THE ROLE OF PHOTODYNAMIC THERAPY FOR THE TREATMENT OF GASTROINTESTINAL CARCINOMAS

Marko Doko[1], Elizabet Glavan[1], Mario Zovak[1], Mario Kopljar[1], Hrvoje Hochstädter[1] and Neven Ljubičić[2]

[1]University Department of Surgery, [2]University Department of Medicine,
Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – The discovery that particular substances can cause photosensitivity is attributed to Oscar Raab, however, the modern era of photodynamic therapy was established by Dr. T.J. Dougherty from Buffalo Memorial Institute. He was the first to report that a systemically injected porphyrin (hematoporphyrin), when activated by red light, caused complete eradication of transplanted experimental tumors. He also was the first to demonstrate the preferential accumulation of the photosensitizer in malignant cells. The first clinical application of photodynamic therapy was in 1980 at the Tokyo Medical College in a patient with a small upper bronchial squamous cell tumor, treated at bronchoscopy with photodynamic therapy using a laser as the light source. The tumor was completely eradicated. Simultaneously, a case of large obstructing esophageal cancer similarly treated with photodynamic therapy with good relief of dysphagia and prolonged survival was reported. The current state-of-the-art and results recorded in the clinical use of photodynamic therapy in the management of gastrointestinal malignancies are presented.

Key words: *Photochemotherapy; Photosensitizing agents – therapeutic use; Photochemotherapy – instrumentation; Gastrointestinal neoplasms – therapy*

History of Clinical Photodynamic Therapy

The discovery that an administered substance could cause photosensitivity is attributed to Oscar Raab, however, the modern era of photodynamic therapy (PDT) was established by Dr. T.J. Dougherty from Buffalo Memorial Institute[1]. He reported that a systemically injected porphyrin (hematoporphyrin), when activated by red light, caused complete eradication of transplanted experimental tumors. He also demonstrated the preferential accumulation of the photosensitizer in malignant tissue[1]. The first clinical application of PDT was at the Tokyo Medical College in a patient with a small upper bronchial squamous

cell tumor, treated in 1980 at bronchoscopy with PDT using a laser as the light source. The tumor was completely eradicated[2]. Simultaneously, large obstructing esophageal cancers were similarly treated with PDT with good relief of dysphagia and possible prolongation of survival[3].

How Does PDT Work?

PDT is a new approach to cancer treatment in which photosensitizers localized in cancers are activated under visible light to interact with oxygen[4]. The interaction produces active singlet oxygen, which causes damage to mitochondria, plasma membranes, and lysosomes in tumor cells leading to tumor cell death[5-11].

At the cellular level, several targets are involved in PDT. It should be noted that all photosensitizers used for PDT are primarily located outside the cell nucleus[12]. Since singlet oxygen has a short lifetime and a radius of action of only about 0.001 micrometer, DNA will not be significantly

Correspondence to: *Elizabet Glavan, M.D.*, University Department of Surgery, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia

E-mail: eglavan@mef.hr

damaged. Therefore, most PDT procedures have a very low mutagenic and carcinogenic potential[12,13].

PDT *in vivo* causes cell death by necrosis and/or by apoptosis[7]. Which of these two processes will play the major role is dependent on the cell type, photosensitizer, and conditions during and after PDT[14-16]. In necrosis, cellular defenses are overcome by toxic injury such as oxidative stress, leading to the impairment of cellular homeostasis[17]. Apoptosis is thought to be a 'programmed cell death' mechanism for the elimination of unwanted cells, acting as a complement of mitosis[18-21]. It is also recognized as a cell response to mild injury or viral infection, resulting in the elimination of damaged cells[22]. Indeed, it can be induced by various stimuli, including oxidants or stimulants of cellular oxidative metabolism[23] and mitochondrial injury[24,25]. Apoptosis and necrosis also differ in the biochemical and morphological changes that lead to cell fragmentation into vesicles ('apoptotic bodies') or cell lysis, respectively.

PDT sometimes affects membrane proteins. This, as well as some intracellular reactions, may explain why PDT has an immune effect[26-28]. Examples have been reported that there are less metastases occurring after PDT of the primary tumor than after its surgical removal. This may be attributed to its immune effect[26,27].

At the tissue level, PDT acts both on the vascular system of the tumor[29-31] and directly on tumor cells[32,33]. Some investigators claim that water-soluble sensitizers act mainly on the vascular system, whereas lipophilic drugs also act directly on the tumor cells. Furthermore, if the time between the application of sensitizer and light exposure is short, vascular damage is thought to be particularly important[34-37]. The significance of vascular damage has been convincingly demonstrated by a combination of *in vivo* and *in vitro* experiments[38-40]: if tumors are excised and their cells brought into culture shortly after PDT, many tumor cells may survive. The survival of tumor cells is much lower if the time between PDT and excision and explantation is long.

