Achieving Clinically Proven Treatment Results With Photodynamic Therapy (PDT) and PHOTOFRIN® (porfimer sodium) for Injection

PHOTOFRIN® (porfimer sodium) IS INDICATED FOR

Palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy.

Treatment of microinvasive endobronchial non–small cell lung cancer (NSCLC) in patients for whom surgery and radiotherapy are not indicated.

Reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial NSCLC.

PHOTOFRIN® (porfimer sodium) is indicated for the ablation of high-grade dysplasia (HGD) in Barrett's esophagus patients who do not undergo esophagectomy.

IMPORTANT SAFETY INFORMATION ABOUT PHOTOFRIN FOR INJECTION

Photodynamic therapy (PDT) with PHOTOFRIN is a two-stage process requiring administration of both drug and light in a properly equipped facility. Refer to the OPTIGUIDE® instructions for use for complete instructions concerning the fiber optic diffuser.

PHOTOFRIN is contraindicated in patients with porphyria. PDT is contraindicated in patients with an existing tracheoesophageal or bronchoesophageal fistula and patients with tumors eroding into a major blood vessel. PDT is not suitable for emergency treatment of patients with severe acute respiratory distress caused by an obstructing endobronchial lesion because 40 to 50 hours are required between injection with PHOTOFRIN and laser light treatment. PDT is not suitable for patients with esophageal or gastric varices, or patients with esophageal ulcers >1 cm in diameter.

Tracheoesophageal or bronchoesophageal fistula can occur if esophageal tumor is eroding into trachea or bronchial tree. Gastrointestinal perforation can occur. There is a high risk of bleeding in patients with esophageal varices and for fatal massive hemoptysis with endobronchial tumors that are: large, centrally located; cavitating; extensive, extrinsic to the bronchus. After treatment of high-grade dysplasia (HGD) in Barrett's esophagus (BE), monitor endoscopic biopsy every three months, until four consecutive negative evaluations for HGD have been recorded. Photosensitivity can be expected; ocular sensitivity is possible. Allow 2-4 weeks between PDT and subsequent radiotherapy. Substernal chest pain may occur after treatment. Treatment-induced inflammation can cause airway obstruction. Administer with caution to patients with tumors in locations where treatment-induced inflammation can obstruct the main airway. Esophageal stenosis occurs frequently after treatment of HGD in BE. Patients with hepatic or renal impairment may need longer precautionary measures for photosensitivity (possibly more than 90 days). Thromboembolic events can occur following photodynamic therapy with PHOTOFRIN.

MOST COMMON ADVERSE REACTIONS reported during clinical trials are:

Esophageal Cancer: Anemia, pleural effusion, pyrexia, constipation, nausea, chest pain, pain, abdominal pain, dyspnea, photosensitivity reaction, pneumonia, vomiting, insomnia, back pain, pharyngitis.

Obstructing Endobronchial Cancer: Dyspnea, photosensitivity reaction, hemoptysis, pyrexia, cough, pneumonia.

Superficial Endobronchial Tumors: Exudate, photosensitivity reaction, bronchial obstruction, edema, bronchostenosis.

High-Grade Dysplasia in Barrett's Esophagus: Photosensitivity reaction, esophageal stenosis, vomiting, chest pain, nausea, pyrexia, constipation, dysphagia, abdominal pain, pleural effusion, dehydration.

Inform patients to report adverse reactions. All patients who receive PHOTOFRIN will be photosensitive for at least 30 days and should be warned about this and counselled to take appropriate precautions. Laser treatment should not be given if an overdose of PHOTOFRIN is administered.

FOR MORE INFORMATION ABOUT PHOTOFRIN visit www.Photofrin.com or call Concordia Laboratories Inc. at 1-877-370-1142.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see full prescribing information for PHOTOFRIN.

