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Evidence-based Series #7-15 Version 2 ARCHIVED 2017

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Role of Photodynamic Therapy (PDT) in Patients with Non-small Cell Lung Cancer: A Clinical Practice Guideline

Members of the Lung Cancer Disease Site Group

An assessment conducted in December 2017 ARCHIVED Evidence-based Series (EBS) 7-15 Version 2. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document.

(PEBC Assessment & Review Protocol)

The reviewed EBS report, which is available on the CCO Lung Cancer page, consists of the following four sections:

Section 1: Guideline Recommendations
Section 2: Systematic Review
Section 3: EBS Development Methods and External Review Process
Section 4: Document Summary and Review Tool

Release Date: December 16, 2013

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version October 2002	1966-2002	Full Report	Web publication	NA
Updated version November 2005	1966-2005	New data added to original full report	Updated web publication	NA
Version 2 Dec 2013	2005- 2013	New data found in Section 3: Document Summary and Review Tool	Updated Web publication	2005 recommendations is **ENDORSED**

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The Role of Photodynamic Therapy (PDT) in Patients with Non-Small Cell Lung Cancer: A Clinical Practice Guideline

D.E. Maziak, B.R. Markman, J.A. Mackay, W.K. Evans,
and members of the Lung Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Lung Cancer Disease Site Group (Lung DSG)

Report Date: December 16, 2013

SUMMARY

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.
Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2005 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

Questions

1. What is the role for PDT in the management of early stage lung cancer?
2. What is the role for PDT in the palliation of patients with symptomatic, locally advanced lung cancer?

The outcomes of interest were response rate, survival, and toxicity. Palliation of symptoms was also of interest for locally advanced lung cancer.

Target Population

This evidence-based series applies to adult patients with primary, non-small cell lung tumours.

Opinions of the Lung Cancer Disease Site Group

The lack of sufficient high-quality evidence precludes definitive recommendations. Instead, the Lung Cancer DSG offers the following opinions based on the evidence reviewed

- Photodynamic therapy could be considered as an option for the treatment of early-stage lung cancer in patients with medically inoperable disease that is accessible by bronchoscopy. Evidence to date suggests that photodynamic therapy may be most effective with small superficial airway lesions, 1cm or less in length. The relative safety and effectiveness of photodynamic therapy compared to radiotherapy, an alternative treatment for patients with inoperable early stage disease, remains undefined.
- In locally advanced and symptomatic lung cancer, photodynamic therapy can contribute to the relief of airway obstruction and hemoptysis, but its role is, as yet, not well defined in relation to other modalities of palliation.
- Serious adverse effects including fatal hemoptysis and respiratory failure can occur; therefore, the suitability of patients for this treatment should be carefully assessed. Since tumour necrosis can result in post-treatment airway obstruction, patients should be closely monitored after undergoing the procedure and toilet bronchoscopies repeated as indicated.

Key Evidence

- Eleven non-controlled studies and one summary paper reporting on the use of photodynamic therapy in early stage lung cancer patients, who generally could not tolerate surgery or refused surgery, showed that photodynamic therapy commonly leads to tumour regression. The reported five-year survival rates in these patients varied from 43.4% to 72%.
- In patients with late stage lung cancer, three randomized controlled trials and four non-controlled studies showed that photodynamic therapy could contribute to the palliation of local cancer-related symptoms. Of the three randomized trials, two comparing photodynamic therapy with Nd:YAG laser therapy and one comparing photodynamic therapy plus external beam radiotherapy with external beam radiotherapy alone, none detected a survival advantage for photodynamic therapy; however, photodynamic therapy did produce improved pulmonary symptom control. There was a significant improvement in the control of hemoptysis and the relief of dyspnea for patients receiving photodynamic therapy plus radiotherapy compared with those receiving radiotherapy alone.
- The most common adverse effect reported in all studies was photosensitivity, which consisted mostly of sunburn. The most serious adverse effects reported were respiratory failure and hemoptysis. The former, resulting from airway edema and tumour necrosis, led to mechanical ventilation in three of 67 patients with early stage lung cancer (two studies). Fatal hemoptysis occurred within one month of treatment in seven of 213 patients (two studies), three with early stage disease and four with locally advanced lung cancer. Three of 20 patients with locally advanced lung cancer also suffered from fatal hemoptysis between two and 18 months post-treatment. The role of photodynamic therapy in producing late fatal hemoptysis is uncertain.
- Contraindications for photodynamic therapy include porphyria or known allergies to porphyrins, tumours that impact on major blood vessels, and existing tracheoesophageal fistulas.

Future Research

Randomized controlled trials comparing photodynamic therapy to surgery, chemotherapy, radiation therapy, and brachytherapy are needed in both early- and late-stage lung cancers, to fully assess the effectiveness of photodynamic therapy and its impact on survival and symptom control.

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

Contact Information

For further information about this series, please contact
Dr. William K. Evans, Co-Chair, Lung Cancer Disease Site Group, McMaster University and Juravinski Cancer Centre, 699 Concession Street, Hamilton ON L8V 5C2; TEL (905) 387-9711 ext. 63001; FAX (905) 575-6323; or
Dr. Yee C. Ung, Co-Chair, Lung Cancer Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, ON, M4N 3M5; TEL (416) 480-4951; FAX (416) 480-6002.

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Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

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Evidence-based Series #7-15 Version 2: Section 2

The Role of Photodynamic Therapy (PDT) in Patients with Non-Small Cell Lung Cancer: A Systematic Review

D.E. Maziak, B.R. Markman, J.A. Mackay, W.K. Evans, and members of the Lung Cancer Disease Site Group

A Quality Initiative of the
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QUESTIONS

1. What is the role for PDT in the management of early stage lung cancer?
2. What is the role for PDT in the palliation of patients with symptomatic, locally advanced lung cancer?

The outcomes of interest were response rate, survival, and toxicity. Palliation of symptoms was also of interest for locally advanced lung cancer.

INTRODUCTION

PDT is a local treatment. It utilizes the local, selective, cytotoxic reaction produced by photosensitizers when activated by red nonthermal laser light of a specific wavelength. This cytotoxic effect is achieved through the generation of free radicals, the production of singlet oxygen via energy transfer from light to triplet oxygen, or by ischemic necrosis through neovascular shutdown partly mediated by thromboxane A2 release (anti-angiogenic effect). For a period after administration, photosensitizers are selectively retained in higher concentrations in tumours than in surrounding tissue. The goal of PDT is to exploit this selectivity by exposing

tumours to laser light of an appropriate wavelength during this time, typically two to four days after systemic administration of the photosensitizer (1).

Although treatment protocols may vary, PDT is a two-stage process that involves the administration of a photosensitizer via the intravenous route, typically at a dose of 2mg/kg of body weight for porfimer sodium (Photofrin®), and laser light irradiation two to four days later. A flexible bronchoscope is used to position a fiberoptic diffuser, either within or at the surface of the tumour, and the tumour is irradiated using a laser light source capable of producing the required wavelength (630nm ± 3nm for porfimer sodium). The choice of the fiberoptic diffuser tip depends on the indication, tumour location, and size of the tumour. For endobronchial tumours, the usual total light energy is 200 joules/cm of tumour length. Topical or local anesthesia is generally administered prior to PDT, and toilet bronchoscopies are performed within a few days of each treatment for debridement of the necrotic tumour to clear the airway of mucous plugging and prevent airway obstruction, atelectasis, dyspnea, or airway infection. Where required, laser light can be re-applied within 4 to 5 days of the photosensitizing drug being administered. The PDT process can be repeated once or twice, with a minimum of 30 days between injections of the photosensitizer (1). The development of new photosensitizers and more compact, powerful laser systems is continuing and may allow for the treatment of tumours of greater depth with fewer side effects.

PDT using porfimer sodium as a photosensitizer has been used in Europe since the 1980's for treatment of lung cancer, esophageal cancer, bladder cancer, brain tumours, and head and neck tumours. It was first approved in Canada in 1993 for bladder cancer. By 1998, QLT Phototherapeutics Inc. (Vancouver) had received U.S. FDA approval for the use of porfimer sodium for treatment of early stage lung cancer and Axcan Pharma Inc. now produces the compound. The use of PDT and porfimer sodium in lung cancer in Canada is still very limited, although there is increasing use of PDT worldwide. The Lung Cancer Disease Site Group (Lung DSG) felt that conducting a systematic review and evaluating the evidence for PDT was appropriate.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by one member of the PEBC's Lung DSG and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on PDT. The body of evidence in this review is primarily comprised of non-randomized controlled trial data. This precludes the development of definitive recommendations and instead, opinions of the DSG are offered. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1966 through June 2005), CANCERLIT (1975 through June 2002), EMBASE (1988 through 2005, week 23) and the Cochrane Library (2005, Issue 4) databases were searched. "Lung neoplasms" (Medical subject heading (MeSH)) was combined with "bronchial neoplasms" (MeSH), "dihematoporphyrin ether" (MeSH), "hematoporphyrins" (MeSH), "hematoporphyrin photoradiation" (MeSH), "phototherapy" (MeSH) and each of the following phrases used as text words: "lung cancer", "lung carcinoma", "lung malignancy", "bronchogenic cancer", "bronchial cancer", "bronchogenic carcinoma", "bronchial carcinoma", "bronchogenic malignancy", "bronchial malignancy", "photofrin", "porphrin", "porphyrin", "hematoporphyrin", "dihematoporphyrin ether", "porfimer sodium". These terms were then combined with the search terms for the following study designs: practice guidelines, systematic or quantitative

reviews, meta-analyses, randomized controlled trials, controlled clinical trials, clinical trials phase ii and phase iii, and multicenter studies.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) were searched for abstracts of relevant trials published between 1997 through 2005. The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Fully published reports or abstracts that met the following criteria were selected for inclusion:

1. Systematic reviews, practice guidelines, randomized controlled trials (RCTs) or non-controlled prospective studies of PDT using porfimer sodium (Photofrin®), alone or in combination with other therapies, for the treatment of stages I through IV primary, non-small cell lung cancers.
2. Outcomes of survival, response rate, or toxicity were reported, or for locally advanced lung cancer, the outcome of symptom palliation was reported.