The frequently used photosensitizers in clinical practice are porphyrins and 5-aminolevulinic acid. Porphyrins have been known to induce photosensitivity for nearly 100 years[41]. In the middle of the 20th century, the photodynamic properties of hematoporphyrin derivatives were more closely studied, later resulting in the appearance of two commercial products for systemic application on the pharmaceutical market: Photofrin, so far the only one registered for clinical use in the United States and Europe, and Photosan. Both represent a mixture of hematoporphyrin esters

and ethers of different lengths. The first approval of Photofrin was obtained in Canada in 1993 for the treatment of bladder cancer, with currently additional indications approved, such as esophageal, pulmonary, gastric and cervical cancer[42]. The intravenous administration of Photofrin at doses of up to 5.0 mg/kg body weight led to maximal tumor-to-normal cell concentration after 24 to 48 hours[43]. The cutaneous accumulation of porphyrin-based photosensitizing drugs and their slow clearance from the skin result in long-lasting cutaneous photosensitivity, requiring photoprotective measures during 4 to 6 weeks after PDT[43]. Attempts have been made to avoid this prolonged general photosensitivity by developing topical porphyrins[44].

In the early 1990s, a promising new molecule was introduced: 5-aminolevulinic acid (5-ALA). 5-ALA itself is not a photosensitizer, but is a precursor of the photoactive substance protoporphyrin IX in the biological heme biosynthesis pathway[13]. It can be applied systemically as well as topically and is of particular interest in dermatology. By topical application, the generalized cutaneous photosensitivity, which generally results after intravenous administration, can be avoided. To date, 5-ALA is the most extensively investigated substance, and today is widely used in PDT.

All photosensitizers that are used in PDT are excited in the UV and visible part of the spectrum. The illumination used in PDT should have the following general characteristics: light intensity should be constant across the illuminated field; the illuminated field should have sharp boundaries; the spectrum should be well defined; and the intensity should be in the range of 100 to 200 mW/sq.cm[45]. Light sources for PDT can be grossly divided into two main categories: conventional light sources and lasers.

Photodynamic Therapy for Advanced Esophageal Cancer

Esophageal cancer accounts for around 2% of cancer deaths in the western world[46]. The diagnosis is associated with a median survival of 10 months, and fewer than 5% of patients are cured. In the past, squamous cell carcinomas accounted for most esophageal cancers (around 90%) but the incidence of adenocarcinoma of lower esophagus has been on an increase and these tumors now account for 20%-40% of cases[47]. The risk of squamous cell cancer is modestly increased with cigarette smoking or alcohol consumption[48], whereas Barrett's esophagus is an important risk factor for adenocarcinoma of the esophagus[49].

The dreadful prognosis of esophageal cancer is related in part to the fact that it remains undetected until the disease is far advanced. Fewer than 10% of patients with esophageal cancer present with the disease confined to the mucosa or submucosa (stage I)[46]. In these patients, esophageal resection remains the treatment of choice and can result in 60%-80% five-year survival. In stage II and III disease, however, only 15% of patients become longterm survivors[46,50].

Patients with esophageal cancer usually present with dysphagia and often only palliative treatment can be offered. The main aim of this therapy is to open the esophageal lumen, allowing adequate oral nutrition. There are many methods for the palliation of malignant esophageal obstruction[51-56]. Surgical bypass for palliation has been curtailed almost completely due to the availability of less invasive endoscopic methods. The two methods most frequently used for the palliation of malignant dysphagia are Nd:YAG laser treatment and expandable metal stents. Effective palliation of malignant dysplasia can be reached in almost 96% of patients treated with Nd:YAG laser. Laser vaporizes or coagulates tumor tissue, and the aim of therapy is to debulk a tumor causing intraluminal obstruction and to coagulate bleeding tumors. This procedure can be done quickly as a day case and produces rapid improvement of symptoms[52]. The disadvantage is that symptomatic relief may be short lived (four to six weeks), requiring repeated treatments[52]. Expandable metal stents have also demonstrated effective palliation for malignant dysphagia[51,53,54]. The reported complications include unrelenting pain, severe gastroesophageal reflux, stent migration, and tumor ingrowth[53,54].

PDT is the most recent Food and Drug Administration (FDA) approved modality for the palliative treatment of obstructing esophageal cancer. Prior to FDA approval, phase II and III trials were reported by several groups for palliation of dysphagia in patients with obstructing esophageal cancer. McCaughan *et al.* have reported on the results of PDT treatment in 77 patients with esophageal carcinoma during a 12-year period[57]. All their patients had failed on conventional treatment or were ineligible for surgical therapy. Median survival in their patients was 6.3 months. Their only major variable affecting survival after PDT treatment was the clinical stage. The low incidence of complications in their series included transient elevation of temperature, pleural effusion, infiltrates, pulmonary edema, aspiration pneumonia, respiratory-esophageal fistula, strictures, and sunburn. Lightdale *et al.* have report-

ed on the only prospective, randomized, multicenter study comparing PDT with Nd:YAG laser therapy for obstructing esophageal cancer[58]. In their study, 236 patients at 24 centers were randomized to undergo PDT or Nd:YAG laser therapy. Improvement of dysphagia was equivalent in the two groups, however, PDT caused fewer acute perforations (1%) than Nd:YAG laser therapy (7%).

