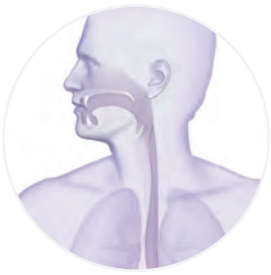
Achieving Clinically Proven Treatment Results for Esophageal Cancer With Photodynamic Therapy (PDT) and PHOTOFRIN® (porfimer sodium) for Injection

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]

FDA APPROVED ESOPHAGEAL CANCER INDICATION[3]

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



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)

IMPORTANT SAFETY INFORMATION ABOUT PHOTOFRIN® (PORFIMER SODIUM) FOR INJECTION

- PHOTOFRIN® should not be used in patients with porphyria.
- Photosensitivity and Ocular Photosensitivity: Observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days. Instruct patients when outdoors to wear dark sunglasses which have an average light transmittance of <4% for at least 30 days and until ocular sensitivity resolves.
- Other photosensitizing agents may increase the risk of photosensitivity reaction.

MOST COMMON ADVERSE REACTIONS

- Esophageal cancer: Anemia, pleural effusion, pyrexia, constipation, nausea, chest pain, pain, abdominal pain, dyspnea, photosensitivity reaction, pneumonia, vomiting, insomnia, back pain, pharyngitis.
- High-Grade Dysplasia in Barrett's Esophagus: Photosensitivity reaction, esophageal stenosis, vomiting, chest pain, nausea, pyrexia, constipation, dysphagia, abdominal pain, pleural effusion, dehydration.

This is not a full list of risks and side effects. See important prescribing and safety information for PHOTOFRIN® (porfimer sodium) for Injection on Page 11. Talk to your health care provider and read the patient labeling for more information on **www.photofrin.com**

PDT with PHOTOFRIN®
TARGETING ~~CANCER MARGINS~~
(porfimer sodium) for injection

The Three Components of Photodynamic Therapy (PDT)

1. PHOTOFRIN® (porfimer sodium) for Injection

PHOTOFRIN® (porfimer sodium) for Injection is injected 40 to 50 hours prior to laser activation, where it's selectively retained in tumor cells. When activated with red laser light, the drug produces a chain reaction of cell death in targeted tissue, with low collateral damage to healthy tissue.

2. Fiber

The Optiguide Fiber Optic Diffuser Series have a range of fiber diffuser lengths which enables the red laser light delivery to multiple tumor sizes. The series includes the Rigid Diffuser and the Flexible Diffuser options. The Flexible Diffuser includes a flexible yet durable material to ease navigation through instruments and anatomy.

OPTIGUIDE™
FIBER OPTIC

Flexible Diffuser

Rigid Diffuser

Flexible Diffuser

3. Laser

The laser generates 630 nm wavelength red non-thermal laser light necessary for PHOTOFRIN® activation.

PHOTOFRIN®
630 PDT Laser

PHOTOFRIN® (porfimer sodium) for Injection Photodynamic Therapy (PDT) Timeline

DAY 1

Step 1

Administration

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

Targeted Retention

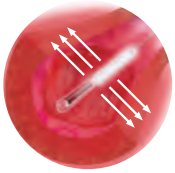
PHOTOFRIN® for Injection is selectively retained in cancer cells.

DAY 3

Step 2

Laser Application[3]

- 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.[3]

DAY 5

Step 3

Endoscopy and second light treatment, if necessary[3]

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

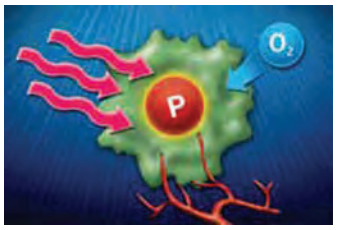
IMPORTANT SAFETY INFORMATION ABOUT PHOTOFRIN® (PORFIMER SODIUM) FOR INJECTION (CONTINUED FROM PAGE 1)

- High-Grade Dysplasia (HGD) in Barrett's Esophagus (BE): After treatment of HGD in BE, conduct endoscopic biopsy surveillance every 3 months, until 4 consecutive negative evaluations for HGD have been recorded.
- Use Before or After Radiotherapy: Allow 2-4 weeks between PDT and subsequent radiotherapy.