PDT WITH PHOTOFRIN® (porfimer sodium) for Injection

Light up the possibilities

Photodynamic Therapy (PDT) Is a Guideline-Recommended Therapy in the Treatment of Esophageal Cancer[1,2]

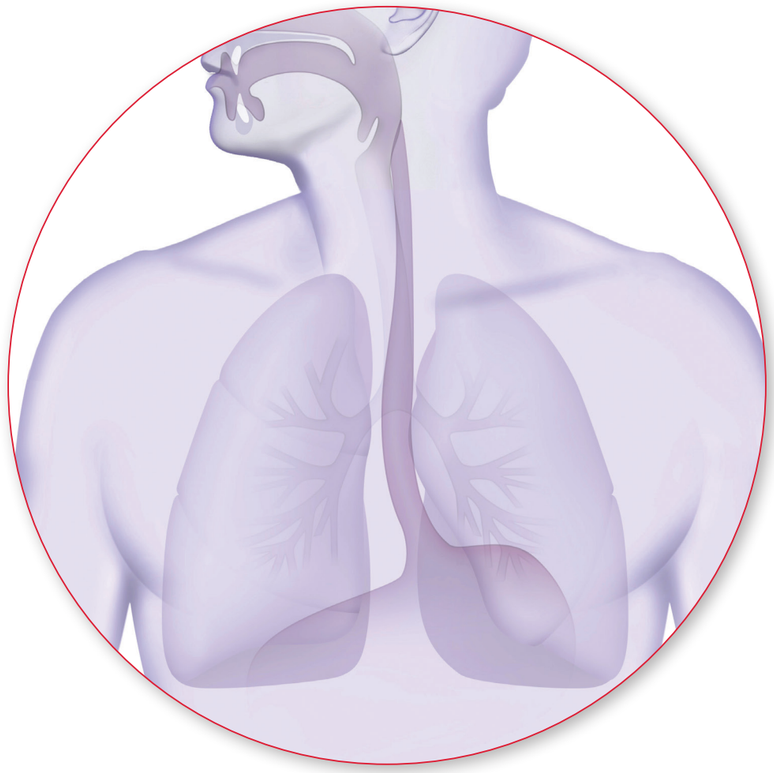
PDT is recommended by both the National Comprehensive Cancer Network (NCCN) and the American Society for Gastrointestinal Endoscopy (ASGE) for the treatment of esophageal cancer.[1,2]

- PDT is an effective palliative treatment for patients with obstructing esophageal cancer[3]
- PDT is effective at improving malignant dysphagia from obstructing esophageal carcinoma[3]
- PDT is effective at controlling bleeding tumors and ablating tumor ingrowth or overgrowth of esophageal stents[3]

NOTE: *This reference is a retrospective study. References quoted may have used settings not approved in prescribing information for PHOTOFRIN.*

APPLICATIONS FOR PDT IN ESOPHAGEAL CANCER[4]

- Patients who are not candidates for endoscopic mucosal resection (EMR) in whom radiofrequency ablation (RFA) has failed
- Patients who are not candidates for EMR in whom cryotherapy has failed
- Patients with bulky and/or nodular Barrett's Disease (not amenable to RFA or EMR)



The 3 Components of Photodynamic Therapy (PDT)

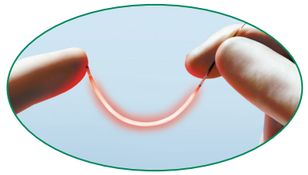
1. PHOTOFRIN® (porfimer sodium) for Injection

PHOTOFRIN (porfimer sodium) is injected 40 to 50 hours prior to laser activation and is selectively retained in tumor cells. When activated with red laser light, the drug produces a chain reaction of cell death in targeted tissue.

2. FIBER

Fibers shown actual size

The OPTIGUIDE® Diffuser Series features a range of fibers for reaching the tumor and delivering red laser light for PHOTOFRIN activation. The Diffuser Series includes the rigid DCYL200 series and the DCYL700 series, featuring new flexible-yet-durable material to ease navigation through instruments and anatomy.



DCYL700 DIFFUSER SERIES

OPTIGUIDE® FIBER OPTIC **DCYL200** CYLINDRICAL DIFFUSER SERIES

OPTIGUIDE® FIBER OPTIC **DCYL700** CYLINDRICAL DIFFUSER SERIES

3. LASER

The laser generates red light with a wavelength of 630 nm to activate PHOTOFRIN.

