Photodiagnosis and Photodynamic Therapy (2014) 11, 259—264

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/pdpdt

Preoperative endobronchial photodynamic therapy improves resectability in initially irresectable (inoperable) locally advanced non small cell lung cancer

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Available online 3 April 2014

KEYWORDS
Photodynamic therapy;
Endobronchial;
Neoadjuvant;
Chemotherapy;
Non-small cell lung cancer

Summary

Objectives: This report describes the result of prospective randomized trial to assess effectiveness and safety of neoadjuvant photodynamic therapy (PDT) and chemotherapy as well as possibility for further surgery for locally advanced NSCLC.

Methods: Patients with stage IIIA and IIIB central NSCLC (main bronchus/distal trachea involvement) who were not initially eligible for surgery but might be considered as surgery candidates after neoadjuvant therapy were enrolled in the study. They were randomized to either neoadjuvant chemotherapy and endobronchial PDT or chemotherapy alone followed by surgical resection. PDT was done with photosensitizer agent chlorine E6 and 662 nm laser light before each of the three courses of chemotherapy.

Results: From January 2008 to December 2011, 42 patients were assigned to PDT arm ($n = 21$) and No-PDT arm ($n = 21$). Groups were similar with respect to age, sex, tumor stage, and histology. No PDT major complications were observed. After neoadjuvant treatment partial response revealed in 19 pts (90%) in PDT arm and 16 pts (76%) in No-PDT arm ($p = 0.460$), these patients underwent thoracotomy. After thoracotomy tumor was unresectable in 3 pts of No-PDT arm (19%). There were 14 pneumonectomies and 5 lobectomies in PDT arm vs. 10 pneumonectomies and 3 lobectomies in No-PDT arm. Completeness of resection was significantly higher in PDT arm (R0-89%, R1-11%) vs. No-PDT arm (R0-54%, R1-46%), $p = 0.038$.

Conclusions: The study demonstrated that neoadjuvant PDT along with chemotherapy is effective, safe and it makes possible to convert to surgery candidates and to improve resection completeness in stage III central NSCLC patients.

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http://dx.doi.org/10.1016/j.pdpdt.2014.03.011
1572-1000/

Introduction

Lung cancer is well recognized as the most common cause of cancer-related death [1].

Surgery in this condition has traditionally been regarded as the mainstay of treatment and the only curative modality aimed at local-regional control of the disease. The use of surgery has been limited in many patients who present with locally advanced disease. Over the last 20 years preoperative chemotherapy has been increasingly used to downstage the tumor and enhance its respectability. Although there is no convincing evidence at present that preoperative chemotherapy is able to convert initially irresectable and/or inoperable tumor into one amendable to surgical resection. However since 1990s, multiple clinical trials of neoadjuvant chemotherapy showed mild improvement in survival vs. only surgical methods [2—6]. From that point of view photodynamic therapy represents an attractive additional modality to achieve preoperative downgrading of the tumor with the aim to facilitate its respectability. For example, two Japanese [7,8] and one American [9] study demonstrated that preoperative photodynamic therapy (PDT) can lead to less extensive pulmonary resections. These studies included small number of patients and did not comment on radicality of surgery.

The therapeutic effect of PDT is based on selective accumulation of photosensitizing agents (PSA) in cancer tissue. Subsequent irradiation of the neoplastic lesion with the light of wavelength that lies within PSA absorption range results in release of singlet oxygen with structural alteration and necrosis of the tumor [10,11]. Since the US Food and Drug Administration approved PDT for the treatment of microinvasive endobronchial non-small cell lung cancer in early 1998 and advanced partially obstructing endobronchial lung cancer in late 1998 [12], there has been increasing interest in using PDT alone or in combination with standard therapeutic or palliative modalities to treat NSCLC [13].

The aim of this study was to assess effectiveness of neoadjuvant endobronchial PDT when combined with chemotherapy in downgrading of the tumor and facilitating surgical resection of locally advanced and initially irresectable and inoperable NSCLC.