Various methods are used for endoscopic photodynamic therapy. Most groups used various derivatives of hematoporphyrin and Photofrin at a dose of 2 mg/kg body weight, given by slow intravenous injection 48 h before irradiation with laser light in the red at 630 nm[57-59]. The light can be delivered circumferentially using cylindrical diffusing quartz fibers; the length of the diffuser can vary from 2 to 7 cm to treat various lengths of tumor. A total light dose of 150-300 J/cm^2 is required to obtain up to 6-mm depth of necrosis[57-59]. The depth of necrosis is highly dependent on the photosensitizer used. The depth of necrosis using exogenously administered photosensitizers is 6 mm, compared to 2 mm following the administration of 5-ALA to generate the photosensitizer protoporphyrin IX[60]. Treatment times of 10-20 min are required to deliver the light at a non-thermal fluence rate[57]. It is important to note that some patients may have temporary worsening of dysphagia caused by edema and tumor necrosis prior to necrotic tissue separation. This usually resolves after 5 days and may be associated with some blood loss[57,58]. Conclusively, PDT is today a safe and effective modality for the palliation of obstructive esophagus cancer and patients can tolerate it under awake sedation. Disadvantages of PDT include the requirement of expensive equipment (laser), the long waiting period between the time of drug injection and treatment, the high cost of the photosensitizing agents, and skin photosensitivity[60].

Photodynamic Therapy for Barrett's Esophagus

Barrett's esophagus has been increasingly recognized as an important premalignant condition[62]. The past two decades have witnessed a striking increase in the incidence of adenocarcinoma of distal esophagus and gastric cardia. It has been estimated that the incidence of these highly lethal cancers is accelerating at a faster rate than any other malignancy in the western world[63]. The cause of these dramatic epidemiologic changes in the incidence of upper gastrointestinal cancer is unclear, however, there is no doubt as to the association of Barrett's esophagus and ad-

enocarcinoma. Barrett's esophagus is characterized by replacement of the normal squamous esophageal mucosa with a metaplastic columnar epithelium defined by the presence of intestinal metaplasia[64]. The development of cancer is thought to progress through a series of molecular events in the unstable metaplastic epithelium, leading to mutant clones of cells that progress morphologically to low-grade and then to high-grade dysplasia, to early invasive carcinoma, and finally to advanced carcinoma. The incidence of adenocarcinoma of the esophagus in Barrett's esophagus has been estimated to 1 *per* 125 patient years, or 800 cases *per* 100,000 population *per* year, an annual incidence of 0.8%[62]. Once high-grade dysplasia is identified and confirmed, the standard recommendation is that patients have esophagectomy, based on data suggesting that the frequency of undetected cancer in such cases is as high as 50%[65]. This treatment is a highly curative but draconian approach involving considerable morbidity and some mortality[65].

There are multiple reasons why photodynamic therapy may turn out to be a successful treatment for Barrett's esophagus with high-grade dysplasia. Barrett's esophagus can involve long segments of the esophagus, and dysplastic changes are often multifocal in an unpredictable distribution. Dysplasia can occur in flat Barrett's tissue that cannot be distinguished from the surrounding nondysplastic tissue.

Photodynamic therapy following both endogenous photosensitization with 5-ALA and exogenous photosensitization with Photofrin has been reported for the treatment of high-grade dysplasia and metaplasia in Barrett's esophagus. There have been two major clinical studies of 5-ALA photodynamic therapy for the ablation of high-grade dysplasia. Both demonstrated eradication of the dysplasia and one series demonstrated successful eradication of T1 tumors that were less than 2 mm in depth[66,67]. A prospective randomized trial of the treatment of low-grade dysplasia using ALA and irradiation with green light rather than usual 630-nm red light has confirmed again how effective this treatment is in reversing dysplasia/metaplasia. Healing proceeded with the regeneration of neosquamous epithelium[68].