DIOMED 630 PDT LASER

PDT WITH PHOTOFRIN® (porfimer sodium) for Injection

Light up the possibilities

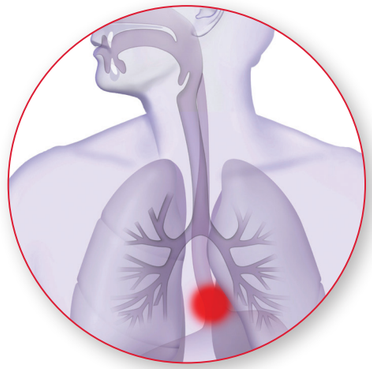
PHOTOFRIN® (porfimer sodium) for Injection

Photodynamic Therapy (PDT) Timeline

DAY 1

ADMINISTRATION

Typically used in an outpatient setting, PHOTOFRIN (porfimer sodium) is reconstituted and administered as a single IV injection over 3 to 5 minutes.



TARGETED RETENTION

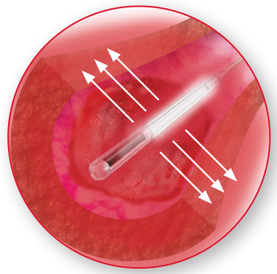
Photosensitizer is selectively retained in cancer cells.

DAY 3

LASER APPLICATION[5]

In esophageal cancer, a laser light dose of 300 J/cm of fiber optic diffuser length is administered 40 to 50 hours following injection of PHOTOFRIN® (porfimer sodium) for Injection.

In high-grade dysplasia (HGD) in Barrett's esophagus, a laser light dose of 130 J/cm of fiber optic diffuser length is administered 40 to 50 hours following injection of PHOTOFRIN.



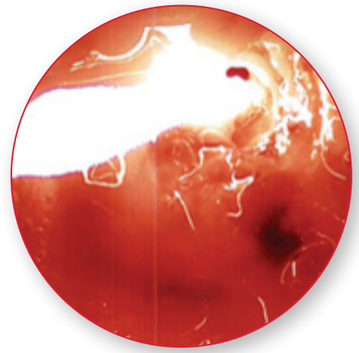
Excited PHOTOFRIN causes vasoconstriction, which leads to vascular occlusion and additional tumor cell death.[5]

DAY 5

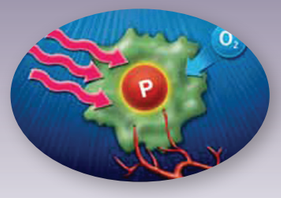
ENDOSCOPY AND SECOND LIGHT TREATMENT, IF NECESSARY[5]

In esophageal cancer, a second laser light dose of 300 J/cm of fiber optic diffuser length is administered 96 to 120 hours after the initial injection.

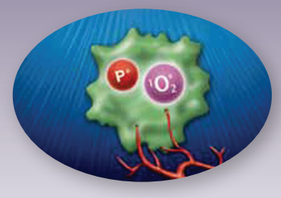
In HGD in Barrett's esophagus, a second laser light dose of 50 J/cm of fiber optic diffuser length is administered 96 to 120 hours after the initial injection.



ACTIVATION

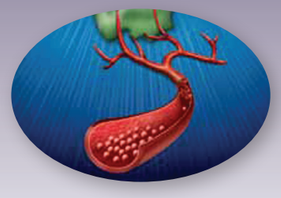


Red light permeates tissue (the indicated light dosimetry for esophageal cancer 300 J/cm) and activates PHOTOFRIN to an excited state.[5]

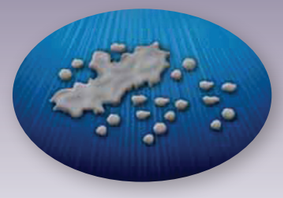


Energy transfer generates reactive singlet oxygen[5] and selective necrosis of the target lesion up to a 6-mm depth.[6]

DESTRUCTION OF CANCER CELLS



Excited PHOTOFRIN causes vasoconstriction, which leads to vascular occlusion and additional tumor cell death.[5]