Materials and methods

Study design

The study was designed as a prospective randomized trial comparing preoperative endobronchial PDT combined with chemotherapy and preoperative chemotherapy alone in downgrading IIIA and IIIB NSCLC (7th edition TNM classification).

Eligibility criteria

To be eligible for the trial, patients had to fulfil the following criteria: ≥18 years of age, tumor involvement of distal trachea, one or both main bronchi, irresectabe tumor on the basis of initial staging investigations as well as potentially resectable tumor in patients with poor pulmonary function precluding intervention. Staging investigations were accomplished by bronchoscopy, computerized tomography (CT) and mediastinoscopy if the latter showed pathologically enlarged (more than 1.0 cm) regional lymph nodes. PET-CT scan was used selectively to exclude distant metastases. The presence of invasive malignancy was confirmed histologically in all patients. Standard assessment of the pulmonary function was carried out including spirometry and DLCO.

Treatment plan

Patients with pretreatment stage IIIA and IIIB central NSCLC were randomly assigned to either preoperative endobronchial PDT and chemotherapy followed by surgery (PDT arm) or preoperative chemotherapy alone followed by surgery (No-PDT arm). Chemotherapy regimen consisted of paclitaxel (200 mg/m^2 IV for 3 h) and carboplatin (AUC < 6, IV, for 1 h) every 21 days for three cycles. The dose of each chemotherapy agent was modified depending on observed toxicity.

PDT involved intravenous administration of PSA: water-soluble chlorine E6 complex (Radachlorin®; Rada-Pharma, Russia) over 30 min in the dose of 1 mg kg^{-1} followed by endoluminal irradiation of the tumor with 662 nm laser light. Laser beam was delivered via cylindrical fibro-optic cable placed into the affected bronchial tree under local anesthetic using flexible bronchoscope. Irradiation commenced in 2 h after PSA administration up to a total dose of 150 J/cm^2, 24—48 h prior to the each chemotherapy cycle.

Response

The response to neoadjuvant treatment was assessed in two weeks of its completion using the same diagnostic modalities with exception of mediastinoscopy.

Radiological response was evaluated using RECIST [14]. Endoscopic response was defined as complete (CR) if no luminal tumor was evident, partial — if 50% reduction in tumor length or degree of bronchial obstruction was observed, no response — if tumor remained unchanged or increased in size.

Surgery

Surgical treatment was offered to patients with positive (complete or partial) response to neoadjuvant therapy within three to six weeks after the last cycle.

Statistical analysis

The ratio of qualitative indicators in groups was assessed by Fisher's exact test. A p-value less than 0.05 was considered statistically significant.

Results

From January 2008 to December 2011 42 patients (36 male and 5 female; median age 66 years, range 43—86 years), were included. 21 were randomized to the PDT arm and 21 — to the No-PDT arm. There was no significant difference

Table 1 Baseline patient characteristics.

	PDT arm ($n=21$)	No-PDT arm ($n=21$)	p-Value
Mean age, years	62 ± 11	59 ± 12	
Sex, male:female	17:4	19:2	0.663
General performance (ECOG) 0:1:2	15:4:2	13:7:1	0.744
Clinical stage, IIIA:IIIB	8:13	9:12	1.0
Squamous: adenocarcinoma	14:7	16:5	0.733

Table 2 Reason of irresectability or inoperability at the time of diagnosis.

	PDT arm ($n=21$)	No-PDT arm ($n=21$)
T4 (trachea)	9 (43%)	10 (48%)
Functional intolerance to pneumonectomy	6 (29%)	4 (19%)
T4 (mediastinum)	2 (10%)	4 (19%)
Multiple N2	2 (10%)	3 (14%)
N3	2 (10%)	–

between two groups in respect of age, sex, tumor stage, and histological characteristics (Table 1).