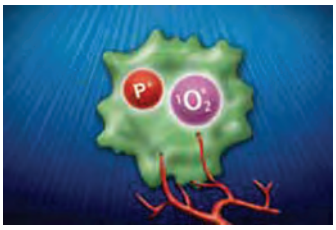
This is not a full list of risks and side effects. See important prescribing and safety information for PHOTOFRIN® (porfimer sodium) for Injection on Page 11. Talk to your health care provider and read the patient labeling for more information on **www.photofrin.com**

PDT with PHOTOFRIN® TARGETING ~~CANCER MARGINS~~ (porfimer sodium) for injection

ACTIVATION



Red light permeates tissue (the indicated light dosimetry for esophageal cancer 300 J/cm) and activates PHOTOFRIN® to an excited state.[3]



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

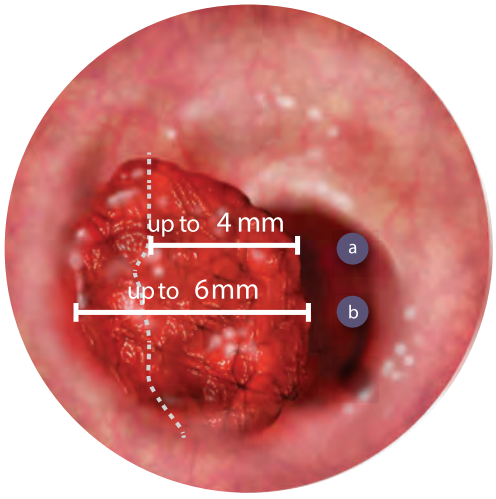
DESTRUCTION OF CANCER CELLS

Excited PHOTOFRIN® causes vasoconstriction, which leads to vascular occlusion and additional tumor cell death.[3]

Treatment results in lysis and ischemic necrosis of cancer cells.[3]

Photodynamic Therapy (PDT) Makes Selective Treatment of Target Lesions and Tumor Margins Possible Up to a Depth of 6mm[5]

PDT provides depth of ablation—up to 6 mm.



A. Cryotherapy

B. PDT with PHOTOFRIN® (porfimer sodium) for Injection

IMPORTANT SAFETY INFORMATION ABOUT PHOTOFRIN® (PORFIMER SODIUM) FOR INJECTION (CONTINUED FROM PAGE 1)

- Hepatic and Renal Impairment: Patients with hepatic or renal impairment may need longer precautionary measures for photosensitivity.
- Thromboembolism: Thromboembolic events can occur.
- Chest Pain: Substernal chest pain can occur.
- Embryo-Fetal Toxicity: May cause embryo-fetal toxicity. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

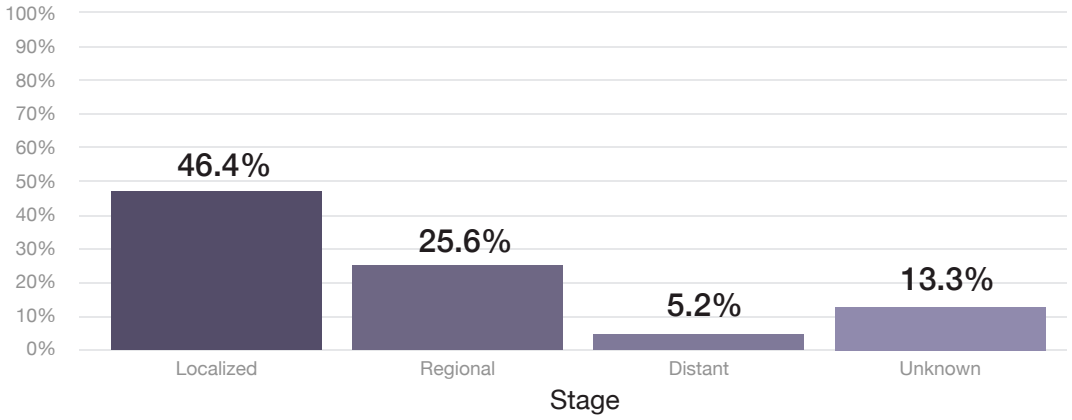
This is not a full list of risks and side effects. See important prescribing and safety information for PHOTOFRIN® (porfimer sodium) for Injection on Page 11. Talk to your health care provider and read the patient labeling for more information on **www.photofrin.com**