Overholt *et al.*[69] have updated their longterm observations of the efficacy of PDT using Photofrin as a method of secondary cancer prevention in patients with neoplastic Barrett's esophagus. Forty-eight hours after the administration of 2 mg/kg of Photofrin, at endoscopy they delivered light from a laser at 630 nm to the esophagus. They used power density of 400 mW/cm^2 to provide an energy density of 100-250 J/cm^2. Out of 80 patients with high-grade dysplasia treated between 1999 and 2001, 65 were still available for follow-up; in 62, complete elimination of dysplasia was reported, two had persistent dysplasia, and one had progressed to cancer. The intention-to-treat analysis showed 78% of the patients with high-grade dysplasia in Barrett's esophagus to have achieved therapeutic success or the primary endpoint of dysplasia elimination and absence of progression. At first glance, the results of this study suggest that PDT is a highly efficacious therapy in patients with Barrett's esophagus and high-grade dysplasia.

Photodynamic Therapy for Gastric Cancer

Gastric cancer is the second most common tumor type globally and the fourth most common in Europe[70]. Although the overall incidence has been decreasing over the past few decades, the incidence of adenocarcinoma of the proximal stomach and esophagogastric junction is rising. Gastric cancer presenting at an early stage can be treated surgically, however, 80% of cases are too advanced at presentation[70]. The use of PDT for the palliation of advanced gastric cancer appears to be of little advantage over the alternative laser or thermal methods[71]. Early gastric cancer has a good prognosis but radical surgical excision carries significant morbidity. Local therapy of high-grade dysplasia and early cancer is possible because there is a low probability of lymph node metastases. For small cancers (<2 cm) of type I to IIa, the 5-year survival is between 80% and 95%[72]. There are few methods to treat early gastric cancers after accurate staging with endosonography: endoscopic mucosal resection, Nd:YAG laser therapy, and PDT. A major advantage of endoscopic mucosal resection is the availability of a specimen for precise histopathologic examination. However, thermal and endoscopic mucosal resection is associated with the risk of perforation and seeding tumor cells in the resection or thermal wound. Several photosensitizers including Photofrin and 5-ALA have been evaluated for PDT or early gastric cancer[73]. A major disadvantage of 5-ALA is that deep destruction is difficult, yet it is highly specific for the mucosa. Light fluences of 150-300 J/cm are required if Photofrin is used. This is particularly important in the stomach, where the geometry is difficult in comparison with the geometry of the cylindrical esophagus. PDT has proved effective in the treatment of type I, IIa and IIb cancers, if less than 2 cm in diameter[73,74].

Photodynamic Therapy for Cholangiocarcinoma

Cholangiocarcinoma can be a relatively indolent tumor, but treatment with surgery, radiotherapy and chemotherapy is very difficult. Aggressive surgical therapy is only possible in a minority of patients with early cancers, and median survival is between 13 and 20 months[75]. At present, endoscopic insertion of plastic or metal stents is the method of choice to relieve obstructive jaundice in nonresectable cholangiocarcinoma. However, palliative intervention is limited in proximal bile duct cancers. In Bismuth type I and II stenoses, technically successful stent insertion is accompanied by effective drainage in up to 91% of cases[76], with a median survival time of 149 days in Bismuth I and 84 days in type II strictures[76]. However, in Bismuth type III and IV stenoses, effective drainage is a rare event, possibly due to intrahepatic tumor spread with development of multiple intrahepatic stenoses. Ducreux *et al.*[76] report on a bilirubin decrease by more than 50% in only 15% of patients with Bismuth type III strictures. Because of the dismal prognosis and frequent treatment failure in nonresectable Bismuth type III and IV cholangiocarcinoma, there is high interest in PDT as a more advanced palliative strategy. The initial reports on the use of PDT in patients with cholangiocarcinoma are promising.

The largest study to date and the only peer-reviewed publication is suggestive of additional quality of life benefits[77]. Ortner *et al.*[77] prospectively evaluated the effect of PDT on cholestasis, quality of life, and survival in 13 patients. All had elevated serum bilirubin levels, nine of whom did not respond adequately to palliative endoscopic stent placement. These nine patients were loaded with 2 mg/kg dihematoporphyrin ether (DHE) and treated with laser light at 630 nm. The power was 180 J/cm². The light fiber was delivered *via* endoscopic retrograde cholangiopancreatography (ERCP) with a mother-baby scope to allow for direct cholangioscopic control. Serum bilirubin levels decreased significantly in all nine patients, and the five in whom a gross decrease in the tumor was noted underwent a second light activation. The patient Karnofsky index, World Health Organization (WHO) index, and performance rating scale all significantly improved. No death occurred within 30 days and median survival in this cohort was 439 days.

Berr *et al.*[78] performed PDT in ten patients with unresectable cholangiocarcinoma with biliary access *via* ERCP. One laser session was performed in four patients and 2 treatment sessions were done in six patients after loading with 2 mg/kg DHE. The laser energy was 200 to 240 J/cm² at 630 nm. Bilateral bile duct patency was achieved in all patients. Six patients were demonstrated to have no tumor on repeat biopsies performed at 94-324 days after therapy. This report suggests that the potential of tumor bulk reduction distant from the treatment site in small bile ducts deserves additional investigations as to whether this is an immune phenomenon or diffusion of light through the biliary tree.