Exclusion Criteria

1. Studies with less than ten patients
2. Studies in which PDT was used for the detection of lung cancer.
3. Individual case reports, pilot studies and retrospective studies.
4. Letters and editorials.
5. Papers published in a language other than English.

Synthesizing the Evidence

The three randomized trials identified in the literature search did not have similar treatment comparisons; therefore, a meta-analysis of this data was not considered appropriate. In addition, the other prospective trials identified in the literature search were non-comparative and were not suitable for meta-analysis.

RESULTS

Literature Search Results

Practice Guidelines

Two evidence-based guidelines, developed by the American College of Chest Physicians (ACCP) (2) and the Scottish Intercollegiate Guidelines Network (SIGN) (3), have provided recommendations for the treatment of lung cancer and included a section on the use of PDT. The SIGN guideline was based on the systematic review examining PDT developed by the Lung DSG previously published (4), and its recommendations were consistent with the Lung DSG's conclusions (3). The ACCP searched a variety of literature sources (including MEDLINE and the Cochrane Library) until July 2001, however the methods of study selection were not clearly described (5). This guideline was funded through an unrestricted educational group from Bristol-Myers Squibb (5). The ACCP recommended photodynamic therapy as a treatment option for early stage superficial squamous cell carcinoma patients who are not surgical candidates. For early stage patients who are surgical candidates, they recognized that PDT appears to be a promising treatment, but that evidence comparing PDT to surgical outcomes remains limited (2).

Clinical Trials

Three RCTs in patients with late stage lung cancer were eligible for inclusion. Two trials (reported in a single abstract) compared PDT with Nd:YAG laser treatment (6) and one trial compared external beam radiotherapy plus PDT with external beam radiotherapy alone (7). Eleven non-controlled studies reporting for early stage lung cancer (three reported in a single abstract) (8-16), one summary paper reporting the cumulative results of PDT studies in early stage disease conducted in Japan over 19 years (17), one non-controlled study that included a mix of stages (18), and four non-controlled studies of PDT in late stage disease (19-22) also met the inclusion criteria.

In abstracts where the results of several trials were reported (6,8), the method of pooling data were not provided. Where the same data were reported in more than one publication, the most recently available data are used. Moghissi et al recently reported the results of the Yorkshire Laser Centre experience with PDT for lung cancer (16). Some of the advanced disease-stage patients in that study were subjects of previous publications included in this review, and it was unclear if that trial included any advanced patients that had not been previously reported (6,21). To avoid repetition of results, only the early-disease stage results from that study are included. Two early studies were excluded because of limited data on lung cancer and the use of inadequate power density in laser treatment (23) and limited data on outcomes (24). One additional study was excluded as no information was provided on the stage of the patients and the data for primary and recurrent cancer patients were not reported separately (25).

The research to date has mostly consisted of small studies that describe clinical experience with the use of PDT at a single centre (9,10,12-16,19-21) or study summaries (17). For many of those studies, it is unclear if all eligible patients received treatment or whether the authors selected or reported on a subset of patients. In addition, three trials are in abstract format, and one is a summary paper, which provides limited detail on trial methodology. Overall, the quality of the published research is relatively poor.

Outcomes

Early Stage Lung Cancer

Tables 1a and 1b summarize the 11 non-controlled prospective studies and the one summary paper of PDT in the treatment of early stage lung cancer. The results of three studies, conducted in Europe and Canada, are reported in one abstract by Lam et al (8). In the summary paper, Kato reported the cumulative results of PDT studies conducted over 19 years at the Tokyo Medical College in Japan (17). Most patients were considered medically inoperable or had refused surgery (8-10,12,15). In one study, patients were oncologically operable but ineligible for surgery due to inadequate cardiorespiratory function or poor general fitness (16). In contract, another study included only patients who were considered candidates for surgery (13). It is also of note that where gender was reported, the overwhelming majority of patients were male (84% to 97%) (9-13,16).

Response

The method of response assessment varied across studies, and it is, therefore, difficult to directly compare the response rates between studies. In some cases, assessment included a combination of chest x-ray, bronchial biopsy or brushings, or sputum cytology (9,16). Other studies determined response from (12,13) endoscopic or histologic tests alone (8,15), and some studies did not report the definition of a complete response or the method of response assessment (14,17). Similarly, the timing of response assessment was variable, with some studies requiring an absence of tumour for at least four weeks post-treatment (11,12,15), some assessing response at a three-month follow-up (13), and others not providing the exact timing of response assessment (8-10,14,17).

Table 1a. Non-controlled prospective studies of PDT for early stage lung cancer: study descriptions.

First author, year (reference)	Disease and stage	No. of pts	No. of lesions	Follow-up (mos)
Edell & Cortese 1987 (9)	Bronchogenic carcinomas of tracheobronchial tree (37 squamous cell, 1 fibrosarcoma, 1 tracheal cylindroma, 1 small cell). Biopsy proven and localized: 28 lesions not visible on chest roentograms and 29 lesions with surface area ≤ 3cm^2.	38	40	NR*
Ono 1992 (10)	ROLC of tracheobronchial tree (38 squamous cell, 1 adenocarcinoma). Biopsy proven lesions identified by sputum cytology and not visible on chest roentogram.	36	39	Mean, 65.1 for 16 survivors (range, 37 - 109)
Furuse 1993 (11)	Early stage central squamous cell lung cancer. TisN0M0, 15/59 lesions †; T1N0M0, 44/59 lesions; histologically proven, clearly visible distal tumour margins or roentographically occult, no hilar or mediastinal lymph node or distant metastasis.	54 ‡	64	Median, 20.2 (range, 7.4 - 40.3)
Imamura 1994 (12) §	ROLC (38 squamous cell, 1 mixed tumour). Histologically confirmed with 21 lesions localized, carcinoma in situ, 17 early invasive carcinomas and 1 mixed tumour.	29	39	Median, 47 (range, 4.4 - 75.5)
Cortese 1997 (13)	ROLC (squamous cell) involving tracheobronchial tree. Localized lesions that were biopsy proven and confirmed with chest roentograms and CT scans.	21	23	Range, 24 - 116
Kawahara 1997 (14) (abstract)	ROLC (50 squamous cell, 2 adenoid cystic). Staging process not described.	46	52	Median, 78
Kato 1998 (17)	Early stage central squamous cell. Staging process not described.	95	116	NR
Lam 1998 (8) (abstract)‖	Early stage superficial. Most cancers radiologically occult although the staging process was not described.	102	NR	NR
Patelli 1999 (15)	Early stage central squamous cell. Biopsy proven lesion with negative CT scan.	23	26	Range, 3 - 120
Moghissi 2004 (16)	Early (intra-epithelial neoplasia) and stage I disease (11 squamous cell, 3 adenocarcinoma, 2 carcinoma I situ)	16	NR	Until patient death

Notes: CT – computed tomography, mos – months, No – number, NR – not reported, PDT – photodynamic therapy, pts – patients, ROLC – roentographically occult lung cancer.

* For the 14 cancers with a complete response post-PDT, median follow-up was 29 mos (3-53 mos).

† Staging data were inconsistently reported by Furuse et al (11). For the 61 carcinomas assessable for toxicity, table 1 indicated that 17 were Tis and 44 were T1s and the text indicated that 14 were Tis and 47 were T1s.

‡ Fifty-one patients with 61 carcinomas were assessable for toxicity and 49 patients with 59 carcinomas were assessable for response.

§ The Imamura et al study (12) was conducted at one of the institutions and with many of the same authors as reported for the Furuse et al study (11). The time period and patient population also overlapped.

‖ Abstract report of three trials conducted in Canada and Europe.

Table 1b. Non-controlled prospective studies of PDT for early stage lung cancer: study outcomes.

