Photodynamic Therapy for Bronchial Microscopic Residual Disease After Resection in Lung Cancer

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Background: **The goal of lung cancer surgery is a complete tumor resection (R0 resection) with clear margins. 4% to 5% of resections have microscopic residual disease associated with worse prognosis. Definitive management is resection of residual tumor, which may not be tolerated by many patients, and definitive management is not well studied in these patients. We treated patients with stage I cancer and bronchial mucosal residual disease (MRD) with bronchoscopic photodynamic therapy (PDT).**

Methods: **All patients who underwent definitive surgery for early-stage lung cancer were reviewed. Patients with R1 resection, stage I disease with MRD and or carcinoma in situ along the stump site were treated with bronchoscopic PDT. Patient characteristics, histology, type and site of surgery, pattern of recurrence, recurrence status, adverse events, and survival data were evaluated.**

Results: **Eleven patients with bronchial mucosal R1 resection were treated with PDT along the stump site. The median age was 67. Three patients had carcinoma in situ and 8 had MRD. One patient (9%) had local recurrence 1 year after PDT treatment and was treated with radiation. Four patients (36%) had no evidence of recurrence to date after a median follow-up of 4 years and the other 6 patients had evidence of regional (16%) or distant (39%) recurrence. The local control rate was 91%. One patient developed pneumonia and other had photosensitivity reaction.**

Conclusion: **Bronchoscopic PDT is safe and effective in selected group of patients with non–small cell lung cancer who have MRD along the stump site.**

Key Words: R1 resection, mucosal residual disease, photodynamic therapy

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Anatomic lobectomy with lymphadenectomy is the accepted therapy for non–small cell lung cancer (NSCLC) up to stage IIIA disease.[1] The operation's goal is a complete tumor resection (R0 resection) with tumor-free resection margins. Residual tumor at the resection margin may determine the postoperative course with regard to complications, for example, bronchus stump insufficiency and locoregional relapse, but also may generally influence the patient's prognosis negatively. The incidence of microscopic residual tumor at the bronchial margin (R1 resection) is 4% to 5% (range, 1.2% to 17%) of all lung operations.[2] To date, there have been no randomized trials comparing different treatment strategies in such patients. Snijder and colleagues reported 28 patients with stage I NSCLC and microscopic residual tumor at the bronchial margin. The 5-year survival rate of patients who underwent reoperation was 40% as compared with 27% in patients with mucosal residual disease (MRD) or peribronchial residual disease (PRD) that did not receive surgery and 58% for patients with carcinoma in situ (CIS).[3] On the basis of the available literature and expert opinion, the panel of the National Comprehensive Cancer Network (NCCN) still recommends repeat resection or radiotherapy (with or without chemotherapy depending on stage) be considered if the patients have positive bronchial margins.[1] A vast majority of these patients, however, may not be suitable for a reoperation because of high stage disease or limited cardiopulmonary capacity. Postoperative radiotherapy (PORT) is often given in clinical practice if microscopic residual tumor is present at the resection margin and if patients are not candidates for reoperation, based on several retrospective studies.[4–6] However, the value of PORT is controversial and some studies have reported high local recurrence rates.[3,7] Concurrent chemoradiotherapy consisting of cisplatin and etoposide, paclitaxel and cisplatin, and paclitaxel and carboplatin regimens has been used for salvage and definitive treatment, according to the

NCCN guidelines. However, data on chemoradiotherapy for bronchial R1 resection is limited to 1 study.[8]

Photodynamic therapy (PDT) is a nonthermal ablative technique where cell death occurs when photosensitized tissue is exposed to light of a specific wavelength. Since the early 1900s, it has been used to treat cancers of the esophagus, stomach, bladder, skin, oropharynx, and biliary tree. PDT is typically a palliative or adjunctive therapy used to relieve non–life-threatening symptomatic airway obstruction (eg, dyspnea, cough, and hemoptysis) due to malignant or, less commonly, benign conditions that are not amenable to first-line therapies. It may also be used to treat patients with inoperable radiographic occult lung cancer (ROLC) or patients with stump recurrence following surgery.[9] We used PDT to treat bronchial MRD following R1 resection for lung cancer in patients who were not considered to be candidates for reoperation. We present our experience giving detailed information of the survival and related side effects, with the intention of providing support for PDT to be a suitable treatment for patients after R1 resection at the bronchial margin.