Conclusion

Photodynamic therapy is a modality with a significant potential as cancer treatment for both curative and palliative therapy. It has yet to be introduced in the routine clinical practice. The recent development of a new, second generation photosensitizers with a decreased toxicity, different kinetic and degradation profiles, improved selectivity and longer activation wavelengths, will improve the efficacy of PDT and continue to broaden its potential application. Further investigation into light dosimetry, changes in sensitizer concentration, and defining optimal oxygen tension and blood flow during PDT must occur to optimize conditions for maximal tumor cell killing effect and minimization of the potential toxicity. Studies combining PDT with other therapeutic modalities including surgery, radiation therapy and chemotherapy, endoscopic and radiologic interventions are needed to further define the role of these modalities in the treatment of this severe disease.

References

1. DOUGHERTY TJ. Activated dyes as antitumor agents. J Natl Cancer Inst 1974;52:1333-6.

2. HAYATA Y, KATO H, KONAKA C, ONO J, TAKIZAWA N. Hematoporphyrin derivative and laser photoradiation in the treatment of lung cancer. Chest 1982;81:269-77.

3. McCAUGHEN JS, HICKS W, LAUFMAN L, MAY E, ROACH R. Palliation of esophageal malignancy with photoradiation therapy. Cancer 1984;54:2905-10.

4. HE XY, SIKES RA, THOMSEN S, CHUNG LWK, JACQUES SL. Photodynamic therapy with photofrin II induces programmed cell death in carcinoma cell lines. Photochem Photobiol 1994;59:468-73.

5. GOMER CJ, RUCHER N, FERRARIO A, WONG S. Properties and application of photodynamic therapy. Radiat Res 1989;120:1-18.

6. HAMPTON JA, SELMAN SH. Mechanism of cell killing in photodynamic therapy using a novel *in vivo* drug/*in vitro* light culture system. Photochem Photobiol 1992;56:235-43.

7. ATHAR M, MUKHTAR H, BICKERS DR. Differential role of reactive oxygen intermediates in photofrin I- and photofrin II-mediated photoenhancement of lipid peroxidation in epidermal microsomal membranes. J Invest Dermatol 1988;90:652-7.

8. WILSON BC, JEEVES WP. Photodynamic therapy of cancer. In: Photomedicine, II. Boca Raton, FL: CRC Press, 1987: 127-77.

9. HENDERSON BW, WALDOW SM, MANG TS. Tumor destruction and kinetics of tumor cell death in two experimental mouse tumors following photodynamic therapy. Cancer Res 1985;45:572-6.

10. WEISHAUPT KR, GOMER CJ, DOUGHERTY TJ. Identification of singlet oxygen as the cytotoxic agent in photoinactivation of a murine tumor. Cancer Res 1976;36:2326-9.

11. DOKO M, JURIN M, SVARC A, TONKOVIC G, LEDINSKY M. The introduction of photodynamic therapy for tumorous patients in Croatia based on our experimental experiences and clinical approaches of the other groups. Coll Antropol 1998;22:315-9.

12. BERG K. Basic principles of 5-aminolevulinic acid-based photodynamic therapy. In: Photodynamic therapy and fluorescence diagnosis in dermatology. Series in photosciences. Elsevier Science BV, 2001:115-62.

13. KENNEDY JC, POTTIER RH, PROSS DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. J Photochem Photobiol 1990;6:143-8.

14. BEDWELL JA, MacROBERT AJ, PHILLIPS D, BROWN SG. Fluorescence distribution and photodynamic effect of ALA-induced PPIX in the DMH rat colonic tumor model. Br J Cancer 1992;65:818-24.

15. BOYLE RW, PAQUETTE B, van LIER JE. Biological activities of phthalocyanines XIV. Effect of hydrophobic phthalimidomethyl groups on the *in vivo* phototoxicity and mechanism of photodynamic action of sulphonated aluminium phthalocyanines. Br J Cancer 1992;65:813-7.

16. GIBSON SL, Van der MEID KR, MURANT RS, HILF R. Increased efficacy of photodynamic therapy of R3230AC mammary adenocarcinoma by intratumoral injection of photofrin II. Br J Cancer 1990;61:553-7.

17. BOOBIS RA, FAWTHROP DJ, DAVIES DS. Mechanisms of cell death. Trends Pharmacol Sci 1989;10:275-80.

18. KERR JFR, WYLLIE AH, CURRIE AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972;26:239-57.

19. CLARKE PGH. Developmental cell death: morphological diversity and multiple mechanisms. Anat Embryol (Berl) 1990;181:195-213.