First author, year (reference)	Response		Survival	Toxicity (No. of pts reporting event)
	# CRs	% CRs		
Edell & Cortese 1987 (9)	14 of 40 lesions	35%	NR	Severity of toxicities not reported. Temporary airway obstruction (5), productive cough (4), sunburn (3), fatal hemoptysis (3), hypercapnic respiratory failure requiring mechanical ventilation (2).
Ono 1992 (10)	12 of 39 lesions	30.8%	1-yr, 91.7% 2-yr, 80.6% 3-yr, 74.5% 4-yr, 57.9% 5-yr, 43.4% *	Mild sunlight photosensitivity (5).
Furuse 1993 (11)	50 of 59 lesions	84.8% † (95% CI, 73.0% - 92.8%)	3-yr, 50% ‡	WHO grade 3 or 4: none. WHO Grade 2: pulmonary (4), allergic reactions (2), elevated ALT (1), sunburn (1). WHO Grade 1: pulmonary (38), allergic reactions (16), sunburn (15), AST, ALT or AlP elevation (8), throat pain (3).
Imamura 1994 (12)	25 of 39 lesions	64.1%	2-yr, 93% 3-yr, 72% 5-yr, 56% Disease-free Median, 38 mos (range, 4 - 169)	Temporary airway stenosis (common), sunburn (12) from mild erythema to intermediate blister formation, transient grade 1 liver dysfunction (3), anaphylactic reaction (1), hypercapnic respiratory failure requiring mechanical ventilation (1).
Cortese 1997 (13)	16 of 23 lesions	69.6%	5-yr, 72%	Sunburn reaction (5), productive expectoration (several) within 2 weeks post-PDT.
Kawahara 1997 (14) (abstract)	40 of 52 lesions	76.9%	5-yr, 47.5%	NR
Kato 1998 (17)	77 of 95 pts	81.1%	5-yr, 68.4% §	NR
Lam 1998 (8) (abstract) ‖	NR	79% of pts	Median, 3.5 yrs Disease-specific Median, 5.7 yrs	Adverse reactions mostly mild to moderate and self-limiting. Photosensitivity reactions (22%), mucous exudate (22%), local edema (18%), dyspnea (7%).
Patelli 1999 (15)	16 of 26 lesions	61.5%	NR	Not described in detail. Edema, hemorrhage and necrobiotic features common within 24 to 48 hours of treatment.
Moghissi 2004 (16)	15 of 15 pts ¶	100%	Mean, 75.4 mos Median, 69 mos	NR #

Notes: AlP – alkaline phosphatase, ALT – alanine aminotransferase, AST – aspartate aminotransferase, CI – confidence interval, CR – complete response, mos – months, No – number, NR – not reported, PDT – photodynamic therapy, pts – patients, WHO – World Health Organization, yr – year.

* Of 20 patients receiving radiation therapy in combination with PDT, 18 had no evidence of local recurrence at last follow-up or on autopsy and the five-yr survival rate for these patients was 41.2%.

† Data from a multicentre trial reported by Kato (17) appear to update the Furuse et al data (11), with CR obtained two months after the final treatment in 58 of 64 early stage lesions (90.6%).

‡ Estimated by reviewer from survival curve for 51 eligible patients.

§ When death due to other diseases was excluded, the five-year survival rate was 94.8%.

‖ Abstract report of three trials conducted in Canada and Europe.

¶ One patient died 1 month after PDT from myocardial infarction and a bronchoscopic check was not conducted

\# Toxicity data was not reported separately for early stage patients

Overall, the response rate associated with PDT in patients with early-stage lung cancer varied considerably, from 30.8% of 39 lesions (10) to 100% for 15 patients (16). One study found a response rate of 84.8% for 59 lesions, and that study involved only tumours that were roentographically occult or had clearly visible margins at bronchoscopy (11). The response rate for patients with operable disease (13) was comparable to that of studies mainly including patients considered medically inoperable or refusing surgery (69.6% compared with 30.8% to 79%). In five studies, the response rates reported were determined after the initial PDT treatment (11-14,16) and varied from 64.1% to 100%, while in three studies, the response rate was assessed after PDT was repeated up to three times (9,10,15) and varied from 30.8% to 61.5%. The number of PDT treatments per patient was not provided in the three studies reported by Lam et al (8) or in the summary paper by Kato (17). In those studies where response was assessed after a number of PDT treatments were administered, the reasons for the variation in the response rates are unclear but could include variation in the method of administering PDT, differences in the extent of disease, and differences in the timing or method of assessment of response.

Four of the studies also conducted subgroup analyses of response to PDT according to tumour length or surface area. Kato (17) reported complete responses in almost 100% of superficial lesions with a maximum dimension of < 2 cm, although precise data were not provided. Furuse et al (11) obtained a greater number of complete responses for tumours of ≤ 1cm in length compared with tumours > 1cm in length (44 of 45 tumours, 97.8%, versus 6 of 14 tumours, 42.9%, p=0.00001). In a multivariate logistic regression analysis, the same investigators found that estimated length of longitudinal tumour extent was the only significant, independent prognostic factor for complete response (p=0.0021). The other factors included in the regression analysis were tumour location, clarity of distal tumour margin, bronchoscopic findings of superficial versus nonsuperficial tumour, and light source of argon dye versus excimer dye laser. For a subset of tumours with a surface area of ≤ 3cm2, Imamura et al (12) obtained complete responses in 71.9% (23 of 32 tumours) compared to a complete response rate of 64.1% for all tumours. Edell and Cortese (9) reported a complete response rate of 48% for a similar subset (14 of 29 tumours) compared to 35% for all tumours.

A comparison of response rates for carcinomas in situ and T1 cancers was available from data reported by Furuse et al (11) and Imamura et al (12), although it is not clear that the two data sets were entirely independent. Both obtained higher response rates with the carcinomas in situ (15 of 15 TiN0M0 versus 35 of 44 T1N0M0 and 17 of 21 carcinoma in situ versus 8 of 18 T1N0M0, respectively). The differences in response rates, however, were not significant.

Survival

Five-year survival rates were reported for five non-controlled studies of early stage disease (10,12-14,17) and varied from 43% among 36 patients with poor pulmonary or cardiac function (10) to 72% among 21 patients who were surgical candidates (13). Those rates are difficult to interpret because the studies all include the use of other modalities at some point, e.g., surgery, radiation, and/or brachytherapy.

Toxicity

Of the eight studies that provided data on adverse effects (8-13), all reported reactions relating to photosensitivity. Between 8% of 38 patients (9) and 41% of 29 patients (12) experienced sunburn, with reactions typically described as mild to moderate. Edell and Cortese (9) reported fatal hemoptysis within one month of treatment in 8% of 38 patients. In two of those cases, the tumours were large, obstructing a major airway, and the authors suggested that the events were likely related to tumour necrosis and bleeding as a result of PDT. The most frequent side effects identified by Furuse et al (11) were pulmonary-related, including

exertional dyspnea, bronchitis, and obstructive pneumonitis, which occurred at World Health Organization (WHO) grades one and two in 75% and eight percent of 51 patients, respectively. Lam et al (8) also indicated that mild to moderate pulmonary effects were common, occurring in 7% to 22% of 102 patients. Productive expectoration or cough was reported as a mainly short-term side effect of treatment in two studies (9,13). The related side effect of temporary airway stenosis or obstruction was reported to be common by Imamura et al (12) and was found in 13% of 38 patients receiving PDT by Edell and Cortese (9). In the two latter studies, hypercapnic respiratory failure requiring mechanical ventilation occurred in one of 29 and two of 38 patients, respectively. One of those patients had a previous right pneumonectomy and subsequently died due to tension pneumothorax, and one patient had a previous left pneumonectomy and a right upper lobectomy (9). The third patient may have died as a result of respiratory insufficiency three weeks after a repeat PDT and 33 months after the first PDT, although this association is not clearly reported (12). Transient elevations in serum transamines have been reported (11), as well as transient grade one liver dysfunction (12) and WHO grade one and two allergic reactions (11). An anaphylactic reaction was also reported in 1 of 29 patients (11,12,12). In the study by Patelli et al (15), the adverse effects were not described in detail but the author did indicate that airway edema, hemorrhage, and necrobiotic features were common within the first 48 hours after PDT.

Mixed Stages of Lung Cancer

There was only one non-controlled study with mixed stages of lung cancer. McCaughan and Williams (18) reported the results of a large series of 175 patients treated with PDT over 14 years (Table 2). Response rates were not reported for all patients. The longest median survival was obtained for patients with the earliest stage disease, and, in a mulitvariate analysis, the factors found to influence survival were disease stage (p=0.0001) and performance status (p=0.013). The length of palliation for patients with incurable disease was reported as equal to, or better than, historical controls.

Of the eight deaths that occurred within 30 days of first PDT treatment, four were due to pulmonary hemorrhage (one stage IIIA, two stage IIIB and one stage IV), two to pneumonia (both stage IIIA), one to stroke (stage IIIB), and one to lung cancer (stage IIIA). All of the patients with fatal pulmonary hemorrhage experienced hemoptysis with clots prior to treatment.

One patient had a tracheoesophageal fistula within one week of treatment, and, after several treatments, some patients had strictures due to scar tissue that completely obstructed the bronchi. McCaughan and Williams (18) detected that airway obstruction can occur due to edema and exudates resulting from PDT, and they emphasized the importance of post-treatment toilet bronchoscopies. Skin photosensitivity was described as lasting for up to eight weeks following injection of the photosensitizer.