PATIENTS AND METHODS

Patients

This is a retrospective review of all consecutive patients undergoing definitive surgery for lung cancer between the years 2007 and 2013 at the University of Florida (UF). A total of 565 patients who had lobar or sublobar resection with complete lymph node dissection were included in the final analysis. All patients were staged preoperatively by computed tomography of the chest and a positron emission tomography scan. Staging postsurgically was performed according to the seventh edition of the American Joint Committee on Cancer Staging.[10] Frozen section analysis on all patients were performed intraoperatively to achieve clean margins. Surgical pathology reports were evaluated after resection and patients with positive bronchial margins were further evaluated. All these patients with R1 resection (n = 36) were presented at our multidisciplinary thoracic oncology tumor board. Those with pathologic stages II and III diseases underwent adjuvant chemotherapy, with or without radiation therapy, and were excluded from the final analysis as these systemic therapies could confound the outcomes of our study. Only patients with pathologic stage I and bronchial R1 resection (n = 16) were reviewed for the purposes of the current manuscript. Tumors were classified as central (inner, 2/3rd) or peripheral (outer, 1/3rd) based on location on computed tomography of the chest. One of these patients underwent reoperation and final margins postsurgery were negative. The remainder of the 15 (n = 15) patients were considered for reoperation but were considered not be surgical candidates due to one of the following factors: anatomy, stage and cardiopulmonary status. Those considered not to be surgical candidates underwent bronchoscopic endobronchial biopsy along the stump site and were further classified as having PRD if endobiopsies were negative (n = 4), MRD for patients having a positive endobronchial biopsy showing invasive cancer (n = 8) and CIS for patients that had CIS on endobronchial biopsy (n = 3). CIS along the stump site after resection represents a challenging problem with 1 review suggesting that it does not negatively impact overall survival (OS).[11] However, more recent study looking at uncertain resections for NSCLC including 5 cases of CIS along the stump site did show worse outcomes including decrease in OS.[12] Because of uncertainty on how best to manage MRD and CIS, we offered endobronchial PDT to all these patients along the stump site. We believe that offering PDT to these patients as a management option was ethical based on absence of consensus recommendation. All patients who underwent PDT had surveillance bronchoscopic biopsy along the treatment site at 6, 12, 18, and 24 months to look for recurrence. The remainder of the management and radiographic surveillance were as per the treating oncologist's discretion. Figure 1 presents an algorithm detailing how patients with bronchial R1 resection were approached at our institution.

The basic and clinical characteristics of the study population are summarized in Table 1. Follow-up data on survival were obtained for at least 3 years post-PDT treatment on all patients.

PDT

PDT was offered typically 6 to 8 weeks after surgery. Patients receiving PDT were given 2 mg/kg porfimer sodium intravenously, followed within 30 to 50 hours by treatment with red (630 nm) light from an argon-dye laser. The red light was delivered to the tumor by a single step index quartz fiber inserted into the biopsy channel of a flexible bronchoscope. All treatments were performed by inserting a cylindrical diffuser tip 2.5 cm length adjacent to the bronchial stump. The power density was 200 J/cm of diffusing cylinder length and the total light dose was 1000 mW. One session of treatment was applied. Two days following the light treatment, a clean-up bronchoscopy was performed to remove