PDT is a clinically proven therapy for Stage 1 (Localized) Esophageal Cancer

Patients with Stage I esophageal cancer have cancer that invades beneath the surface lining of the esophagus, but not into the muscle wall of the esophagus, the lymph nodes or other locations in the body. This is also called an early, superficial or localized cancer that is surgically resectable[6].

Esophageal Survival by Stage

5-Year Relative Survival



5-Year Relative Survival
19.9%
2011-2017

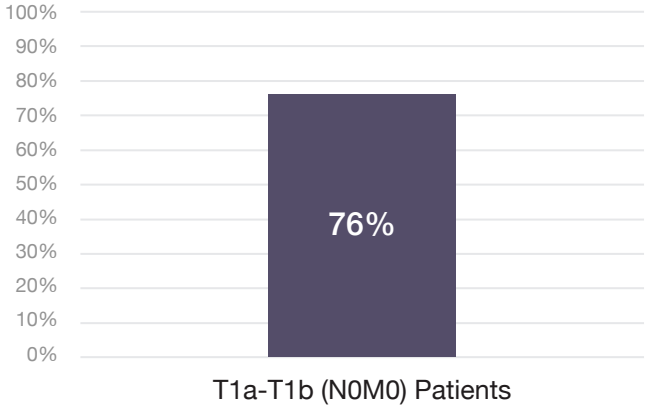
SEER 18 2011–2017, All Races, Both Sexes by SEER Summary Stage 2000[7]

Photodynamic therapy for large superficial squamous cell carcinoma of the esophagus[8]

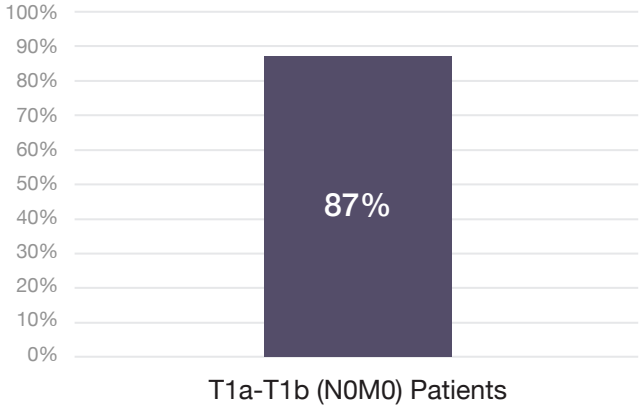
Patients:

- A total of 38 patients with superficial SCC of the esophagus
- All patient had a large unifocal lesion or multifocal lesions that were too large to be resected endoscopically
- All patients were physiologically unfit for esophagectomy or had refused surgery