Table 2. Non-controlled prospective study of PDT for mixed stage lung cancer.

First author, year (reference)	Disease and stage	No. of pts	Survival	
			Median (months)	5-yr survival
McCaughan & Williams 1997 (18)	Endobronchial and tracheal carcinomas (90% squamous cell, 10% adenocarcinoma).	175	All pts, 7	Estimated disease-related Stage I, 93%
	Stage I, 16 pts		NYR	
	Stage II, 9 pts		22.5	Overall *
	Stage IIIA, 42 pts		5.7	Stage I, 69%
	Stage IIIB, 64 pts		5.5	
	Stage IV, 44 pts		5.0	

Notes: No – number, NYR – not yet reached, PDT – photodynamic therapy, pts - patients, yr – year.

* Quote from Dr. D. E. Wood, published in the discussion following the full study report.

Late Stage Lung Cancer

Table 3 summarizes the two RCTs (both reported in a single abstract) comparing PDT with Nd:YAG laser therapy, one RCT comparing PDT plus external beam radiotherapy with external beam radiotherapy alone, and four non-controlled prospective studies of PDT for the treatment of late-stage lung cancer. All studies reported that disease was advanced or late stage, although one RCT did not detail the methods used to determine stage of disease (6,22). The remainder assessed disease stage histologically, bronchoscopically, or radiologically. The majority of the patients were male for the one RCT and two non-controlled studies that reported gender composition (7,19,21). Median follow-up data were not available for the late stage disease studies.

Response

Wieman et al (6) reported the results of two randomized trials, one conducted in Europe and one in North America, comparing PDT with Nd:YAG laser treatment in 211 patients. The baseline characteristics of the patients in both groups were comparable. Objective response was assessed one month after treatment and the response rate was significantly higher for patients treated with PDT (55% versus 30%, p=0.00029). However, the definition of complete and partial response and the method of response assessment were not provided, and it is, therefore, difficult to compare these response rates with those obtained in other studies. In the randomized trial by Lam et al (7), a standard definition of response was not used; however, bronchial obstruction was estimated from bronchoscopy as the point of maximum narrowing of the most central airway. The bronchial lumen was completely opened and post-treatment bronchoscopy revealed no gross, visible tumour in 14 of 20 patients receiving PDT plus radiotherapy compared with two of 21 patients receiving radiotherapy alone. In total, treatment failures were reported to be zero and four, respectively, although the timing of response assessment was not clearly stated. Neither study reported if assessment of response was blinded.

In a non-controlled study, Hugh-Jones and Gardner (19) treated nine patients and assessed response visually and radiologically after one treatment. With the stated aim of palliation, a complete response was broadly defined as the enlargement of the diseased airway to at least 90% of normal and a partial response was considered as an enlargement of 50 to 90% of normal. The use of this broad definition resulted in an objective response rate of 100%. An independent radiologist subsequently reclassified one of the responses from ‘complete’ to ‘partial’. Interestingly, this study was the only one that reported an independent assessment of response.

Survival

In the two randomized trials reported by Wieman et al (6), overall survival was reported to be similar for both the PDT and Nd:YAG laser treatment groups; however, detailed survival data were not provided. Lam et al (7) found that median survival was similar for patients randomly allocated to radiotherapy alone or to PDT with radiotherapy, although the 20 patients in the PDT group remained recurrence free for significantly longer than the 21 patients in the radiotherapy alone group. In all three randomized trials, it was unclear if patients whose initial treatment was unsuccessful subsequently received additional treatments, a situation that could influence the results.

Table 3. PDT for the treatment of late stage lung cancer.

First author, year (reference)	Disease and stage	Treatment	No. of pts	Response (CR+PR)	Survival	Toxicity (No. of pts reporting event)
RANDOMIZED CONTROLLED TRIALS						
Lam 1991 (7)	Inoperable, obstructive endobronchial NSCLC. Stage III. Squamous cell, 83%.	PDT + XRT XRT *	20 21	NR †	PDT+XRT vs XRT Median survival, 444 vs 445 days. Median local-recurrence-free interval, 233 vs 107 days; p=0.005.	PDT+XRT vs XRT Photosensitivity with mild erythema (4) vs NR. Fatalities: hemoptysis, 3 (at 67, 187 and 567 days post-treatment) vs 0; respiratory failure, 0 vs 1; pneumonia, 1 vs 2; metastases/other, 10 vs 13.
Wieman 1998 (6) (abstract) ‡	Advanced lung cancer with endobronchial obstruction.	PDT Nd:YAG laser	102 109 §	55% 30% ‖	Overall survival reported as similar for both arms, no statistical analyses reported.	Greater number of events reported for PDT group: dyspnea 32%, photosensitivity 20%, hemoptysis 18%, bronchitis 11%. Event rate for Nd:YAG laser group not reported.
NON-CONTROLLED PROSPECTIVE STUDIES						
Hugh-Jones & Gardner 1987 (19)	Advanced, inoperable, bronchogenic, squamous carcinoma.	PDT	10	100% ¶	NR	Sunburn or light reaction (2), infection (2), severe transient worsening breathlessness (2).
Locicero 1990 (20)	Inoperable, endstage NSCLC with endo-bronchial obstruction. Squamous cell, 80%.	PDT	10	NR	Median survival, 4 months.	Second-degree burn (1), minor sunburn (1), facial edema (1), mild anasarca (1).
Moghissi 1999 (21)	Advanced inoperable bronchogenic cancer with endoluminal obstruction. NSCLC 90%, SCLC 10%. Squamous cell, 59%. Stage IIIA, 73%; IIIB, 17%; IV, 10%.	PDT	100	NR #	Median survival, 5 months for 90 pts dead at last follow-up and 29 months for 10 pts alive at final follow-up. Overall 2-yr survival, 19%.	Mild skin photosensitivity (5 episodes in 4 pts).
Friedberg 2004 (22)	NSCLC with pleural dissemination. Stage IIIB.	PDT + surgery and CT or XRT	22 **	NR	Median survival, 21.7 months †† Overall 1-yr survival, 68%	Grade 3 or 4 PDT-related: hypotension (1), acidosis (2), hypothermia (1) thrombocytopenia (1), increased protime (1) increased PTT (2), pneumonia or sepsis (1), increased alkaline phosphatase (1) elevated liver transaminases (2), ARDS (1)

Notes: ARDS – acute respiratory distress syndrome, CR – complete response, CT – chemotherapy, Nd:Yag laser – neodymium-yttrium aluminum garnet laser, No – number, NR – not reported, NSCLC – non-small cell lung cancer, PDT – photodynamic therapy, PR – partial response, pts – patients, PTT – partial thromboplastin time, SCLC – small cell lung cancer, vs – versus, XRT – external beam radiotherapy, yr – year.

* Radiotherapy dosed at 3000 cGy in 10 fractions over 2 weeks using a linear accelerator.
† CR and PR not defined. Reported no gross visible tumour post-treatment for 70% (PDT+XRT) and 10% (XRT) of patients.
‡ Abstract report of two trials conducted in North America and Europe.
§ Number of patients in each group obtained from the 1998 ASCO poster presentation provided by the author.
‖ Reviewer calculated chi-square = 13.103, df = 1, p = 0.00029.

¶ Response rate was provided for 9 of 10 patients that were treated and evaluable; one was untreated due to laser failure. An additional five patients were treated as part of a pilot study.
# Pathological response reported as partial for all patients, although 'partial' is not defined.
** Two patients were not treated with PDT as one has intraperitoneal disease and one had unsuspected intrapericardial disease.
†† Median

Three of the four non-controlled studies reported median survival. Locicero et al (20) administered PDT to 10 patients and achieved a median survival of four months. Six of the 10 patients subsequently received external beam radiation averaging 60 Gy, three patients were retreated with PDT an average of nine months after the initial treatment, and one patient was later treated with Nd:YAG laser. In a study involving 100 patients receiving multiple treatments of PDT (21), the results of a multivariate analysis indicated that performance status had a significant effect on survival. Patients with a WHO performance status rating less than or equal to two survived longer than those with a rating greater than two (median: 14 months versus four months, $p<0.0001$). Histology, disease stage, age, and sex did not significantly influence survival. In a study of combined modality therapy, including PDT, Friedberg et al (22) reported a median survival of 21.7 months, considerably longer than the two other studies. Twenty patients in that study underwent surgery and received PDT intra-operatively. Chemotherapy or radiotherapy was also administered pre- or post-surgery.

Palliation

In the trial by Lam et al (7), respiratory symptoms were measured on a scale of 0 (no symptom) to 4 (unbearable), although no data were provided on the reliability or validity of the scale. Compared to radiotherapy alone, PDT with radiotherapy produced a significant improvement in hemoptysis and shortness of breath at three months post-treatment ($p<0.05$), although both groups improved from baseline. In the PDT group, coughing was also significantly reduced at one month and three months post-treatment compared to baseline ($p<0.05$). Additional palliation of symptoms was not reported for radiotherapy alone. Comparing PDT with Nd:YAG laser therapy, Wieman et al (6) found that more patients showed an improvement in dyspnea grade one month after PDT when assessed on an unspecified symptom severity scale (17% versus 30% of patients, p-value not reported), although the PDT group had a greater number of adverse events related to photosensitivity, dyspnea, hemoptysis, and bronchitis. Neither study reported if assessment of symptoms was blinded.

