated PDT, then had HDR-BT, obtaining a CR, then died of gastrointestinal cancer;
- 1 (who had already been given chemo- and radio-therapy) repeated PDT then died of disease progression;
- 1 was treated with the Nd:YAG laser, then HDR-BT, obtaining a CR, but died of a second cancer.

One-, 2-, [8]-year overall survival (OS) rates in the 40 patients were 92.03%, 72.78%, and 59.55%, respectively. The mean OS was 75.5 months, median 91.4 months. The survival curves are shown in Figure 1.

The 36 lesions in CR achieved a mean LRFS of 74.26 months (standard error 8.34), with 1-, 2-, and 3- to 5-year LRFS rates of 77.7%, 74%, and 65%, respectively. The related curve is shown in Figure 3a.

The mean LRFS was 72.14 months for Tis cases and 8.37 months for T1 carcinomas ($P = 0.54$). The curves are shown in Figure 3b.

Toxicity
No severe early or late PDT-related sequelae were noted. PDT was well tolerated by all patients. There were no cases of tissue necrosis or perforation related to the PDT or

### Table 3. Patients With Recurrent Disease Were Treated as Follows

<table>
<thead>
<tr>
<th>NR 12 Patients</th>
<th>II PDT</th>
<th>Response</th>
<th>Other therapy</th>
<th>Response</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>CR</td>
<td>HDR-BT 35 Gy/7 f</td>
<td>CR</td>
<td>Alive</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>PR</td>
<td>ERT</td>
<td>CR</td>
<td>Alive</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>PR</td>
<td>Nd:YAG</td>
<td>Pro</td>
<td>Dead</td>
</tr>
<tr>
<td>1</td>
<td>No</td>
<td>—</td>
<td>Surgery (upper left lobectomy)</td>
<td>—</td>
<td>Alive</td>
</tr>
<tr>
<td>1</td>
<td>No</td>
<td>—</td>
<td>Nd:YAG + HDR-BT 60 Gy/30 f</td>
<td>CR</td>
<td>Dead</td>
</tr>
</tbody>
</table>

- No severe disease.
- Negative for disease at the next follow-up.

### Table 4. Seven Patients Achieved Partial Response After Initial PDT Were Subsequently Treated as Follows

<table>
<thead>
<tr>
<th>NR 7 patients</th>
<th>II session</th>
<th>PDT</th>
<th>Response</th>
<th>Other therapy</th>
<th>Response</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>No</td>
<td>—</td>
<td>ERT</td>
<td>HDR-BT 30 Gy/6 f</td>
<td>CR</td>
<td>Alive</td>
</tr>
<tr>
<td>1</td>
<td>No</td>
<td>—</td>
<td>HDR-BT</td>
<td>CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>PR</td>
<td>Nd:YAG</td>
<td>Pro</td>
<td>Dead</td>
<td>Progression</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>PR</td>
<td>HDR-BT 30 Gy/6 f</td>
<td>CR</td>
<td>Dead</td>
<td>Gastrointestinal cancer</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>NC</td>
<td>—</td>
<td>Pro</td>
<td>Dead</td>
<td>Disease progression</td>
</tr>
<tr>
<td>1</td>
<td>No</td>
<td>—</td>
<td>Nd:YAG + HDR-BT 30 Gy/6 f</td>
<td>CR</td>
<td>Dead</td>
<td>Second cancer</td>
</tr>
</tbody>
</table>

- Who had already been given chemio- and radio-therapy.
Fig. 1. Kaplan–Meier curve for overall survival of 40 NSCLC patients treated with photodynamic therapy. The survival rates were 92.03% at 1 year, 72.78% at 2 years, 59.55% at 5 years. Mean overall survival was 75.5 months, median 91.4 months. [Figure can be viewed in color online via www.interscience.wiley.com.]