Treatment results in lysis and ischemic necrosis of cancer cells.[5]

PDT WITH PHOTOFRIN® (porfimer sodium) for Injection

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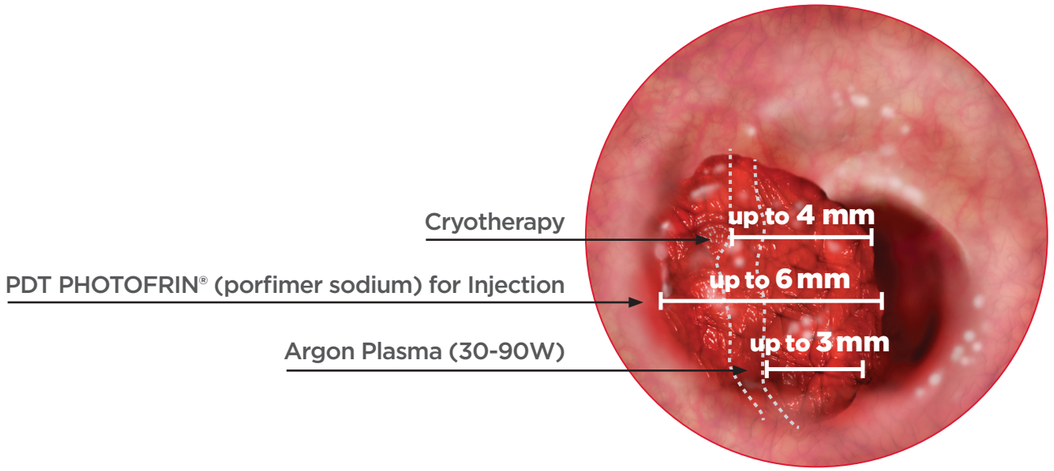
Photodynamic Therapy (PDT) Makes Selective Treatment of Target Lesions and Tumor Margins Possible Up to a Depth of 6 mm[6]

PDT provides depth of ablation—up to 6 mm.



ESTIMATED DEPTH OF DAMAGE FOR VARIOUS METHODS OF ENDOSCOPIC MUCOSAL ABLATION[6]

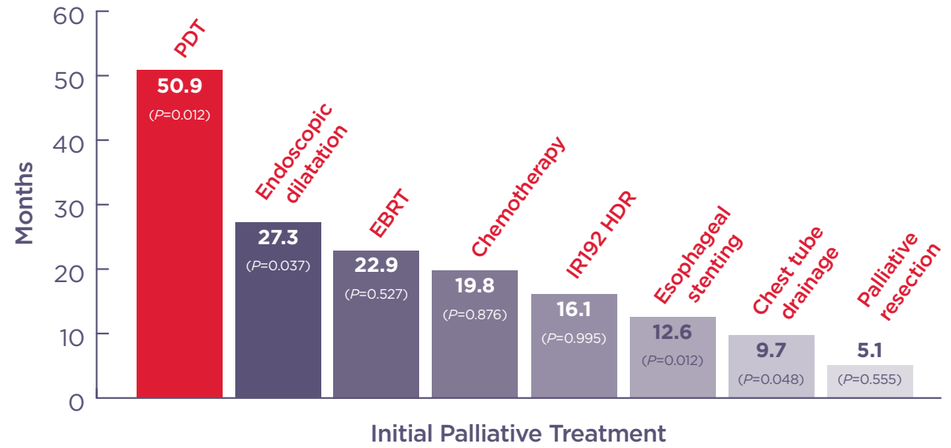
Method of ablation	Approximate depth of ablation (mm)	Author/ref
Argon laser (514 nm)	0.3	Weston 2003
KTP laser (532 nm)	0.4	Dix 1996
Diode laser (805 nm)	1.3	Dix 1996
Nd:YAG laser (1064 nm)	4–6	Dix 1996
APC (30–90 W)	1–3	Barham 1996 Franchimont 2003
MPEC 15–20 W	1.7–4.8	Sampliner 2003
ALA PDT	2	Tan 1999 Gossner 1990
Exogenous PDT	4–6	Barr 1990 Heier 1995
Cryotherapy	1–4	Johnston 2003

KTP, potassium titanyl phosphate; Nd:YAG, neodymium yttrium aluminium garnet; APC, argon beam plasma coagulation; MPEC, multipolar electrocoagulation; ALA PDT, 5-aminolevulinic acid photodynamic therapy.