5-Year Relative Survival



Complete Remission

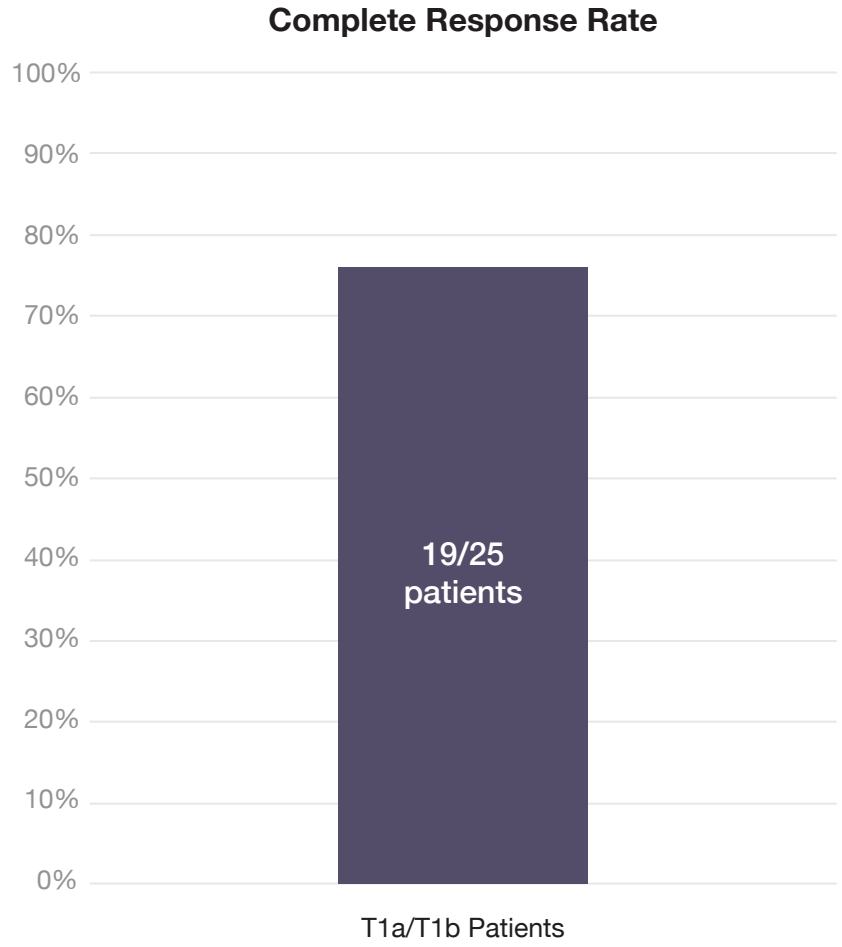


Conclusions:

- This long-term follow-up study revealed that PDT was a potentially curative treatment for large superficial esophageal SCC.
- PDT might be a reasonable alternative to esophagectomy or to endoscopic resection for patients with superficial SCC of the esophagus without lymph node metastasis.

Photodynamic therapy for Esophageal Cancer[9]

A 25-patient prospective study was conducted to confirm the efficacy and safety of salvage PDT for local failure after chemoradiotherapy.



IMPORTANT SAFETY INFORMATION ABOUT PHOTOFRIN® (PORFIMER SODIUM) FOR INJECTION (CONTINUED FROM PAGE 1)

- Gastroesophageal Fistula and Perforation: Do not initiate PHOTOFRIN with photodynamic therapy (PDT) in patients with esophageal tumors eroding into the trachea or bronchial tree or bronchial wall.
- Pulmonary and Gastroesophageal Hemorrhage: Assess patients for tumors eroding into a pulmonary blood vessel and esophageal varices. Do not administer light directly to an area with esophageal varices.
- Photosensitivity and Ocular Photosensitivity: Observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days. Instruct patients when outdoors to wear dark sunglasses which have an average light transmittance of <4% for at least 30 days and until ocular sensitivity resolves.
- Airway Obstruction and Respiratory Distress: Administer with caution to patients with tumors in locations where treatment-induced inflammation can obstruct the main airway. Monitor patients closely between the laser light therapy and the mandatory debridement bronchoscopy for any evidence of respiratory distress.
- Esophageal Strictures: Esophageal strictures can occur.