Fig. 2. Survival (S) for 28 patients with Tis disease at 1, 2, and 5 years was 92.7%, 81%, and 67%, respectively (Log-Rank test $P = 0.03$). Mean and median survival was 86.5 and 120.4 months (standard error 9.5). Survival for 12 patients with stage T1 disease at 1, 3, and 5 years was 90%, 50%, and 37.5%. 
Fig. 3. a: Disease-free survival (DFS) curves for 36 cancers in CR after photodynamic therapy. Mean DFS was 74.26 months (standard error 8.34); LRFS at 1, 2, and years was 77.7%, 74%, and 65%, respectively. b: Disease-free survival curves for 36 carcinomas in CR after photodynamic therapy divided by stage (T1 and Tis) $P = 0.54$. The mean DFS was 72.14 months for Tis and 8.37 months for T1 carcinomas.
subsequent radiotherapy. Grade 1 photosensitivity-related skin toxicity was observed in one patient (2.3%). There were no cases of allergic reaction to the photosensitizer.

DISCUSSION

Surgical resection is the first treatment of choice for patients with early stage lung cancer if their general and oncological condition permits. Early stage cancer is defined as a radiographically occult squamous cell carcinoma <2 cm in surface area, appearing superficially at endoscopy with clearly visible margins, with no invasion beyond the bronchial cartilage at histological assessment or available imaging, including high-resolution CT (HR-CT) [8]. A recent study on 9 patients with carcinoma in situ indicated that about half of such lesions evolve into invasive lung cancer within 6 months of follow-up [9]. Lesions <10mm in greatest dimension with only superficial thickening of the epithelium have been reported to invade beyond the bronchial cartilage in <5% of cases [10]. The accuracy of the initial evaluation of the lesion's extent and depth is unquestionably fundamental to obtaining a better, more durable clinical response to treatment. Hence the importance of new endobronchial staging methods, such as endobronchial ultrasonography (EBUS) [11,12], which provides more accurate information on the depth of tumor invasion than conventional bronchoscopy or HR-CT. Fluorescence bronchoscopy using blue light (440 nm wavelength)
can enhance diagnostic accuracy and the definition of the extent of early cancer [13].

We used ABF with the SAFE system from 1999 onwards to follow up patients who had already undergone surgery, as these techniques are also useful for the early diagnosis of recurrences in the bronchial or resection region, or new foci of disease.

Patients who have already been operated and have limited pulmonary reserves require conservative endobronchial treatment to avoid further reducing their residual respiratory function. Among such treatments, PDT has been the most extensively studied.

Patients who have refused surgery or are in poor general condition, and those who have localized and oncologically early disease, or who relapse after surgery can all be offered various endobronchial treatments, for example PDT, Nd:YAG laser, electrocautery (EC), cryotherapy or brachytherapy [14]. There is no evidence-based consensus on the relative merits of each of these procedures.

Central type early stage lung cancer ≤10 mm in diameter shows almost 100% CR rates to PDT. Furukawa et al. [15] report CR and 5-year survival rates for patients with lesions <1.0 cm of 92.8% (77/83 patients) and 57.9%, respectively, and there was a significant difference ($P < 0.001$) in the efficacy of PDT in terms of response and recurrence between lesions < or > 1 cm.

To reduce the recurrence rate, it is essential to ascertain the extent and depth of the bronchogenic carcinoma accurately before performing PDT.

In a review article based on a meta-analysis, Mathur et al. [8] reviewed the evidence on the use of PDT or Nd:YAG laser and EC, cryotherapy, and brachytherapy as treatment options for early lung cancer. They used a grading system for treatment recommendations, indicating PDT as grade B, EC, brachytherapy, and cryotherapy as grade C, and Nd:YAG laser therapy as the least recommended treatment.

Data in the literature suggest that the best rate of response is achieved in tumors <1 cm in size [16,17]. In patients with intraepithelial disease, PDT offers results that match those of surgical resection [18,20].

PDT has been successfully applied to the direct, endoscopic or interstitial treatment of various malignancies. In 1991, Okunaka et al. reported on a large series of 145 lung cancer patients treated with PDT [19]: the mean survival was 38 months, which compares favorably with the results of radiotherapy.

A small study from the Netherlands Cancer Institute, using i.v. Photofrin II, showed a CR in 10/11 patients with stage I NSCLC [21].