Individualized Multimodality Treatment With Photodynamic Therapy (PDT)[7]

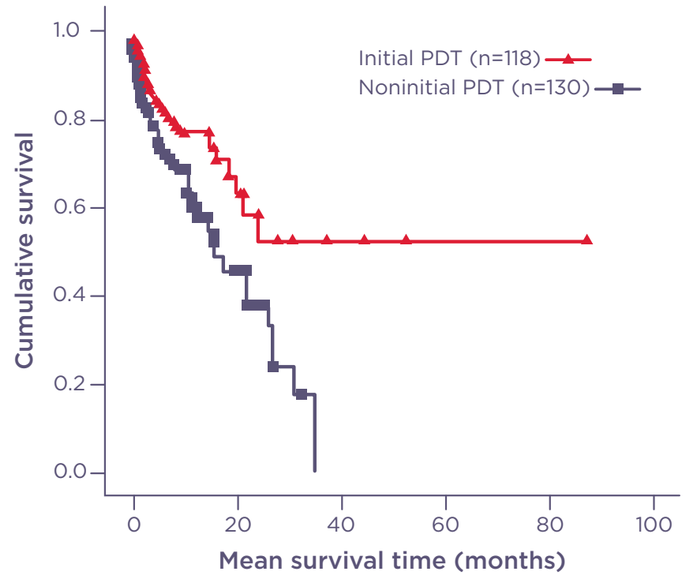
MEDIAN SURVIVAL BY TREATMENT MODALITY

Median Survival Depending on the Type of Initial Palliative Treatment



The long mean survival time of 50.9 months recorded in our patients following initial PDT was biased by the fact, that the method was used as first therapeutic step only in absence of gross tumor infiltration into the mediastinum, the great vessels or the tracheo-bronchial tree.

MEDIAN SURVIVAL[7]



Median survival in the 118 patients in whom PDT was used as a first treatment was 50.9 months, compared to 17.3 months for those in whom other options were used as the initial modality (*P*=0.012).

The use and timing of PHOTOFRIN® (porfimer sodium) for Injection with PDT and other treatment modalities in this study has not been addressed in the prescribing information. A multimodality palliative approach was individualized for each patient. The findings in this publication are from a retrospective study without randomization.

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Chemotherapy and Photodynamic Therapy (PDT)

PDT MAY BE USED WITH CHEMOTHERAPY, WHICH MAY PROVIDE ADDITIONAL BENEFITS[8]

PDT combined with chemotherapy can prolong survival and improve quality of life in patients with advanced esophageal cancer.

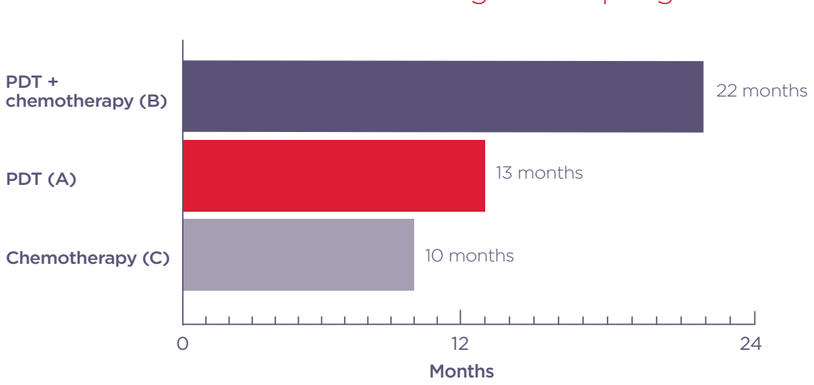
Median Survival Time in Patients With Advanced Esophageal Cancer (Stages III-IV)[8]