The reasons why patients were considered unsuitable for surgical resection at the time of initial presentation are summarized in Table 2. There were: the tumor spread to the trachea (19), as well as intolerance to pneumonectomy (10). Six patients had CT signs of great vessels invasion. The remaining 7 patients had metastases in mediastinal lymph nodes proved by mediastinoscopy. In total mediastinoscopy was performed in 24 patients, N2 disease was diagnosed in 10, N3 — in 2 patients.

Tumor was localized the right main bronchus in 12 (29%) patients, left main bronchus — in 11 (26%), tracheal bifurcation — in six (14%) and distal tracheal segment — in 13 (31%) patients. 12 (29%) patients had complete occlusion of the main bronchus with atelectasis of the affected lung.

The mean level of FEV1 was 69 ± 17% predicted in PDT arm and 71 ± 19% predicted in No-PDT arm. All functionally inoperable patients (6 in PDT arm and 4 in No-PDT arm) were candidates for pneumonectomies. In these patients the level of FEV1 was 29 ± 6% predicted (from 19% to 37%), DLCO — 52 ± 9% predicted (from 41% to 78%) in PDT arm and 27 ± 4% predicted and 56 ± 5% predicted in No-PDT arm, respectively.

The average duration of PDT session to reach the desired radiation dose was 11.5 min (range from 9 to 14). Complications of PDT were observed in 2 (10%) out of 21 irradiated patients who developed hemoptysis. This complication was regarded as minor and did not require hospital admission. None of the patients had abnormal cutaneous or retinal reaction which could have been attributed to photosensitivity.

Planned chemotherapy was completed in 36 (86%) patients. In six patients (14%) (three in each group) it had to be discontinued due to the either toxicity ($n=5$) or disease progression with the development of distant metastases ($n=1$). Less severe adverse effects such as neutropenia occurred in 26% (28% in PDT arm and 24% in No-PDT arm), anemia and thrombocytopenia (6 patients) did not interfere with chemotherapy regimen.

The observed response of tumor to neoadjuvant treatment is outlined in Table 3. 35 (83%) patients had partial response (19 (90%) in the PDT arm and 16 (76%) in No-PDT arm). Patients in PDT arm had higher rate of partial radiological ($p=0.158$) and endoscopic ($p=0.249$) response, although the difference between two groups failed to reach statistical significance. Fewer patients had no response in the PDT arm.

The mean level of FEV1 improved insignificantly after neoadjuvant treatment in 10 initially inoperable patients in both groups. In PDT arm it has increased by 10% (from 29 ± 6% predicted to 32 ± 12% predicted) and in No-PDT arm — by 7% (from 27 ± 4% predicted to 29 ± 6% predicted). The level of DLCO also remained unchanged. It was more important that 8 of these 10 patients (5 in the PDT arm and 3 — in the No-PDT one) unfit for pneumonectomy due to poor pulmonary function were able to have lobectomies instead due to tumor disappearance from main bronchus (Fig. 1).

Post-treatment bronchoscopy showed complete disappearance of the tumor in seven patients after PDT (33%) and only two without PDT treatment (10%) ($p=0.054$). Of importance in planning the extent of subsequent resection, neoadjuvant treatment led to complete recanalisation of trachea with no visible tumor in 16 out of 19 patients who had initial tracheal involvement (nine out of nine (100%) of PDT arm and seven out of 10 (70%) of No-PDT arm, $p=0.124$).

In two patients with N3 disease contralateral mediastinal lymphadenopathy has resolved in the PDT arm.

In accordance with the trial protocol 19 patients in PDT arm and 16 in No-PDT arm had sufficient response and proceeded with the surgical treatment. In 32 patients resection of the tumor proved possible and in the remaining three cases procedure was limited to explorative thoracotomy only (Table 4).

Preoperative PDT allowed significantly higher proportion of patients to be offered radical (R0) resection in comparison with No-PDT arm in 17 of 19 (89%) patients vs. seven of 16 patients (54%) ($p=0.038$). Histological analysis of the pattern of microscopically incomplete excision (R1) invariably showed the residual disease in the bronchial stump in no other surrounding structures. There were no cases of macroscopically incomplete resection (R2).