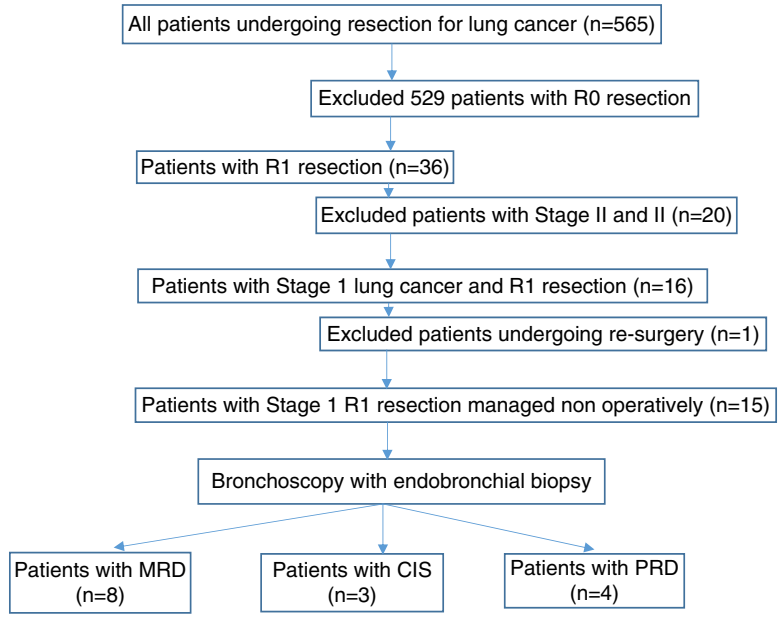

FIGURE 1. Detailed algorithm showing approach to patients with R1 resection. CIS indicates carcinoma in situ; MRD, mucosal residual disease; PRD, peribronchial residual disease; R0 resection, resection with negative margins; R1 resection, resection with positive surgical margins.

tumor debris. At the bronchoscopists discretion, a second light application was performed in some patients 24 to 48 hours later. The patients were seen at multidisciplinary thoracic oncology clinic, queried for symptoms and followed-up with imaging as per standard of care. All patients had surveillance bronchoscopy with endobronchial biopsy at the treatment site at 6, 12, 18, and 24 months.

Treatment Assessment

Local failure was defined as recurrence at the bronchial stump along the treatment site. Regional failure was defined as hilar and mediastinal lymph node recurrence or recurrence in the ipsilateral lung. Distant failure was defined as recurrence in the contralateral lung, pleura, or extrathoracic sites. Side effects including photosensitivity, hemoptysis, pneumonia, etc. were recorded.

Mean and median calculations were performed using standard statistical methodology. Time to recurrence and OS were also measured. Since it is a retrospective study, it was approved by institutional review board (IRB) at UF as exempt. All patients signed informed consent for the bronchoscopic PDT treatment after discussing risks and benefits and potential alternatives.

RESULTS

A total of 11 patients with mucosal R1 resection were treated with PDT along the stump site between 2007 and 2013. The median age of the group was 67 with 6 female individuals and 5 male individuals. The tumor was located in the right lung in 6 (55%) and left lung in 5 (45%) patients. Lobectomy was performed in 8 (73%), sleeve lobectomy in 1 (1%), and segmentectomy in 2 (16%) patients. The breakdown according to the pattern of residual disease was as follows: CIS in 3 and MRD in 8 patients. None of the patients had lymphatic infiltration at the resection margin. Histologically squamous cell carcinoma accounted for 7 of 11 (64%) patients and adenocarcinoma 4 of 11 (26%) patients. Sites of treatment involved the left lower lobe stump in 3 patients, the left upper lobe stump in 2 patients, the right upper lobe in 2 patients, the right middle lobe in 2 patients, and the right lower lobe in 2 patients.