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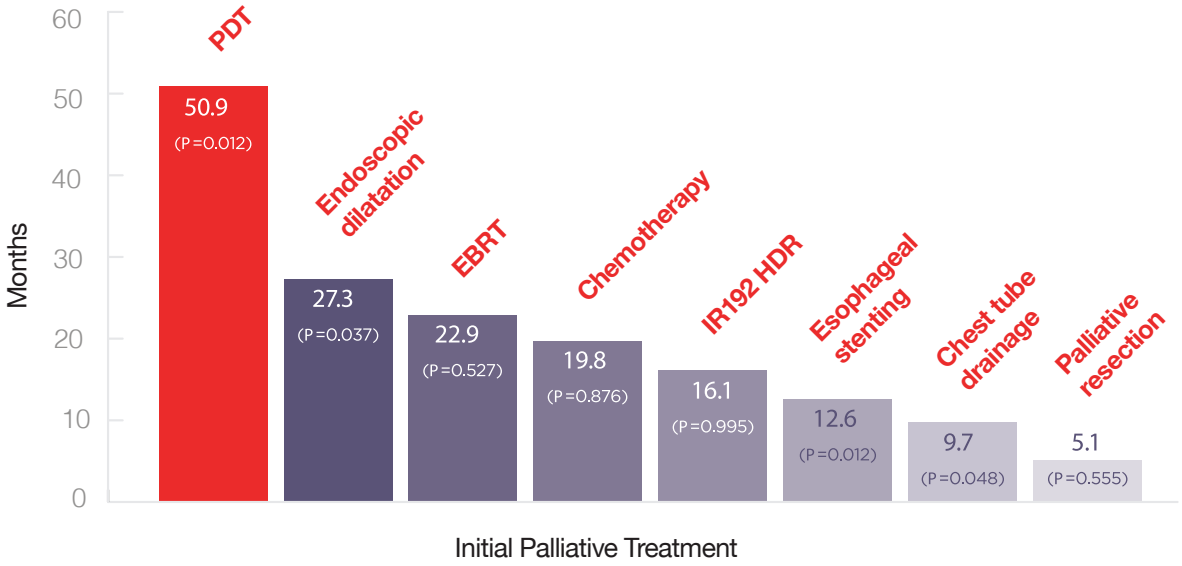
Individualized Multimodality Treatment With Photodynamic Therapy (PDT)[10]

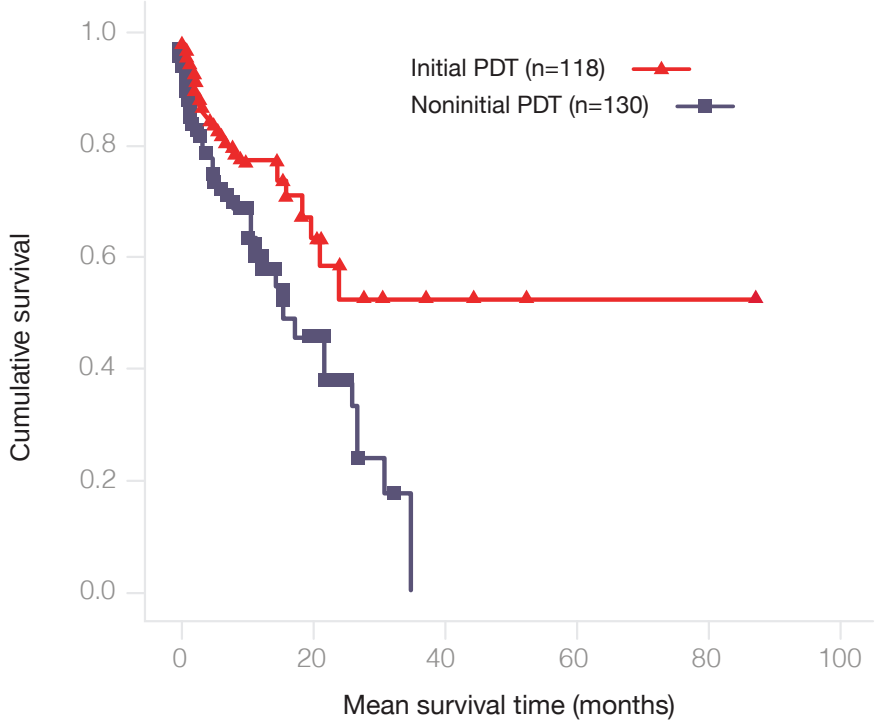
Median Survival by treatment modality

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[10]