Among the non-controlled studies, Hugh-Jones and Gardner (19) used a self-report analogue scale and reported improvement from baseline in breathing for all nine evaluable patients and a cessation of hemoptysis in six patients. In the study by Locicero et al (20), all 10 patients experienced a reduction in coughing from baseline and most experienced reduced dyspnea, although the methods of evaluation were not provided. Average bronchial obstruction, estimated by comparing the widest projected area of the tumour with a measure of the area of the bronchus obtained from transbronchoscopic photography, decreased from 86% (± 2%) to 57% (± 3%) following PDT; however, obstruction remained > 70% for half of the patients. There were no significant post-treatment changes in measures of pulmonary function. Moghissi et al (21) also reported a decrease in mean percentage bronchial obstruction, assessed bronchoscopically six to eight weeks after PDT, from 85.8% (± 19.6%) to 18.5% (± 17.3%). In that study, pulmonary function as measured by forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) did improve following PDT from 2.07L (± 0.78) to 2.50L (± 0.74) for FVC and from 1.38L (± 0.56) to 1.66L (± 0.57) for FEV1.

Toxicity

Three of 20 patients randomized to PDT in the study by Lam et al (7) experienced massive and fatal hemoptysis at 67, 187, and 567 days after treatment. It was suggested that those events could be the result of either disease progression or weakening of the bronchial

wall as a result of PDT. In the same study, of 21 patients who received radiotherapy alone, one died of respiratory failure and two of pneumonia, while one patient receiving both PDT and radiotherapy died of pneumonia. Wieman et al (6) also found that hemoptysis, dyspnea, and bronchitis occurred more frequently in patients who received PDT compared to those who received Nd:YAG laser therapy. However, many of the events reported by Wieman et al (6) occurred more than 30 days after treatment, suggesting that they were not directly attributable to the therapy. Photosensitivity associated with PDT occurred in 20% of patients in both the Lam et al (7) and the Wieman et al (6) studies.

Three of the four non-controlled studies also reported adverse effects associated with photosensitivity for patients receiving PDT, mainly in the form of mild sunburn. However, in the study by Locicero et al (20), one of 10 patients had a severe second-degree burn as a result of prolonged exposure to the sun post-PDT, and one patient experienced mild anasarca. Transient worsening of breathlessness was reported by Hugh-Jones and Gardner (19) for two of nine patients receiving PDT. In one case, that led to mechanical ventilation, and the patient subsequently died one month after treatment, although it was unclear if the patient remained on a ventilator until death. In the same study, two patients also experienced post-treatment infection. Friedberg et al (22) reported a wide range of toxicities. The most common toxicities included elevation in transaminases and creatinine, edema, hypotension, acidosis, thrombocytopenia, increased protime, and increased partial thromboplastin time. The operative mortality from surgery and PDT was 9% (two of 22 patients), with one death due to pneumonia resulting in sepsis and respiratory failure and the other death due to acute respiratory distress syndrome.

DISCUSSION

PDT is relatively easy to administer, can be performed on an outpatient basis, and can be repeated. For early-stage lung cancers, the published data from non-controlled prospective studies, which mainly included patients with medically inoperable disease, showed a varied response rate from 30.8% to as high as 100%. Three of four studies that reported subgroup analyses according to tumour length or surface area found a tendency towards improved response rates for smaller tumours. In one of those studies, patients with small tumours of ≤ 1 cm experienced a significantly better response rate than patients with tumours > 1 cm in length (97.8% versus 42.9%, respectively). The five-year survival rate varied from 43.4% to 72%, although for most studies this outcome reflected the effects of a combination of treatments rather than PDT alone. Overall, the data suggest that PDT can produce moderate response rates in early-stage lung cancer, particularly where the tumour is small. The effect of PDT on survival for patients with early-stage lung cancer is less clear.

For treatment of late-stage lung cancers, there were three RCTs: two studies involved PDT versus Nd:YAG laser therapy and the third study involved external beam radiotherapy plus PDT versus external beam radiotherapy alone. None of the RCTs detected a survival advantage for PDT, but there was an advantage for PDT with radiotherapy over radiotherapy alone with respect to symptom control, although the validity of the symptom measurement scale was unclear. In comparison to Nd:YAG laser therapy, PDT did improve dyspnea grade but that was offset by the higher number of adverse events in the PDT group. Three of the non-controlled studies also resulted in post-PDT reductions in dyspnea, hemoptysis, cough, or bronchial obstruction in these palliative patients. The palliative effect of PDT in late-stage lung cancer is promising, although its effectiveness in comparison to traditional therapies requires further study.

Most treatment side effects were considered mild to moderate, with photosensitivity being evident in most studies and pulmonary side effects occurring commonly. There were three cases of hypercapnic respiratory failure requiring mechanical ventilation among 67 patients with early stage lung cancer. One RCT in locally advanced disease reported

improvement in hemoptysis after treatment with PDT plus radiotherapy compared to radiotherapy alone. However, in the same study, three of the 20 patients receiving PDT had fatal hemoptysis at two, nine, and 18 months post-treatment. In two non-controlled studies, seven of 213 patients died from hemoptysis or pulmonary hemorrhage within one month of treatment (three with early stage disease and four with locally advanced lung cancer). The data on toxicity emphasize the need to ensure that patients understand the risks of exposure to sunlight in the period following treatment. The product monograph for Photofrin® indicates that the most common side effect in patients who have received Photofrin® is photosensitivity for 30 days or more, even up to 90 days. Patients must avoid exposure of eyes and skin to direct sunlight or brightly focused indoor light. The risk for serious adverse events should be taken into consideration in light of the patient's history and clinical condition. Toilet bronchoscopies should always be completed following endobronchial PDT to minimize the risk of bronchial obstruction, and the risk of hemoptysis should be considered prior to therapy and monitored post therapy.

There are a number of contraindications for the use of PDT in patients with lung cancer. These include porphyria or known allergies to porphyrins, tumours that erode into a major blood vessel, and existing tracheoesophageal fistulas. To date, drug-to-drug interactions involving Photofrin® have not been documented. Its use in pregnant women, nursing women, and children has not been established, and, therefore, Photofrin® is not recommended for use in those cases (1).

Much current research is of limited quality and is mainly obtained from non-controlled prospective studies with small sample sizes and, at times, it is difficult to compare results between studies as the endpoints, and their definitions vary. There is a need to fully assess the effectiveness of PDT through RCTs comparing PDT to surgery, chemotherapy, radiation therapy, and brachytherapy, in both early- and late-stage lung cancers.

ONGOING TRIALS

Table 4: Ongoing randomized phase II or III trials of photodynamic therapy in NSCLC

Protocol IDs	Title and details of trial
Mayo Clinic Trial 281-92	An Evaluation of the Effectiveness of Photodynamic Therapy (PDT) Compared to Surgical Resection in Early Stage Roentgenographically Occult Lung Cancer Status: Open for enrolment

[a]Reported in the Mayo Clinic clinical trials database on the Internet (http://clinicaltrials.mayo.edu/) and accessed on October 27, 2005.

CONCLUSION

PDT could be considered as a treatment option for patients with medically inoperable early-stage disease that is accessible by bronchoscopy. Evidence to date suggests that PDT may be most effective with small, superficial airway lesions, 1cm or less in length. The relative safety and effectiveness of PDT compared to radiotherapy, an alternative treatment for patients with inoperable early-stage disease, remains undefined.

In locally advanced and symptomatic lung cancer PDT, with or without radiotherapy, can contribute to the relief of airway obstruction and hemoptysis, but it has not shown a survival advantage when compared with current treatments such as Nd:YAG laser therapy or radiotherapy alone. There is a role for PDT in the palliation of advanced lung cancer; however, this is not well defined in relation to other modalities of palliation.

Serious adverse effects including fatal hemoptysis and respiratory failure can occur; therefore, the suitability of patients for this treatment should be carefully assessed. Since tumour necrosis can result in post-treatment airway obstruction, patients should be closely monitored after undergoing the procedure and toilet bronchoscopies repeated as indicated.

CONFLICT OF INTEREST

The primary authors of this guideline report declared no potential conflicts of interest.

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Maziak DE, Markman BR, Mackay JA, Evans WK; Cancer Care Ontario Practice Guidelines Initiative Lung Cancer Disease Site Group. Photodynamic therapy in nonsmall cell lung cancer: a systematic review. Ann Thorac Surg. 2004;77(4):1484-91.

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For a complete list of the Lung DSG members and the Report Approval Panel members, please visit the CCO Web site at http://www.cancercare.on.ca/

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Contact Information

For further information about this series, please contact

Dr. William K. Evans, Co-Chair, Lung Cancer Disease Site Group, McMaster University and Juravinski Cancer Centre, 699 Concession Street, Hamilton ON L8V 5C2; TEL (905) 387-9711 ext. 63001; FAX (905) 575-6323; or

Dr. Yee C. Ung, Co-Chair, Lung Cancer Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, ON, M4N 3M5; TEL (416) 480-4951; FAX (416) 480-6002.