20. ELLIS RE, YUAN J, HOROWITZ HR. Mechanism and functions of cell death. Annu Rev Cell Biol 1991;7:663-98.

21. SCHWARTZ LM, SMITH SW, JONES MEE, OSBORNE BA. Do all programmed cell deaths occur *via* apoptosis? Proc Natl Acad Sci USA 1993;90:980-4.

22. BURSCH W, OBERHAMMER F, SCHULTE-HERMANN R. Cell death by apoptosis and its protective role against disease. Trends Pharmacol Sci 1992;13:245-51.

23. BUTTKE TM, SANDSTROM PA. Oxidative stress as a mediator of apoptosis. Immunol Today 1994;15:7-10.

24. RICHTER C. Pro-oxidants and mitochondrial Ca^{2+}: their relationship to apoptosis and oncogenesis. FEBS Lett 1993;325:104-7.

25. WOLVETANG EJ, JOHNSON KL, KRAUER K, RALPH SJ, LINANNE AW. Mitochondrial respiratory chain inhibitors induce apoptosis. FEBS Lett 1993;339:40-4.

26. KORBELIK M, NARAPARAJU VR, YAMAMOTO N. Macrophage-directed immunotherapy as adjuvant to photodynamic therapy of cancer. Br J Cancer 1997;75:202-7.

27. KORBELIK M, SUN J. Cancer treatment by photodynamic therapy combined with adoptive immunotherapy using genetically altered natural killer cell line. Int J Cancer 2001;93:269-74.

28. REITER I, SCHWAMBERGER G, KRAMMER B. Activation of macrophage tumoricidal activity by photodynamic treatment *in vitro* – indirect activation of macrophages by photodynamically killed tumor cells. J Photochem Photobiol B 1999;50:99-107.

29. KRAMMER B. Vascular effects of photodynamic therapy. Anticancer Res 2001;21(6B):4271-7.

30. HSI RA, ROSENTHAL DI, GLATSTEIN E. Photodynamic therapy in the treatment of cancer: current state of the art. Drugs 1999;57:725-34.

31. FINGAR VH, KIK PK, HAYDON PS, CERRITO PB, TSENG M, ABANG E, *et al.* Analysis of acute vascular damage after photodynamic therapy using benzoporphyrin derivative (BPD). Br J Cancer 1999;79:1702-8.

32. LAM M, OLEINICK NL, NIEMINEN AL. Photodynamic therapy-induced apoptosis in epidermoid carcinoma cells. Reactive oxygen species and mitochondrial inner membrane permeabilization. J Biol Chem 2001;276:47379-86.

33. WISPRIYONO B, SCHMELZ E, PELAYO H, HANADA K, SEPAROVIC D. A role for the *de novo* sphingolipids in apoptosis of photosensitized cells. Exp Cell Res 2002;279:153-65.

34. MICHELS S, SCHMIDT-ERFURTH U. Sequence of early vascular events after photodynamic therapy. Invest Ophthalmol Vis Sci 2003;44:2147-54.

35. HAGER A, SCHMIDT-ERFURTH U. BARBAZETTO I, MICHELS S, LAQUA H. Photodynamic therapy: ICG angiography findings. Ophthalmologe 1999;96:291-9.

36. FERRARIO A, von TIEHL KF, RUCKER N, SCHWARZ MA, GILL PS, GOMER CJ. Antiangiogenic treatment enhances photodynamic therapy responsiveness in a mouse mammary carcinoma. Cancer Res 2000;60:4066-9.

37. KESSEL D, WOODBURN K, HENDERSON BW, CHANG CK. Sites of photodamage *in vivo* and *in vitro* by a cationic porphyrin. Photochem Photobiol 1995;62:875-81.

38. HAJRI A, WACK S, MEYER C, SMITH MK, LEBERQUIER C, KEDINGER M, *et al. In vitro* and *in vivo* efficacy of photofrin and pheophorbide, a, a bacteriochlorin, in photodynamic therapy of colonic cancer cells. Photochem Photobiol 2002;75:140-8.

39. KUROHANE K, TOMINAGA A, SATO K, NORTH JR, NAMBA Y, OKU N. Photodynamic therapy targeted to tumor-induced angiogenic vessels. Cancer Lett 2001;167:49-56.

40. LIN GC, TSOUKAS ML, LEE MS, GONZALEZ S, VIBHAGOOL C, ANDERSON RR, *et al.* Skin necrosis due to photodynamic action of benzoporphyrin depends on circulating rather than tissue drug levels: implications for control of photodynamic therapy. Photochem Photobiol 1998;68:575-83.

41. HAUSMANN W. Über die giftige Wirkung des Hämatoporphyrins auf Warmbluter bei Belictung. Wien Klin Wochenschr 1909;22:1820-1.