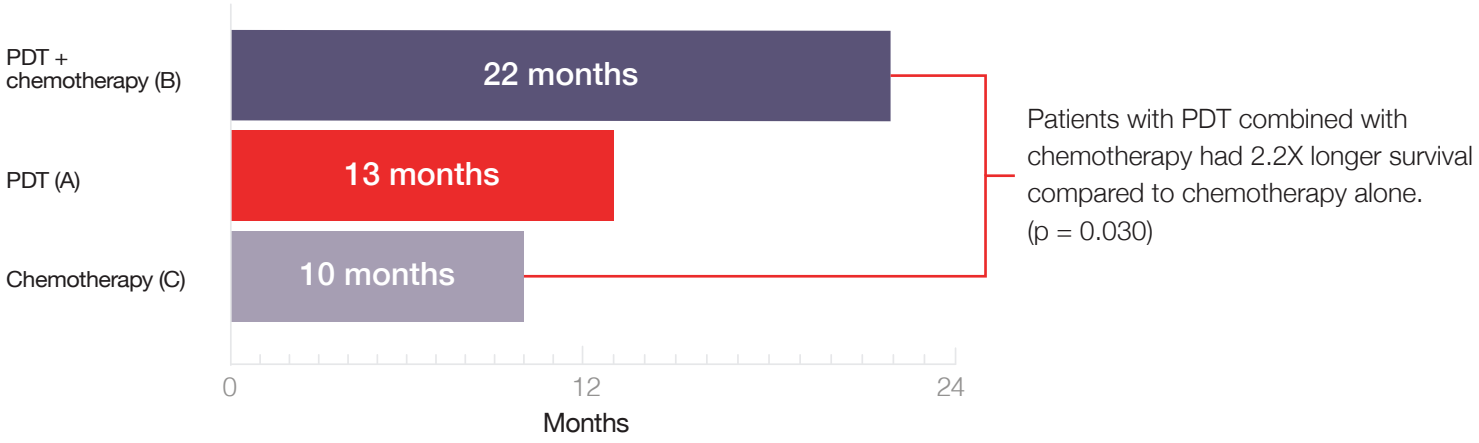


Median survival in the 118 patients in whom PDT was used as a first treatment was 50.9 months, compared to 17.3 months for those in whom other options were used as the initial modality (P=0.012).

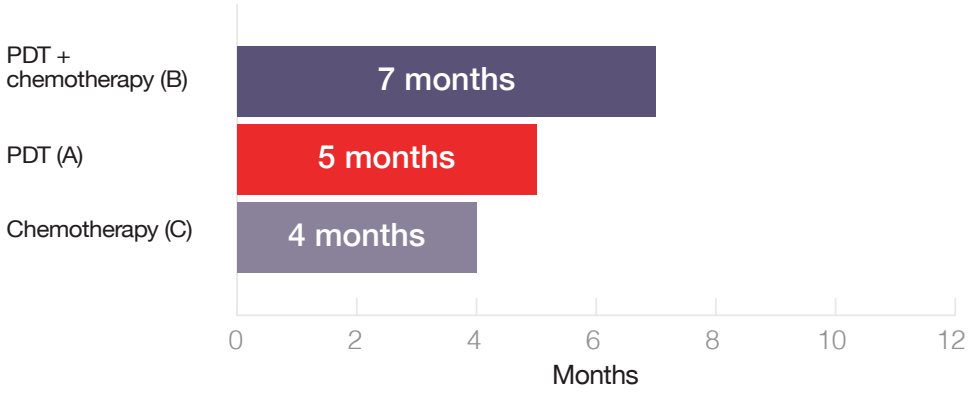
The use and timing of PHOTOFRIN® (porfimer sodium) for Injection with PDT and other treatment modalities in this study has not been addressed in the prescribing information. A multimodality palliative approach was individualized for each patient. The findings in this publication are from a retrospective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