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Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

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Evidence-based Series #7-15 Version 2: Section 3

The Role of Photodynamic Therapy (PDT) in Patients with Non-Small Cell Lung Cancer: Guideline Development and External Review - Methods and Results

D.E. Maziak, B.R. Markman, J.A. Mackay, W.K. Evans,
and members of the Lung Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Lung Cancer Disease Site Group (Lung DSG)

Report Date: December 16, 2013

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making.
Please see Section 4:Document Review Summary and Tool for a summary of updated evidence published between 2005 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province

for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Lung Cancer DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the role of PDT in patients with NSCLC, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

The systematic review on this topic is reported in Section 2 of the Series and describes the body of relevant clinical evidence and the interpretation of this evidence by members of the DSG. The final recommendations developed by the Lung DSG and approved by the DSG and the Practice Guidelines Coordinating Committee (PGCC) are summarized in Section 1 of the Series.

External Review by Ontario Clinicians

An earlier version of this practice guideline and systematic review, dated February 26, 2002, was circulated to 114 Ontario clinicians for feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence that was circulated to clinicians from the earlier version.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review February 26, 2002)

Target Population
These recommendations apply to adult patients with primary, non-small cell lung tumours.

Recommendation
The lack of sufficient high quality evidence precludes definitive recommendations. Instead, the Lung Cancer DSG offers the following opinions based on the evidence reviewed

- Photodynamic therapy could be considered as an option for the treatment of early stage lung cancer in patients with medically inoperable disease that is accessible by bronchoscopy. Evidence to date suggests that photodynamic therapy may be most effective with small superficial airway lesions, 1cm or less in length. The relative safety and effectiveness of photodynamic therapy compared to radiotherapy, an alternative treatment for patients with inoperable early stage disease, remains undefined.
- In locally advanced and symptomatic lung cancer, photodynamic therapy can contribute to the relief of airway obstruction and hemoptysis, but its role is, as yet, not well defined in

relation to other modalities of palliation.
- Serious adverse effects including fatal hemoptysis and respiratory failure can occur; therefore, the suitability of patients for this treatment should be carefully assessed. Since tumour necrosis can result in post-treatment airway obstruction, patients should be closely monitored after undergoing the procedure and toilet bronchoscopies repeated as indicated.

Key Evidence
- Ten non-controlled studies and one summary paper reporting on the use of photodynamic therapy in early stage lung cancer patients, who generally could not tolerate surgery or refused surgery, showed that photodynamic therapy commonly leads to tumour regression. The reported five-year survival rates in these patients varied from 43.4% to 72%.
- In patients with late stage lung cancer, three randomized controlled trials and four non-controlled studies showed that photodynamic therapy could contribute to the palliation of local cancer-related symptoms. Of the three randomized trials, two comparing photodynamic therapy with Nd:YAG laser therapy and one comparing photodynamic therapy plus external beam radiotherapy with external beam radiotherapy alone, none detected a survival advantage for photodynamic therapy; however, photodynamic therapy did produce improved pulmonary symptom control. There was a significant improvement in the control of hemoptysis and the relief of dyspnea for patients receiving photodynamic therapy plus radiotherapy compared with those receiving radiotherapy alone.
- The most common adverse effect reported in all studies was photosensitivity, which consisted mostly of sunburn. The most serious adverse effects reported were respiratory failure and hemoptysis. The former, resulting from airway edema and tumour necrosis, led to mechanical ventilation in three of 67 patients with early stage lung cancer (two studies). Fatal hemoptysis occurred within one month of treatment in seven of 213 patients (two studies), three with early stage disease and four with locally advanced lung cancer. Three of 20 patients with locally advanced lung cancer also suffered from fatal hemoptysis between two and 18 months post-treatment. The role of photodynamic therapy in producing late fatal hemoptysis is uncertain.
- Contraindications for photodynamic therapy include porphyria or known allergies to porphyrins, tumours that impact on major blood vessels, and existing tracheoesophageal fistulas.

Methods

Feedback was obtained through a mailed survey of 114 practitioners in Ontario (37 medical oncologists, 22 radiation oncologists, 29 surgeons, 25 respirologists, and one hematologist). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on February 26,2002. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Lung DSG reviewed the results of the survey.

Results

Sixty-five responses were received out of the 114 surveys sent (57% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 47 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 5.

Table 5. Responses to the items on the practitioner feedback survey.

Item	Number (%) *			
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**	**Missing**
The rationale for developing an evidence summary, as stated in the "*Choice of Topic*" section of the report, is clear.	42 (89%)	2 (4%)	1 (2%)	2 (4%)
There is a need for an evidence summary on this topic.	31 (66%)	10 (21%)	5 (11%)	1 (2%)
The literature search is relevant and complete in this evidence summary.	42 (89%)	3 (6%)	0	2 (4%)
I agree with the methodology used to summarize the evidence.	45 (96%)	1 (2%)	0	1 (2%)
I agree with the overall interpretation of the evidence in the evidence summary.	41 (87%)	3 (6%)	1 (2%)	2 (4%)
The *Opinions of the Disease Site Group* section of this evidence summary is useful.	38 (81%)	4 (8%)	3 (6%)	2 (4%)
An evidence summary of this type will be useful for clinical decision-making.	34 (72%)	5 (11%)	7 (15%)	1 (2%)
At present, there is insufficient evidence to develop a practice guideline on this topic.	29 (62%)	8 (17%)	9 (19%)	1 (2%)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.	31 (66%)	12 (26%)	3 (6%)	1 (2%)
Do you believe that the evidence supports the use of photodynamic therapy in your own practice? †	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**	
	NA	NA	NA	NA

Notes: NA – not available.

* Percentages do not always total to 100% due to rounding errors.
† This question incorrectly referred to a treatment other than PDT in the original survey sent to practitioners; therefore the responses to this question were not analyzed.

Summary of Written Comments

Thirteen respondents (28%) provided written comments. The main points contained in the written comments were:

1. Evidence for the use of PDT in lung cancer is limited.
2. This technique is not currently widely available and, unless funding for the photosensitizer and laser equipment is provided, it will not be possible to use the information contained in this evidence summary.
3. Evidence for the use of PDT as standard care for patients with early inoperable lung cancer or advanced lung cancer is unconvincing.

Modifications/Actions

1. The Lung DSG agreed that the current evidence for the use of PDT is limited; however, the Lung DSG felt that it was appropriate to summarize the available evidence on this procedure to date.
2. The Lung DSG acknowledged the current, limited availability of PDT as a treatment option and noted the following:
   a) This evidence summary could have an impact on the provincial decision regarding funding for Photofrin ®.

b) The establishment of PDT centres in the province is currently under consideration.

3. Although the current evidence for the use of PDT is limited, the Lung DSG felt that it was sufficient to support this procedure as one of several treatment options for inoperable lung cancer.

Practice Guidelines Coordinating Committee Approval Process

The evidence summary report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All 11 members of the PGCC returned ballots. Six PGCC members approved the evidence summary report as written, three members approved the report as written and provided suggestions for consideration by the Lung DSG, and two members approved the report conditional on the Lung DSG addressing specific concerns. The Lung DSG responded to the PGCC concerns as detailed below and the evidence summary was subsequently approved.

The PGCC noted that the evidence for PDT appears to be of a preliminary nature. They asked if response to radiotherapy was comparable to that obtained with PDT and questioned whether PDT as a treatment option should routinely be considered in early stage lung cancer. The PGCC indicated that the evidence for PDT in advanced disease was limited with only one small published RCT and one abstract report of an RCT available. They felt that substantial critical appraisal of this evidence was lacking. The PGCC also suggested that the very severe toxicities that occurred in a small number of patients were understated.

The Lung DSG agreed that the evidence for PDT is generally not of high quality and indicated that it did not propose PDT as a treatment option to be routinely used in early stage lung cancer. However, the five-year survival data obtained in studies of early stage disease (43% to 72%) rivals that generally obtained using external beam radiotherapy in medically inoperable patients. In patients with poor respiratory function and early stage disease that is treated with surgery or external beam radiotherapy, lung tissue is lost and this may preclude definitive interventions. For these reasons, PDT could be considered as the treatment option of choice in a small population of patients. The Lung DSG believes the data do support the fact that PDT can relieve airway obstruction in a significant proportion of patients with late stage lung cancer. Although PDT is only one of a number of treatment options for bronchial obstruction, it may be the most useful approach to symptom palliation in some circumstances, e.g., where tumours have become resistant to external beam radiotherapy or where the bronchial lumen is completely blocked and the tumour cannot be accessed for brachytherapy or Nd:YAG laser therapy. The Lung DSG acknowledged the serious toxicities experienced by some patients but felt that these were clearly indicated in the evidence summary, particularly in the Opinions section of the document SUMMARY.

Peer-Review Feedback

When the Evidence Summary Report was submitted to a journal for publication, one reviewer questioned the inclusion of the study by Friedberg et al because it involved intra-operative pleural PDT rather than endobronchial PDT. The authors acknowledged that PDT is generally administered endobronchially; however, other forms of PDT administration are considered of interest for treatment of patients with NSCLC and these were not excluded from the Evidence Summary Report.