Group	Stage	Median Survival Time (months)	*P-value**
PDT + chemotherapy (B)	III (19/33)	22	0.030
	IV (14/33)	7	
PDT (A)	III (19/27)	13	0.046
	IV (8/27)	5	
Chemotherapy (C)	III (17/30)	10	0.345
	IV (13/30)	4	

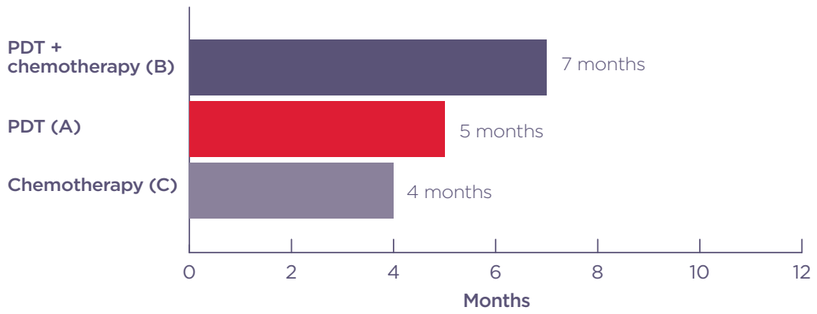
**P<0.05 was considered to be statistically significant.*

P value: Group A vs. Group B=0.046, Group B vs Group C=0.030, Group A vs Group C=0.345

Median Survival Time in Patients With Stage III Esophageal Cancer[8]



Median Survival Time in Patients With Stage IV Esophageal Cancer[8]



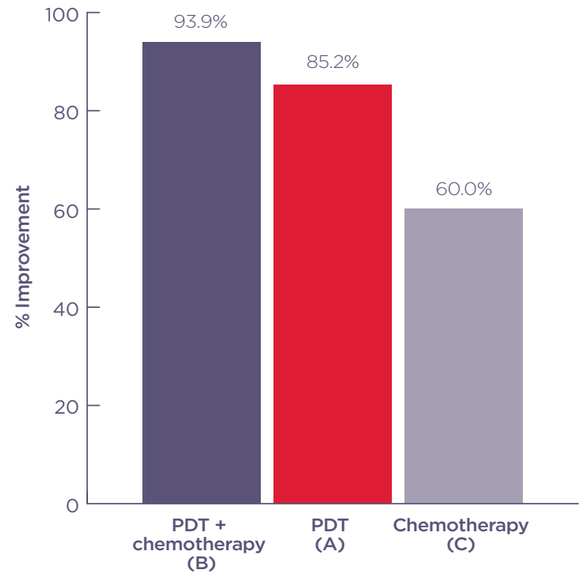
Dysphagia Improvement in Patients With Advanced Esophageal Cancer[8]

Group	n	CR + PR†	*P-value‡*
PDT + chemotherapy (B)	33	31 (93.9%)	0.002
PDT (A)	27	23 (85.2%)	0.394
Chemotherapy (C)	30	18 (60.0%)	0.043

†CR, complete response; PR, partial response.

‡P<0.05 was considered to be statistically significant.

Dysphagia Improvement (CR + PR) in Patients With Advanced Esophageal Cancer[8]



The findings in this publication are from a retrospective study without randomization. In addition, the light dosage and time of light application in the study were outside of the guidelines provided in the PHOTOFRIN® (porfimer sodium) for injection prescribing information.

The use and timing of PHOTOFRIN with PDT and with other treatment modalities in this study have not been addressed in the PHOTOFRIN prescribing information.