42. CEBURKOV O, GOLLINCK H. Photodynamic therapy in dermatology. Eur J Dermatol 2000;10:568-76.

43. OCHNER M. Photodynamic therapy: the clinical perspective. Arzneimittelforschung Drug Res 1997;47:1185-94.

44. FRITSCH C, GOERTZ G, RUZICKA T. Photodynamic therapy in dermatology. Arch Dermatol 1998;134:207-14.

45. BRANCALEON L, MOSELEY H. Laser and non-laser light sources for photodynamic therapy. Lasers Med Sci 2002;17:173-86.

46. ELLIS P, CUNNINGHAM D. Current issues in cancer: management of carcinomas of the upper gastrointestinal tract. BMJ 1994;308:834-8.

47. PERA M. Trends in incidence and prevalence of specialized intestinal metaplasia, Barrett's acute esophagus, and adenocarcinoma of the gastroesophageal junction. World J Surg 2003;27:999-1008.

48. REHM J, ROOM R, GRAHAM K, MONTEIRO M, GMEL G, SEMPOS CT. The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: an overview. Addiction 2003;98:1209-28.

49. GOPAL DV, LIEBERMAN DA, MAGARET N, FENNERTY MB, SAMPLINER RE, GAREWAL HS, *et al.* Risk factors for dysplasia in patients with Barrett's esophagus (BE): results from a multicenter consortium. Dig Dis Sci 2003;48:1537-41.

50. LEONARD GD, McCAFFREY JA, MAHER M. Optimal therapy for oesophageal cancer. Cancer Treat Rev 2003;29:275-82.

51. ACUNAS B, ROZANES I, AKPINAR S, TUNACI A, TUNACI M, ACUNAS G. Palliation of malignant oesophageal strictures with self-expanding nitinol stents: drawbacks and complications. Radiology 1996;199:648-52.

52. ADAM A, ELLUL J, WATKINSON AF, TAN BS, MORGAN RA, SAUNDERS MP, *et al.* Palliation of inoperable esophageal carcinoma: a prospective randomized trial of laser therapy and stent placement. Radiology 1997;202:344-8.

53. FAN Z, DAI N, CHEN L. Expandable thermal-shaped memory metal esophagus stent: experiences with a new nitinol stent in 129 patients. Gastrointest Endosc 1997;46:352-7.

54. LAGATTOLLA NR, ROWE PH, ANDERSON H, DUNK AA. Restenting malignant oesophageal strictures. Br J Surg 1998;85:261-3.

55. LUKETICH JD, NGUYEN NT, WEIGEL TL, KEENAN RJ, FERSON PF, BELANI CP. Photodynamic therapy for treatment of malignant dysplasia. Surg Laparosc Endosc Percutan Tech 1999;9:171-5.

56. SCHEIDER DM, SIEMENS M, CIROCCO M, HABER GB, KANDEL G, KORTAN P, *et al.* Photodynamic therapy for the treatment of tumor ingrowth in expandable esophageal stents. Endoscopy 1997;29:271-4.

57. McCAUGHAN JS Jr, ELLISON EC, GUY JT, HICKS WJ, JONES JJ, LAUFMAN LR, *et al.* Photodynamic therapy for esophageal malignancy: a prospective twelve-year study. Ann Thorac Surg 1996;62:1005-9; Discussion 1009-10.

58. LIGHTDALE CJ, HEIER SK, MARCON NE, McCUAGHAN JS Jr, GERDES H, OVERHOLT BF, *et al.* Photodynamic therapy with porfimer sodium *versus* thermal ablation therapy with Nd:YAG laser for palliation of esophageal cancer: a multicenter randomized trial. Gastrointest Endosc 1995;42:507-12.

59. HEIER SK, ROTHMAN KA, HEIER LM, ROSENTHAL WS. Photodynamic therapy for obstructing esophageal cancer: light dosimetry and a randomized comparison with Nd:YAG laser therapy. Gastroenterology 1995;109:63-72.

60. TAN WC, FULLJAMES C, STONE N, *et al.* Photodynamic therapy using 5-aminolevulinic acid for oesophageal adenocarcinoma associated with Barrett's metaplasia. J Photochem Photobiol B 1999;53:75-80.

61. LUKETICH JD, CHRISTIE NA, BUENAVENTURA PO, WEIGEL TL, KEENAN RJ, NGUYEN NT. Endoscopic photodynamic therapy for obstructing esophageal cancer: 77 cases over a 2-year period. Surg Endosc 2000;14:6537.

62. SPECHLER SJ. Barrett's esophagus. Semin Oncol 1994;21:431-7.

63. BLOT WJ, DEVESA SS, KNELLER RW, *et al.* Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991;265:1287-9.

64. SAMPLINER RE. Updated guidelines for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol 2002;97:1888-95.

65. RICE TW, FALK GW, ACHKAR E, PETRAS RE. Surgical management of high-grade dysplasia in Barrett's esophagus. Am J Gastroenterol 1993;88:1832-6.