RELATED PRINT AND ELECTRONIC PUBLICATIONS

Maziak DE, Markman BR, Mackay JA, Evans WK; Cancer Care Ontario Practice Guidelines Initiative Lung Cancer Disease Site Group. Photodynamic therapy in nonsmall cell lung cancer: a systematic review. Ann Thorac Surg. 2004;77(4):1484-91.

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.

Evidence-based Series #7-15 Version 2: Section 4

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

The Role of Photodynamic Therapy (PDT) in Patients with Non-Small Cell Lung Cancer: A Systematic Review

D.E. Maziak, R. Poon, and members of the Lung Cancer Disease Site Group

Guideline Review Summary

Review Date: December 16, 2013

The 2005 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2002. In December 2012, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Lung Cancer Site Group (DSG) endorsed the recommendations found in Section 1 (Guideline Recommendations) in 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

1. What is the role for PDT in the management of early stage lung cancer?
2. What is the role for PDT in the palliation of patients with symptomatic, locally advanced lung cancer?

The outcomes of interest were response rate, survival, and toxicity. Palliation of symptoms was also of interest for locally advanced lung cancer.

Literature Search and New Evidence

The new search (June 2005 to October 2013) yielded 2 practice guidelines, 1 systematic review, and 4 full text publications of non-controlled prospective studies. Additional searches on clinicaltrials.gov, ASCO, the Cochrane Library, the Canadian Medical Association Infobase, and the National Guidelines Clearinghouse yielded no results. Brief results of these publications are shown in the Document Review Summary and Tool.

Impact on Guidelines and Its Recommendations

The new data supports existing recommendations. Hence, the members of the Lung Cancer DSG ENDORSED the 2005 recommendations on The Role of Photodynamic Therapy (PDT) in Patients with Non-Small Cell Lung Cancer.

Document Review Summary and Tool

Number and title of document under review	#7-15 The Role of Photodynamic Therapy (PDT) in Patients with Non-Small Cell Lung Cancer
Current Report Date	November 1, 2005
Clinical Expert	Dr. Donna Maziak
Research Coordinator	Raymond Poon
Assessment Date	December 18, 2012
Approval Date and Review Outcome (once completed)	December 16, 2013 (ENDORSE)

Original Question(s):

1. What is the role for PDT in the management of early stage lung cancer?
2. What is the role for PDT in the palliation of patients with symptomatic, locally advanced lung cancer?

The outcomes of interest were response rate, survival, and toxicity. Palliation of symptoms was also of interest for locally advanced lung cancer.

Target Population:

This evidence-based series applies to adult patients with primary, non-small cell lung tumours.

Study Section Criteria:

Inclusion Criteria

Fully published reports or abstracts that met the following criteria were selected for inclusion:

1. Systematic reviews, practice guidelines, randomized controlled trials (RCTs) or non-controlled prospective studies of PDT using porfimer sodium (Photofrin®), alone or in combination with other therapies, for the treatment of stages I through IV primary, non-small cell lung cancers.

2. Outcomes of survival, response rate, or toxicity were reported, or for locally advanced lung cancer, the outcome of symptom palliation was reported.

Exclusion Criteria

1. Studies with less than ten patients
2. Studies in which PDT was used for the detection of lung cancer.
3. Individual case reports, pilot studies and retrospective studies.
4. Letters and editorials.
5. Papers published in a language other than English.

Search Details:
June 2005 to October 24, 2013 (Medline, Embase, ASCO annual meetings, the Cochrane Library, clinicaltrials.gov, the Canadian Medical Association Infobase, and the National Guidelines Clearinghouse)

Brief Summary/Discussion of New Evidence:
Of 149 hits from Medline and Embase + 3 hits from clinicaltrials.gov, 7 references representing 2 practice guidelines, 1 systematic review, and 4 non-controlled prospective studies were found. Additional searches from ASCO, the Cochrane Library, the Canadian Medical Association Infobase, and the National Guidelines Clearinghouse yielded no results.

Guidelines

Working Group	Recommendations	References
German Respiratory Society and the German Cancer Society	● The use of photodynamic therapy (PDT) in palliative treatment of lung cancer is only slightly superior to conventional laser. With the currently available sensitizers, the quality of life of patients is disproportionately affected by skin sensitization. As a result, PDT can hardly be recommended for palliation. (Grade of recommendation: Weak) ● PDT is the most effective method for eradication of early tumors that are limited to the mucosa and less than 1 cm in diameter. (Grade of recommendation: Weak) ● A combination of PDT with brachytherapy should be used for cancer lengths between 1 cm and 2 cm without deep invasion. (Grade of recommendation: Weak) ● PDT can be justified in patients with inoperable cancer. In individual cases, local operability can be achieved by PDT. (Grade of recommendation: missing or inconsistent studies, recommendation based on expert opinion)	Goeckenjan et al., 2011
The American College of Chest Physicians (ACCP)	● Endobronchial treatment with PDT, brachytherapy, cryotherapy, or electrocautery is recommended for patients with superficial limited mucosal lung cancer in the central airway who are not candidates for surgical resection. (Grade of recommendation: 1C, strong recommendation on low strength evidence)	Wisnivesky et al., 2013

Systematic Reviews

Interventions	Study	Population (N)	Outcomes	Brief results	References
Comparison 1: photodynamic therapy + radiotherapy vs. radiotherapy	3 RCTs	91	● OS ● Morbidity	● One trial reported no differences in mortality rates or survival times between PDT + radiotherapy (444 days) and radiotherapy alone (445 days). ● One trial reported a significantly greater reduction of haemoptysis and shortness of breath, and cough at 1 and 3 months for PDT + radiotherapy ($p<0.05$). There was also a significant difference in the median interval between treatment and local recurrence (PDT + radiotherapy=233 days vs. radiotherapy=107 days, $p=0.005$). There were 14 of 20 patients in the PDT + radiotherapy group achieving complete bronchial lumen re-opening vs. 2 of 21	Fayter et al., 2010

				patients in the radiotherapy alone group.	
Comparison 2: photodynamic therapy vs. Nd:YAG laser resection	3 RCTs	198	● OS ● Response rate ● Morbidity	● One trial reported a significantly longer survival time for PDT (265 days vs. 95 days, p=0.007). ● One trial reported similar response rates between the two treatment groups. Another trial found significant differences in response rate at 1 month between PDT (61%) and Nd:YAG laser resection (35%, p<0.05). The same trial also found a significantly longer time elapsed to failure in favor of PDT (50 days vs. 38 days, p=0.03). ● One trial found that both FVC (mean difference=0.47 vs. -0.06, p<0.05) and FEV_1 (mean difference=0.35 vs. 0.01, p<0.05) improved significantly more with PDT at 1 month after treatment.	

Non-controlled Prospective Studies

Interventions	Population	N	Median follow up	Outcomes	Brief results	References
photodynamic therapy (20 patients received hematoporphyrin derivative and the other 20 received porfimer sodium)	Twelve patients with 13 lesions staged as T1 carcinomas (T1N0M0) were inoperable for medical reasons. Twenty-eight patients with 37 lesions staged as recurrent in situ carcinoma (TisN0M0). Tumor size ≤2 cm. Mean age=65 years.	40 patients with 50 NSCLC lesions	43.59 months	● OS ● Response rate ● Toxicity	● The OS rates were 92.03% at 1 year, 72.78% at 2 years, and 59.55% at 5 years. The mean and median OS were 75.5 and 91.4 months, respectively. The difference in survival was significant in favor of TisN0M0 cases compared with T1N0M0 cases (p=0.03). ● The complete response rate was 72% (36 of 50 lesions); of which 27 were stage TisN0M0 and 9 were T1N0M0. ● There were no severe early or late PDT-related adverse events noted. Only 1 patient had Grade 1 photosensitivity-related skin toxicity (2.3%).	Corti et al., 2007
photodynamic therapy (porfimer sodium)	Patients with lesions of central-type early stage lung cancer. Thirteen synchronous lesions in 6 cases, 15 metachronous lesions in 6 cases, and 5 synchronous/metachronous lesions in 1 case.	93 patients with 114 lesions	Not reported	● OS ● Response rate	● The 5-year OS rates of patients with <1.0 and ≥1.0 cm lesions were 57.9% and 59.3%, respectively. The difference was not significant (p=0.207). ● The overall complete response rate was 83.3% (95 of 114 lesions). The complete response rates were 92.8% (77 of 83 lesions) for patients with lesions <1.0 cm and 58.1% for patients with lesions ≥1.0 cm (18 of 31 lesions). The difference was significant (p<0.001). Local Recurrences after complete response were observed in 9 of 77 lesions <1.0 cm (11.7%) and 3 of 18 lesions ≥1.0 cm (16.7%).	Furukawa et al., 2005
photodynamic therapy (porfimer sodium and Laserphyrin in	Patients with centrally located stage 0 (185 lesions) or stage 1 (79 lesions) lung	204 patients with 264 lesions	Not reported	● Response rate	● The overall complete response rate was 84.8% (224 of 264 lesions). The complete response rates were 94.6% (53 of 56 lesions), 93.5% (116 of	Kato et al., 2006