PDT WITH PHOTOFRIN® (porfimer sodium) for Injection

Light up the possibilities

Photodynamic Therapy (PDT) in the Treatment of High-Grade Dysplasia (HGD) in Barrett's Esophagus

PDT IS A GUIDELINE-RECOMMENDED THERAPY IN THE TREATMENT OF HGD IN BARRETT'S ESOPHAGUS BY BOTH THE AMERICAN COLLEGE OF GASTROENTEROLOGY (ACG) AND THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION (AGA)[9,10]

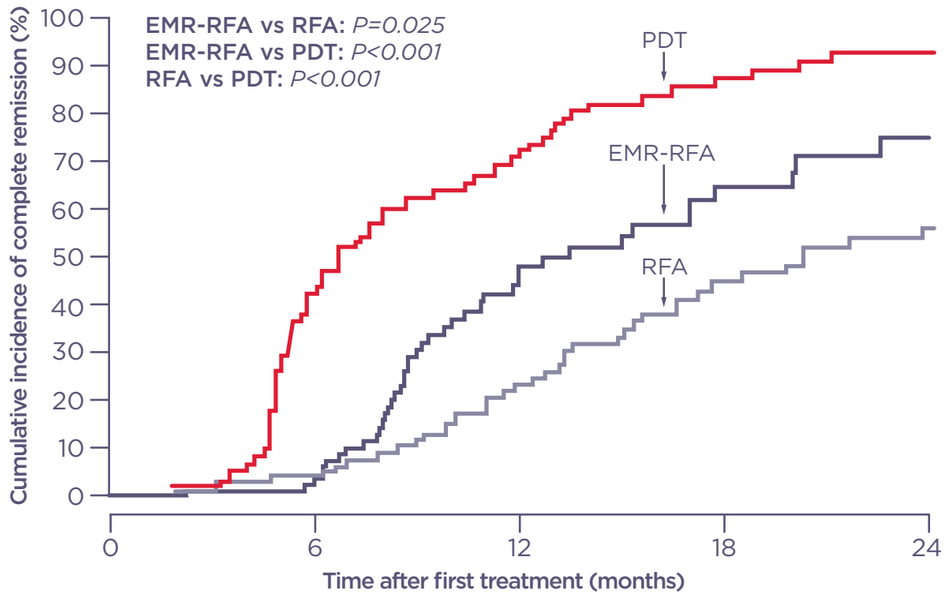
INDICATION

PHOTOFRIN® (porfimer sodium) for Injection is indicated for the ablation of HGD in Barrett's esophagus patients who do not undergo esophagectomy.[5]

COMPARISON OF ENDOSCOPIC TREATMENT MODALITIES FOR BARRETT'S NEOPLASIA[11]

Complete remission was achieved more often and more rapidly after PDT with similar disease recurrence rates compared with endoscopic mucosal resection (EMR) or radiofrequency ablation (RFA).

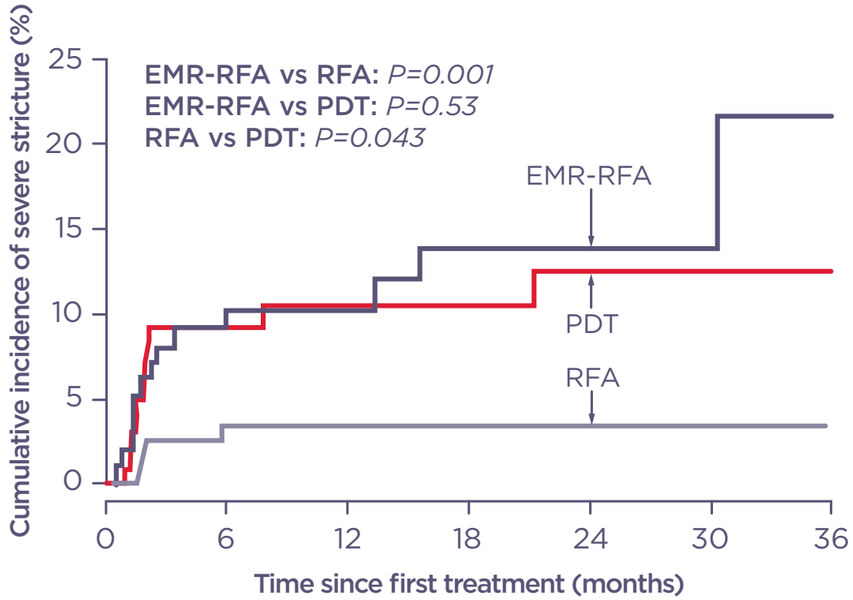
Cumulative Incidence of Complete Remission of Intestinal Metaplasia (CRIM) After the Start of Treatment in EMR-RFA, RFA, and PDT Patients[11]