Potential influence of combined chemotherapy and PDT on the extent of subsequent resection was analyzed as a secondary endpoint. Both PDT and No-PDT neoadjuvant treatment regimens led to less extensive resections (lobectomy instead of pneumonectomy and pneumonectomy instead of carinal pneumonectomy) reducing surgical risks. Four of 8 patients who underwent lobectomy instead of pneumonectomy had microscopically incomplete resection — one patient of the PDT arm (20%) and all patients (100%) of the No-PDT arm ($p=0.142$).

Intraoperative frozen section of bronchial margin was done in six from eight patients with further established

Table 3 Radiographic and endoscopic responses to preoperative treatment.

Response	Radiographic		Endoscopic	
	PDT arm ($n=21$)	No-PDT arm ($n=21$)	PDT arm ($n=21$)	No-PDT arm ($n=21$)
Complete	0	0	7 pts (33%)	2 pts (10%)
Partial	19 pts (90%)	16 pts (76%)	13 pts (62%)	16 pts (76%)
No response	2 pts (10%)	5 pts (24%)	1 pt (5%)	3 pts (15%)

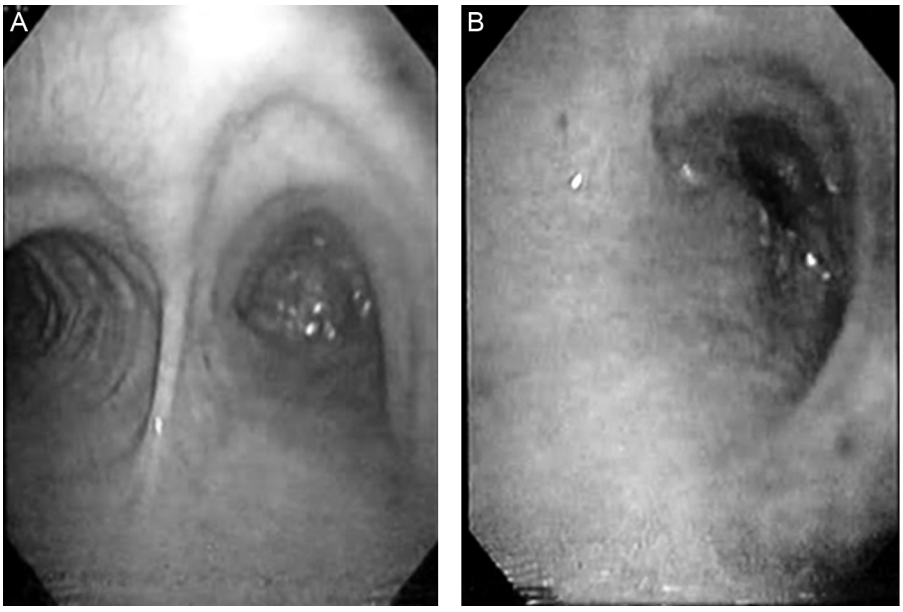

Figure 1 (A) Complete tumor occlusion of the right main bronchus. (B) Tumor disappeared from the right main bronchus after neoadjuvant PDT and chemotherapy.

Table 4 Surgical procedures and complete resection rates.

	PDT arm ($n=21$)	No-PDT arm ($n=21$)	p-Value
Resections	19 (90%)	13 (62%)	
Pneumonectomy	14	10	
Lobectomy	5	3	
Exploratory thoracotomy	0	3 (14%)	0.086
No thoracotomy	2 (10%)	5 (24%)	0.158
Radicality			
R0 (% of resections)	17(89%)	7 (54%)	0.038
R1 (% of resections)	2 (11%)	6 (46%)	

R1 resection. Expedited evaluation in two cases out of six showed no cancer cells, i.e. false-negative result incidence was 33%. Out of other four patients two underwent re-resection and in both cases new resection margin was found to be cancer positive again. In remaining two cases repeated surgery was rejected due to the need for wide tracheal resection. Post-surgery morphological evaluation showed mucosal disease in bronchial resection margin in one patient, submucosal one — in three patients, and peribronchial vessel one — in four.