40 lesions)	cancer (258 squamous cell carcinoma, 2 severe dysplasia, 1 carcinoid, 3 adenocarcinoma, and 1 small cell carcinoma). Mean age=67.5 years.				124 lesions), 80.0% (40 of 50 lesions), and 44.1% (15 of 34 lesions) for patients with lesions <0.5, 0.5-0.9, 1.0-2.0, and >2.0 cm, respectively. Recurrence after complete response occurred in 26 of 224 lesions (11.6%).	
photodynamic therapy (porfimer sodium)	Male patients with roentgenographically occult bronchogenic squamous cell carcinoma who were current or ex-smokers (4 synchronous multiple primary lung cancer). Mean age=70 years.	48 patients	63 months	● OS ● Response rate	● The 5-year and 10-year OS rates were 81% and 71%, respectively. There was no significant difference in the 5-year survival rates between patients with (100%) and without (76%) local recurrence. The 5-year survival rate of patients with metachronous multiple primary lung cancer was significantly lower than that of patients without it (56% vs. 88%, p=0.031). A total of 11 deaths were observed. ● The complete response rate was 94% (45 of 48 patients). Recurrence after complete response occurred in 9 patients.	Endo et al., 2009

Abbreviations: PDT=photodynamic therapy; FVC=forced vital capacity; FEV_1=forced expiratory volume in one second; NSCLC=non-small cell lung cancer; Nd:YAG= neodymium-doped yttrium aluminum garnet; OS=overall survival; RCT=randomized clinical trial

Clinical Expert Interest Declaration:
None

Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?	No
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	Yes to both question 2a and 2b

3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	No
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	N/A

Review Outcome	ENDORSE
DSG/GDG Approval Date	December 16, 2013
DSG/GDG Commentary	Not applicable

New References Identified (alphabetic order):

1. Corti L, Toniolo L, Boso C, Colaut F, Fiore D, Muzzio PC, et al. Long-term survival of patients treated with photodynamic therapy for carcinoma in situ and early non-small-cell lung carcinoma. Lasers in Surgery & Medicine. 2007;39(5):394-402.

2. Endo C, Miyamoto A, Sakurada A, Aikawa H, Sagawa M, Sato M, et al. Results of long-term follow-up of photodynamic therapy for roentgenographically occult bronchogenic squamous cell carcinoma. Chest. 2009 01 Aug;136(2):369-75.

3. Fayter D, Corbett M, Heirs M, Fox D, Eastwood A. A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. Health technology assessment (Winchester, England). 2010 Jul;14(37):1-288.

4. Furukawa K, Kato H, Konaka C, Okunaka T, Usuda J, Ebihara Y. Locally recurrent central-type early stage lung cancer < 1.0 cm in diameter after complete remission by photodynamic therapy. Chest. 2005 November;128(5):3269-75.

5. Goeckenjan G, Sitter H, Thomas M, Branscheid D, Flentje M, Griesinger F, et al. Prevention, diagnosis, therapy, and follow-up of lung cancer: Interdisciplinary guideline of the German respiratory society and the German cancer society. Pneumologie. 2011;65(1):39-59.

6. Kato H, Usuda J, Okunaka T, Furukawa K, Honda H, Sakaniwa N, et al. Basic and clinical research on photodynamic therapy at Tokyo Medical University Hospital. Lasers in Surgery and Medicine. 2006 June;38(5):371-5.

7. Wisnivesky JP, Yung RCW, Mathur PN, Zulueta JJ. Diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of the central airways: Diagnosis and

management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 SUPPL):e263S-e77S.

Literature Search Strategy:

Medline

1. exp lung neoplasms/
2. non small cell lung.tw.
3. (lung adj3 neoplas$).tw.
4. (lung adj3 cancer$).tw.
5. (lung adj3 carcin$).tw.
6. (lung adj3 tumo$).tw.
7. (lung adj3 metasta$).tw.
8. (lung adj3 malig$).tw.
9. exp bronchial neoplasms/
10. (bronch$ adj3 neoplas$).tw.
11. (bronch$ adj3 cancer$).tw.
12. (bronch$ adj3 carcin$).tw.
13. (bronch$ adj3 tumo$).tw.
14. (bronch$ adj3 metasta$).tw.
15. (bronch$ adj3 malig$).tw.
16. or/ 1-15
17. exp dihematoporphyrin ether/
18. exp hematoporphyrins/
19. exp hematoporphyrin photoradiation/
20. exp phototherapy/
21. dihematoporphyrin ether$.tw.
22. hematoporphyrin$.tw.
23. photodynamic thera$.tw.
24. photothera$.tw.
25. photofrin$.tw.
26. porphrin$.tw.
27. porphyrin$.tw.
28. porfimer sodium$.tw.
29. or/ 17-28
30. 16 and 29
31. meta-analysis as topic/
32. meta analysis.pt.
33. (meta analy$ or metaanaly$).tw.
34. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
35. (systematic adj (review$ or overview?)).tw.
36. (exp Review Literature as topic/or review.pt or exp review/) and systematic.tw.
37. or/ 31-36
38. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or chinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
39. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
40. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
41. (study adj selection).ab.

42. 40 or 41
43. review.pt.
44. 42 and 43
45. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
46. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
47. random allocation/ or double blind method/ or single blind method/
48. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
49. or/ 45-48
50. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
51. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
52. (50 or 51) and random$.tw.
53. (clinic$ adj trial$1).tw.
54. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
55. placebos/
56. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
57. (allocated adj2 random).tw.
58. or/ 53-57
59. exp cohort studies/
60. cohort$.tw.
61. controlled clinical trial.pt.
62. epidemiologic methods/
63. or/ 59-62
64. 37 or 38 or 39 or 44 or 49 or 52 or 58 or 63
65. 30 and 64
66. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
67. 65 not 66
68. limit 67 to English
69. Animal/
70. Human/
71. 69 not 70
72. 68 not 71
73. (200506$ or 200507$ or 200508$ or 200509$ or 200510$ or 200511$ or 200512$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).ed.
74. 72 and 73

Embase

1. exp lung neoplasms/
2. non small cell lung.tw.
3. (lung adj3 neoplas$).tw.
4. (lung adj3 cancer$).tw.
5. (lung adj3 carcin$).tw.
6. (lung adj3 tumo$).tw.
7. (lung adj3 metasta$).tw.
8. (lung adj3 malig$).tw.
9. exp bronchial neoplasms/
10. (bronch$ adj3 neoplas$).tw.
11. (bronch$ adj3 cancer$).tw.
12. (bronch$ adj3 carcin$).tw.
13. (bronch$ adj3 tumo$).tw.

14. (bronch$ adj3 metasta$).tw.
15. (bronch$ adj3 malig$).tw.
16. or/ 1-15
17. exp dihematoporphyrin ether/
18. exp hematoporphyrins/
19. exp hematoporphyrin photoradiation/
20. exp phototherapy/
21. dihematoporphyrin ether$.tw.
22. hematoporphyrin$.tw.
23. photodynamic thera$.tw.
24. photothera$.tw.
25. photofrin$.tw.
26. porphrin$.tw.
27. porphyrin$.tw.
28. porfimer sodium$.tw.
29. or/ 17-28
30. 16 and 29
31. exp Meta Analysis/ or exp “Systematic Review”/
32. (meta analy$ or metaanaly$).tw.
33. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
34. (systematic adj (review$ or overview?)).tw.
35. exp “Review”/ or review.pt.
36. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
37. (study adj selection).ab.
38. 35 and (36 or 37)
39. or/ 31-34, 38
40. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or chinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
41. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
42. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
43. randomization / or single blind procedure/ or double blind procedure/
44. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
45. or/ 42-44
46. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
47. 46 and random$.tw.
48. (clinic$ adj trial$1).tw.
49. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
50. placebo/
51. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
52. (allocated adj2 random).tw.
53. or/ 48-52
54. exp cohort analysis/
55. exp longitudinal study/
56. exp prospective study/
57. exp follow up/
58. cohort$.tw.
59. or/ 54-58

60. 39 or 40 or 41 or 45 or 47 or 53 or 59
61. 30 and 60
62. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
63. 61 not 62
64. limit 63 to English
65. Animal/
66. Human/
67. 65 not 66
68. 64 not 67
69. (200506$ or 200507$ or 200508$ or 200509$ or 200510$ or 200511$ or 200512$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).dd.
70. 68 and 69

Searched http://www.ascopubs.org/serach (ASCO Meeting Abstracts), http://clinicaltrials.gov/ct2/search/advanced (clinicaltrials.gov), http://onlinelibrary.wiley.com/cochranelibrary/search/ (the Cochrane Library), http://www.cma.ca/index.php?ci_id=54293&la_id=1 (the Canadian Medical Association Infobase), and http://www.guideline.gov/ (the National Guidelines Clearinghouse) with keywords: “photodynamic” AND “porfimer sodium” AND “non-small cell lung”.

OUTCOMES DEFINITION

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “ARCHIVED”.

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY –** A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.