Chemotherapy and Photodynamic Therapy (PDT)

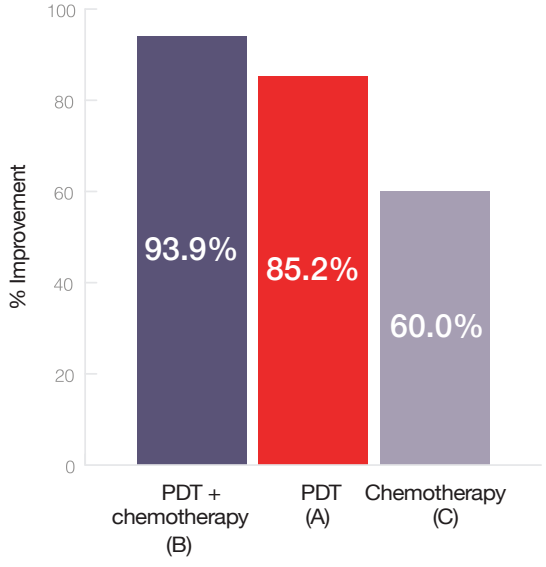
Median Survival Time in Patients With Stage III Esophageal Cancer[11]



Median Survival Time in Patients With Stage IV Esophageal Cancer[11]



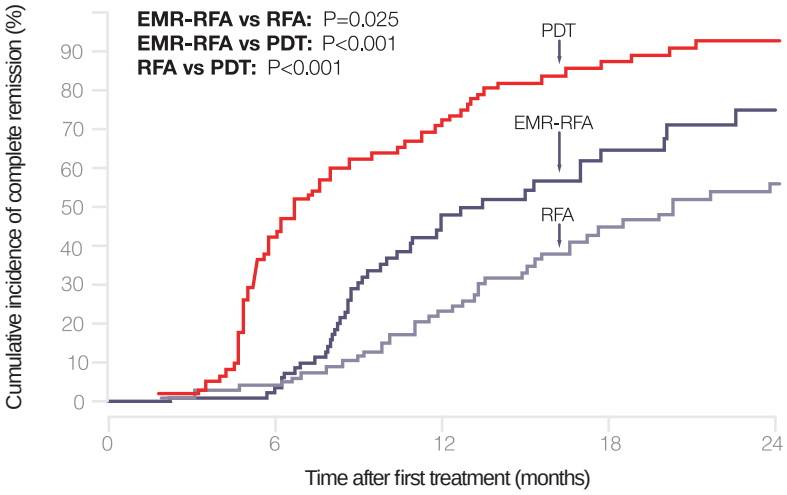
Dysphagia Improvement (CR + PR) in Patients With Advanced Esophageal Cancer[11]



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)[12,13]