Recurrences

Surveillance bronchoscopy with endobronchial biopsy was performed on patients treated with PDT every 6 months for 2 years. One patient (9%) had local recurrence 1 year after treatment and was treated with radiation along the stump site. Four patients (36%) had no evidence of recurrence to date after a median follow-up of 4 years. The remaining other 6 patients had no evidence of local recurrence but did have regional (16%) or distant (39%) recurrence and were treated appropriately. The overall local control rate was 91%. The median time between PDT therapy and recurrence was 26 months in the 7 patients who had recurrent

TABLE 1. Patient Characteristics, Histology, Type and Site of Surgery, Pattern of Recurrence, Recurrence Status, and Survival Data are Shown in the Current Table

Patient Number	Age	Sex	Operation	Central Versus Peripheral	Histology	Type of Residual Disease	Site of Treatment	Pattern of Recurrence	PFS (mo)	Overall Survival (mo)	Alive
1	53	M	Lobectomy	Central	Adeno ca	MRD	LLL	Regional	49	66	Y
2	80	F	Lobectomy	Peripheral	SCCa	CIS	LUL	NA	NA	45	N
3	80	F	Segmentectomy	Central	Adeno ca	MRD	RML	Distant	10	11	N
4	57	M	Lobectomy	Central	SCCa	CIS	RLL	NA	NA	70	Y
5	66	M	Lobectomy	Peripheral	SCCa	MRD	LLL	Distant	28	32	N
6	40	M	Lobectomy	Central	Adeno ca	MRD	RUL	Regional	36	59	N
7	66	F	Lobectomy	Peripheral	Adeno ca	MRD	RLL	NA	NA	86	Y
8	67	F	Lobectomy	Central	SCCa	MRD	RML	Distant	26	34	N
9	76	M	Sleeve lobectomy	Central	SCCa	MRD	LLL	NA	NA	39	N
10	72	F	Segmentectomy	Peripheral	SCCa	CIS	RUL	Local	24	73	Y
11	74	F	Lobectomy	Central	SCCa	MRD	LUL	Distant	21	25	N

Adeno ca indicates adenocarcinoma; CIS, carcinoma in situ; F, female; LLL, left lower lobe; LUL, left upper lobe; M, male; MRD, mucosal residual disease; N, no; NA, not available; PFS, progression-free survival; RML, right middle lobe; RUL, right upper lobe; SCCa, squamous cell carcinoma; Y, yes.

disease. Although the gold standard to judge curative intent therapy (ie, surgery) has been progression-free survival (PFS) and OS, local ablative therapies like stereotactic body radiation therapy have been evaluated on local response and thus we included local recurrences as one of the end points.

Survival

The median OS in our cohort of patients with bronchial R1 resection was 45 months with 4 patients still alive at the time of current analysis. Seven patients (64%) survived for at least 3 years post-PDT therapy to the stump site. Median PFS was 26 months in the 7 patients who had evidence of recurrent disease. Overall and PFS for patients with CIS were 70 months and 24 months respectively as compared with patients with MRD in whom the median overall and PFS were 34 and 27 months respectively. Therefore, patients with CIS at the stump site seemed to have a longer OS as compared with patients with MRD.

Toxicity

There were no severe complications such as hemoptysis, fistulas, postobstructive pneumonia, or death which could be attributed directly to PDT therapy. There were no cases of airway edema or sloughing. All the patients were well informed about light protection. The patients tolerated the procedure well with 1 patient admitted for pneumonia postprocedure and 1 patient developing photosensitivity. Both the patients were treated successfully on an outpatient basis and had a complete recovery.

DISCUSSION

To our knowledge, this is the first report of bronchoscopic PDT for postsurgical microscopic residual tumor at the bronchial margin in patients with NSCLC. PDT therapy achieved a median OS of 45.0 months among those NSCLC patients after bronchial R1 resection, with minimal treatment-related toxicity.