66. BARR H, SHEPHERD NA, DIX A, ROBERTS DJ, TAN WC, KRASNER N. Eradication of high-grade dysplasia in columnar-lined (Barrett's) oesophagus by photodynamic therapy with endogenously generated protoporphyrin IX. Lancet 1996;348(9027):584-5.

67. GOSSNER L, MAY A, STOLTE M, SEITZ G, HAHN EG, ELL C. KTP laser destruction of dysplasia and early cancer in columnar-lined Barrett's esophagus. Gastrointest Endosc 1999;49:8-12.

68. ACKROYD R, BROWN NJ, DAVIS MF, STEPHENSON TJ, MARCUS SL, STODDARD CJ, *et al.* Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomised, placebo controlled trial. Gut 2000;47:612-7.

69. OVERHOLT BF, PANJEHPOUR M, HALBERG DL. Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. Gastrointest Endosc 2003;58:183-8.

70. HOHENBERGER P, GRETSCHEL S. Gastric cancer. Lancet 2003;362(9380):305-15.

71. GOSSNER L, ELL C. Photodynamic therapy of gastric cancer. Gastrointest Endosc Clin North Am 2000;10:461-80.

72. TORII A, SAKAI M, KAJIYAMA T, KISHIMOTO H, KIN G, INOUE K, *et al.* Endoscopic aspiration mucosectomy as curative en-

doscopic surgery: analysis of 24 cases of early gastric cancer. Gastrointest Endosc 1995;42:475-9.

73. ELL C, GOSSNER L, MAY A, SCHNEIDER HT, HAHN EG, STOLTE M, *et al.* Photodynamic ablation of early cancers of the stomach by means of mTHPC and laser irradiation: preliminary clinical experience. Gut 1998;43:345-9.

74. NAKAMURA H, YANAI H, NISHIKAWA J, OKAMOTO T, HIRANO A, HIGAKI M, *et al.* Experience with photodynamic therapy (endoscopic laser therapy) for the treatment of early gastric cancer. Hepatogastroenterology 2001;48:1599-603.

75. PICHLMAYR R, WEIMANN A, KLEMPNAUER J, OLDHAFER KJ, MASCHEK H, TUSCH G, *et al.* Surgical treatment in proximal bile duct cancer. A single-center experience. Ann Surg 1996;224:628-38.

76. DUCREUX M, LIGUORY C, LEFEBVRE JF, INK O, CHOURY A, FRITSCH J, *et al.* Management of malignant hilar biliary obstruction by endoscopy. Results and prognostic factors. Dig Dis Sci 1992;37:778-83.

77. ORTNER MA, LIEBETRUTH J, SCHREIBER S, HANFT M, WRUCK U, FUSCO V, *et al.* Photodynamic therapy of nonresectable cholangiocarcinoma. Gastroenterology 1998;114:536-42.

78. BERR F, WIEDMANN M, TANNPFEL A, HALM U, KOHLHAW KR, SCHMIDT F, *et al.* Photodynamic therapy for advanced bile duct cancer: evidence for improved palliation and extended survival. Hepatology 2000;31:291-8.

Sažetak

ULOGA FOTODINAMSKE TERAPIJE U LIJEČENJU KARCINOMA PROBAVNOG SUSTAVA

Marko D., Elizabet G., Mario Z., Mario K., Hrvoje H. and Neven Lj.

Otkriće da određene tvari mogu uzrokovati fotosenzitivnost pripisuje se Oscaru Raabu, međutim, ocem moderne ere fotodinamske terapije smatra se T. J. Dougherty s Instituta Buffalo Memorial. On je naime prvi objavio da sistemski dan porfirin (hematoporfirin), kada se aktivira crvenom svjetlošću, uzrokuje potpuno uništenje transplantiranog eksperimentalnog tumora. Također je prvi otkrio i objavio da fotosenzibilizirajuće tvari imaju sklonost nakupljanju u malignim stanicama. Prvi slučaj kliničke primjene fotodinamske terapije učinjen je na Tokyo Medical Collegeu 1980. godine. Bolesnik s malim skvamoznim tumorom gornjeg bronha bio je bronhoskopski podvrgnut fotodinamskoj terapiji, pri čemu se kao izvor svjetlosti rabio laser, a rezultat je bio potpuna eradikacija tumora. Istodobno je objavljen slučaj kliničke primjene fotodinamske terapije kao palijacijske metode u bolesnika s velikim karcinomom jednjaka, što je dovelo do uklanjanja disfagije te produžilo bolesnikov život. Ovaj rad prikazuje dosadašnje spoznaje i rezultate kliničke primjene fotodinamske terapije u liječenju malignih bolesti probavnog sustava.

Ključne riječi: *Fotokemoterapija; Fotosenzibilizacijska sredstva – terapijska primjena; Fotokemoterapija – instrumentarij; Gastrointestinalne neoplazme – terapija*