There was one post-surgery death in each group. Causes of death were pneumonia and COPD exacerbation. Both patients had pneumonectomy. One patient from PDT arm had tracheobronchial anastomosis failure treated conservatively. No other serious complications were noted.

Discussion

Many prospective randomized trials found trends for survival improvement in favor of preoperative chemotherapy followed by surgery vs. surgery alone in stage III NSCLC patients [3—5].

However, there is no consensus on the major issue for all surgeons whether preoperative chemotherapy improves

surgical resection results and operability. About one-third of NSCLC patients has stage III disease often characterized by irresectable locally advanced tumor or would not stand surgery due to functional issues (i.e. are functionally inoperable). In theory, after special preparation some of these patients can undergo surgery. For example, in patients with limited pulmonary function (who would not tolerate pneumonectomy) it would therefore be beneficial to reduce the extent of resection.

In this paper, we discuss possibility to extend indications for endobronchial PDT as one of components of neoadjuvant treatment. In other words, patients with locally advanced disease may be treated with PDT to enhance resectability or to reduce the required resection extent.

The PDT mechanism of action has been extensively previously described though there is still no complete understanding of its therapeutic effects in oncology [10,15]. Method of PDT has a great deal of advantages. PDT can be applied in outpatient settings; it can be combined with conventional therapies; PDT can be employed when other methods are already ineffective; mutations as a source of resistance to chemo- or radiation therapy do not affect PDT efficacy; treatment toxicity is minimal, especially due to development of new photosensitizers [16]. Despite these advantages, limitations of PDT include patient photosensitivity following therapy, risks in case of bronchogenic tumors invading large vessels, and dependence of treatment on cancer location and size. Some of these limitations as our study shows can be overcome due to development of new photosensitizers in the recent years [17].

PDT has been employed even before as a means to reduce the extent of planned resection or to convert originally inoperable patients to surgical candidates. However, among various medical publications we managed to find only three such works — two from Japan published in the previous century and one from the USA (2006) [7—9]. In the latter PDT and chemo- or radiation therapy were applied as induction treatment in 41 NSCLC patients including 78% with stage III disease. Thus, 57% of patients considered as unresectable underwent surgical resection and 27% initially requiring pneumonectomy underwent lobectomy [9]. It should be noted that the study did not pay sufficient attention to resection completeness issues.

When cancer affects a main bronchus or trachea, resection margin is located quite closely to cancer tissue growth border. No cancer is large bronchi after preoperative treatment does not guarantee no cancer cells in mucosa, submucosa or peribronchial lymph nodes. All those cases sometimes result in clinical situations when elective morphological evaluation producing reports usually in several days after surgery showed cancer cell complexes in resection margin. Preoperative autofluorescence bronchoscopy may be useful to determine the exact required level of airway resection [18]. But if doing more aggressive bronchial (tracheal) resection is not possible due to technical or functional reasons, prevention of such clinical issues dramatic both for patients and surgeons may be an indication for preoperative PDT facilitating additional cancer cell death along with chemotherapy.

Our study demonstrated that neoadjuvant PDT treatment along with chemotherapy is effective, safe and it makes possible to convert to surgery candidates and to improve resection completeness in patients initially considered as unresectable or inoperable.

Although our results should be interpreted with cautions taking into account our small patient sample, no data concerning follow-up are provided. To the best of our knowledge, this study is the first randomized one evaluating DT effectiveness in neoadjuvant mode. We hope that this study will provide physicians with relevant evidence-based information and enhance their interest to PDT as a treatment modality for lung cancer and cancer disease in general.

Conflict of interest

None declared.

Acknowledgement

We are grateful to Mr. D.Y. Artioukh, Consultant Surgeon, Southport and Ormskirk Hospital, UK, for his help in preparation of the manuscript.

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