Although the classification of an R1 resection at the bronchial margin is not uniform in the literature, Wind et al[2] concluded that it could be divided into MRD, PRD, and extrabronchial residual disease. The incidence of microscopic residual tumor at the bronchial margin (R1 resection) is 4% to 5% (range, 1.2% to 17%) of all lung operations.[2] It is even seen in the more peripheral localized tumors in which there seems to be sufficient macroscopic tumor-free margin. Microscopic residual tumor might negatively affect prognosis, with 1- and 5-year survival rates among these patients between 20% to 50% and

0% to 20%, respectively. Some authors have suggested that for stage I NSCLC patients with bronchial positive margins, repeat resection should be considered[3,13] and that is recommended by the NCCN guidelines.[1] In the study by Snijder et al,[3] the median survival for stage I patients who underwent reoperation was 38 months. For patients with stage I or II with bronchial R1 resection who are not candidates for surgery, definitive management remains unclear. Some guidelines on lung cancer recommend adjuvant radiotherapy in all patients irrespective of their stage.[14] The literature supporting this only comprises of small retrospective studies collected over many years.[15,16] Other reports suggest a no favorable outcomes after adjuvant radiotherapy and some studies suggest worse prognosis with PORT.[3,7,17,18] Therefore, it is difficult to assess a potential beneficial effect of radiotherapy on residual disease after resection. There are no studies reporting on the value of adjuvant chemotherapy alone after an R1 resection of the bronchial margin. A recent study by Zhou et al[8] found NSCLC patients with postsurgical microscopic residual tumor achieved a median PFS and OS of 23.0 and 32.0 months, respectively with combined chemotherapy and radiotherapy. However, a significant portion of their patients had treatment-related toxicity. Moreover, they evaluated a mix of patients with N0, N1, and N2 disease and it is unclear as to which subgroup of patients derived the most benefit.

Bronchoscopic PDT is a nonthermal ablative technique that can be used to treat malignant central airway disease in adults. It is typically a palliative or adjunctive therapy used to relieve non–life-threatening symptomatic airway obstruction due to lung cancer that is not amenable to first-line therapies. Less commonly it may be used to treat hemoptysis due to benign airway lesions and inoperable benign conditions of the airway (eg, papillomatosis and granulation tissue). PDT has also been used to treat early-stage NSCLC confined to the airway wall, also known as ROLC, in patients who are not candidates for surgery or who decline surgery. In 1 prospective study of 48 patients with operable ROLC and a tumor length of <1 cm, the complete response rate of PDT was 94 percent.[19] In a review of 15 studies totaling 626 patients with ROLC, the complete response rate of PDT ranged from 30 to 100 percent with a median 5-year survival of 61%.[20] Because of the poor prognosis of R1 compared with R0 resection along with limited treatment strategies, we decided to treat our R1 patients with PDT who were not candidates for reoperation.

Our data shows that PDT was safe and effective for the treatment of MRD and CIS post-R1 resection with a local control rate of >90%. Median OS in our cohort was 45 months with a median PFS of 26 months. Our results compare favorably to PORT. In a review of PORT for bronchial stump recurrence, the overall pooled median OS was 28.5 months[21] Our local disease control rate was similar to combined chemotherapy and radiation therapy in the study by Zhou and colleagues with less side effects. In comparison, median OS and PFS in the study Zhou et al[8] were 32 and 23 months, respectively. We excluded patients with stages 2 and 3 diseases as most of them received systemic treatment with chemotherapy with or without radiation therapy as these therapies could have confounded the results. We also restricted our cohort to MRD compared with peribronchial disease which is known to have worse survival.[6] The above factors may be responsible for improved survival outcomes in our patients compared with other studies looking at the management of bronchial R1 resections.

Some of the limitations to our study include a small sample size and a retrospective design. Our approach however was systematic where the patients were presented at a multidisciplinary tumor board and those with MRD and those who were not surgical candidates were treated with bronchoscopic PDT. Compared with other studies looking at similar patient populations, all of our patients had bronchoscopic follow-up with biopsies at the treatment site for 2 years as well as radiographic follow-up ruling out both macroscopic and microscopic residual disease at the treatment site.

In conclusion, based on our findings, PDT is a safe and effective alternative therapy for patients with bronchial MRD post-R1 resection. Although this was a retrospective evaluation with a small sample, our data suggests that selected NSCLC patients after bronchial R1 resection may benefit from bronchoscopic PDT. Larger prospective randomized trials are required to further study the role of PDT for this complex problem.

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