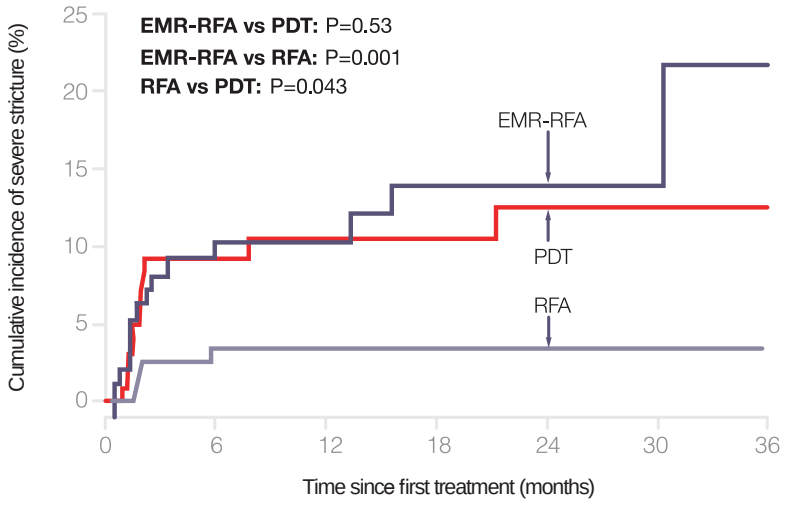
Cumulative Incidence of Complete Remission of Intestinal Metaplasia (CRIM) After the Start of Treatment in EMR-RFA, RFA, and PDT Patients[14]



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

The Cumulative Incidence of Strictures was Not Significantly Different Between EMR-RFA and PDT[14]



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

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PHOTOFRIN® (porfimer sodium) for Injection Indications

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.
Ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) patients who do not undergo esophagectomy.

Important Safety Information About PHOTOFRIN® (porfimer sodium) for Injection

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

IMPORTANT WARNINGS AND PRECAUTIONS USING PHOTOFRIN® INCLUDE:

Gastroesophageal Fistula and Perforation: Do not initiate PHOTOFRIN with photodynamic therapy (PDT) in patients with esophageal tumors eroding into the trachea or bronchial tree or bronchial wall.
Pulmonary and Gastroesophageal Hemorrhage: Assess patients for tumors eroding into a pulmonary blood vessel and esophageal varices. Do not administer light directly to an area with esophageal varices.
High-Grade Dysplasia (HGD) in Barrett's Esophagus (BE): After treatment of HGD in BE, conduct endoscopic biopsy surveillance every 3 months, until 4 consecutive negative evaluations for HGD have been recorded.
Photosensitivity and Ocular Photosensitivity: Observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days. Instruct patients when outdoors to wear dark sunglasses which have an average light transmittance of <4% for at least 30 days and until ocular sensitivity resolves.
Use Before or After Radiotherapy: Allow 2-4 weeks between PDT and subsequent radiotherapy.
Chest Pain: Substernal chest pain can occur
Airway Obstruction and Respiratory Distress: Administer with caution to patients with tumors in locations where treatment-induced inflammation can obstruct the main airway. Monitor patients closely between the laser light therapy and the mandatory debridement bronchoscopy for any evidence of respiratory distress.
Esophageal Strictures: Esophageal strictures can occur
Hepatic and Renal Impairment: Patients with hepatic or renal impairment may need longer precautionary measures for photosensitivity.
Thromboembolism: Thromboembolic events can occur.
Embryo-Fetal Toxicity: May cause embryo-fetal toxicity. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

MOST COMMON ADVERSE REACTIONS reported during clinical trials (>10% of patients) 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.

Other photosensitizing agents may increase the risk of photosensitivity reaction. Because of the potential for serious adverse reactions in the breastfed infant, advise patients that breastfeeding is not recommended during treatment with PHOTOFRIN and for 5 months after the last dose.

Please see full Prescribing Information for PHOTOFRIN® (porfimer sodium) for Injection at: www.photofrin.com

FOR MORE INFORMATION about PHOTOFRIN®, or if there are any questions regarding the information provided, visit **www.photofrin.com** or please contact the Medical Information Department at **1-866-248-2039**. 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**.

PHOTOFRIN® is distributed in the United States by Pinnacle Biologics, Inc., Bannockburn, IL 60015

ADP-051 v.02 10/2021

PDT with PHOTOFRIN®
TARGETING ~~CANCER MARGINS~~
(porfimer sodium) for injection

PINNACLE™
BIOLOGICS