No. at risk					
PDT	125	45	21	8	3
EMR-RFA	98	78	28	13	5
RFA	119	94	55	32	22

- The likelihood of CRIM was significantly greater for PDT patients compared with RFA patients in both the single-variable and multivariable analyses
- The mean number of PDT treatments is 1 compared with a mean of 3 for RFA

Cumulative Incidence of Strictures After the Start of Treatment for EMR-RFA, RFA, and PDT Patients[11]



No. at risk							
PDT	125	76	61	45	37	34	30
EMR-RFA	98	84	62	39	23	11	7
RFA	119	100	78	55	45	38	32

Study Methodology: Retrospective, single-site, observational cohort study approved by Mayo Clinic Institutional Review Board. Dr. Wolfson is a clinical research consultant for Pinnacle Biologics, Inc and Concordia Laboratories Inc.

- Baseline demographics were not comparable between groups
- PDT light dose: The light dose utilized in this study was 200 to 250 J/cm, as compared to the on-label light dose of 130 J/cm for high-grade dysplasia (HGD) in Barrett's esophagus

PDT WITH PHOTOFRIN® (porfimer sodium) for Injection

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Pinnacle Biologics™ Support

Pinnacle Biologics™ offers a comprehensive suite of programs and services to support your practice and patients.

FOR YOUR PRACTICE

- On-site assistance to help establish the use of photodynamic therapy (PDT) in your facility
- PDT Laser support
- PDT Academy certification
- Insurance benefit verification
- Reimbursement and billing support

FOR YOUR PATIENTS

- Patient education materials
- Patient co-pay assistance
- Referral to independent nonprofit co-pay foundations
- Underinsured patient assistance program

Visit www.PHOTOFRIN.com or call 1-855-215-2720 to learn more.

References: 1. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Esophageal and Esophagogastric Junction Cancers. Version 2.2016. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Published July 7, 2016. Accessed July 20, 2016. **2.** ASGE Standards of Practice Committee, Evans JA, Early DS, et al; American Society for Gastrointestinal Endoscopy. The role of endoscopy in the assessment and treatment of esophageal cancer. *Gastrointest Endosc.* 2013;77(3):328-334. **3.** Litle VR, Luketich JD, Christie NA, et al. Photodynamic therapy as palliation for esophageal cancer: experience in 215 patients. *Ann Thorac Surg.* 2003;76(5):1687-1693. **4.** PDT Academy. Faculty Recommendation. 2015. **5.** PHOTOFRIN® (porfimer sodium) for Injection [package insert]. Chicago, IL: Pinnacle Biologics, Inc.; 2015. **6.** Barr H, Stone N, Rembacken B. Endoscopic therapy for Barrett's oesophagus. *Gut.* 2005;54(6):875-884. **7.** Lindenmann J, Matzi V, Neuboeck N, et al. Individualized, multimodal palliative treatment of inoperable esophageal cancer: clinical impact of photodynamic therapy resulting in prolonged survival. *Lasers Surg Med.* 2012;44(3):189-198. **8.** 8. Li L, Xie J, Zhang X, Chen J, Luo Y, Zhang L, Luo R. Retrospective study of photodynamic therapy vs photodynamic therapy combined with chemotherapy and chemotherapy alone on advanced esophageal cancer. *Photodiagnosis and Photodynamic Therapy.* 2010;7:139-143. **9.** Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. *Am J Gastroenterol.* 2016;111(1):30-50; quiz 51. doi:10.1038/ajg.2015.322. **10.** Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ; American Gastroenterological Association. American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterology.* 2011;140(3):e18-e52; quiz e13. doi:10.1053/j.gastro.2011.01.031. **11.** David WJ, Qumseya BJ, Qumsiyeh Y, et al. Comparison of endoscopic treatment modalities for Barrett's neoplasia. *Gastrointest Endosc.* 2015;82(5):793-803.e3.

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