Edell and Cortese [14] confirmed an impressive CR rate (13/14 cases) obtained in tracheobronchial tumors treated with hematoporphyrin-derivative phototherapy.

In 1993, a phase II study conducted by the Japan Lung Cancer PDT Study Group on 59 lung carcinomas treated with photofrin II PDT recorded a CR in 50/59 cases, the median duration of which was 14.0 months [22].

Several issues remain to be solved, however, such as the most suitable indications for PDT, the use of photosensitizing agents other than porfimer sodium, or the comparison of PDT with other endobronchial therapies, such as EC, brachytherapy, cryotherapy, or its association with HDR-BT or ERT.

Animal cell culture studies indicate a potential synergistic effect of combining PDT with ionizing radiation, but the latter affects tissue vascularization and an impaired perfusion of the tumor might result in a lower uptake of sensitizes and have a negative fallout on the effectiveness of PDT [23,24].

There are few reports of studies on the association between PDT and HDR-BT or ERT.

A pilot study on PDT in patients with inoperable NSCLC achieved an objective response rate of 85% (22/26). All the patients involved had received ERT, Nd:YAG laser or brachytherapy before PDT [21]. Freitag et al. reported on their experience of sequential PDT and HDR-BT for bulky endobronchial tumors in 32 patients with limited, technically inoperable or recurrent bronchogenic carcinomas. The combined treatment obtained a complete histological response rate of 97% (31/32) and 75% already after initial PDT. Cancer recurred in 19% of cases. There were no severe complications, such as hemoptysis, fistulas or post-obstructive pneumonia [25].

Imamura’s experience concerns 29 patients treated with initial PDT with or without ERT for occult lung cancer.

The initial PDT achieved a CR in 25/29 of the cancers (64%); 10 of the 14 initially failing to do so subsequently became CR after RT, yielding an overall CR rate of 89.7% [26].

In the present study, we obtained a high CR rate for in situ lesions (72%). The CR rate for early primary T1 NSCLC was 69%, which was comparable with the response rates recorded in previous studies, but lower than in Tis cases. It may be that the development of intratumoral hypoxia during invasive tumor growth counteracts the efficacy of PDT. Indeed, in an earlier study, we found that hypoxia-related gene expression is linked to resistance to PDT [27].

Our findings confirm the data in the literature, according to which patients treated with PDT reach a CR in approximately 75% of cases, with a long-term CR rate of 66% and a recurrence rate of approximately 30%, with a statistically significant correlation between cancer stage and survival. Our study also revealed a statistically significant difference between stage and survival.

In our 40 patients, overall survival (OS) at 1 and 5 years was 92.03% and 59.55%, respectively, with a CR in 72% of cases.

The overall 5-year survival for our patients with T1 and Tis disease was 37.5% and 67%, respectively, revealing a statistically significant difference ($P = 0.03$).

Ono et al. [27] described a series of cases who had less than CRs to PDT and subsequently received ERT: these patients showed no evidence of local recurrence after PDT had been combined with radiotherapy; the 5-years survival of the patients treated with PDT and ERT was 41.2%. One of the problems with ERT is that, like surgical resection, it reduces the functioning lung parenchyma.
Intraluminal radiation therapy may be effective in combination with PDT for patients who have either already received maximum ERT or whose lung function makes ERT unfeasible.

In conclusion, PDT can be used with impressive success rates in early stage inoperable lung carcinomas. Combining PDT with subsequent radiotherapy emerges as a promising therapeutic option for patients who are inoperable for medical reasons. Given its very high efficacy and lack of collateral toxicity, endoluminal PDT should be incorporated in the standard care of patients with in situ carcinoma recurring after surgery.

The natural history of early stage lung cancer, the risk of multifocal synchronous or metachronous lesions and, above all, the need for conservative treatments for patients with limited pulmonary reserves all justify endobronchial treatments. Several issues remain to be clarified, however, such as the most suitable indications for PDT, the use of photosensitizing agents other than porfimer sodium, and the comparison of PDT with other endobronchial therapies, such as brachytherapy or cryotherapy.

We believe that combining radiotherapy or brachytherapy with PDT can offer the best chance of long-term survival for inoperable patients.

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