

# Photodynamic ablation of early cancers of the stomach by means of mTHPC and laser irradiation: preliminary clinical experience

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## Abstract

**Background**—Radical surgical treatment has been the first choice for early gastric cancer, but high resolution endosonography allows in situ diagnosis with a high sensitivity and specificity and in consequence the option of local endoscopic treatment.

**Aims**—To evaluate photodynamic therapy (PDT) using *meso*-tetrahydroxyphenylchlorin (mTHPC) as the photosensitiser in superficial gastric cancer.

**Methods**—Twenty two patients with superficial early gastric cancer received mTHPC (0.075 mg/kg intravenously) and were treated 96 hours later with red light at 652 nm (20 J/cm<sup>2</sup>). Tumour response was assessed by endoscopy and extensive biopsy.

**Results**—Endoscopies performed two to three days after PDT showed a haemorrhagic fibrinoid necrosis of the mucosal layer. Complete remission was achieved in 16/22 (73%) patients: 13/16 (80%) with intestinal type cancer and 3/6 (50%) with a diffuse Lauren's carcinoma. The mean follow up period was 12 months and 20 months, respectively. An average of 1.8 treatment sessions was required. Severe side effects were not observed. Seven patients had mild to moderate skin photosensitivity reactions; 12 had local pain after PDT for 1-10 days.

**Conclusion**—PDT using mTHPC as the photosensitiser represents a safe and efficient method for topical treatment of early gastric cancer, especially of Lauren's intestinal carcinoma. If the preliminary results can be verified in larger patient series and during long term follow up, local treatment of early cancers of the stomach by PDT could be considered as a therapeutic option for selected patients.

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Keywords: photodynamic therapy; early gastric cancer; local endoscopic therapy

Before the introduction of endosonography the diagnosis of an early cancer of the stomach was established by pathological examination of the resected operative specimen. High resolution endosonography allows the diagnosis to be made in situ with a sensitivity and specificity of nearly 90%.<sup>1-4</sup> With a sufficient degree of diagnostic experience, the risk of understaging is estimated as less than 5% and that of overstaging

as approximately 20%.<sup>5-7</sup> The option of endosonographic in situ diagnosis of an early cancer allows local endoscopic therapy with a curative goal to be offered to inoperable patients, taking into account the histological classification. Endoscopic mucosectomy, photodynamic therapy (PDT), and non-selective laser destruction or electrodestruction are techniques applied in this context. We report on the application of photodynamic therapy with a curative objective in 22 patients with early cancer of the stomach.

## Materials and methods

### PATIENTS

Twenty two patients (eight women and 14 men; aged 41-89 years, mean age 75) with a histologically proven carcinoma were included in the prospective study.

All patients were treated at the Department of Medicine I of the FAU of Erlangen-Nuremberg. All treated patients were either ineligible for or had refused conventional surgery. All were informed about the experimental character of this clinical pilot study and had given their written informed consent to participate (table 1). All patients were hospitalised for the diagnostic work up and photodynamic treatment until at least two days after the PDT sessions.

Patient histories were obtained and patients underwent complete physical examination. Complete blood cell counts, blood chemistry studies, and urine analyses were performed. Clinical staging encompassed endoscopy, endoscopic ultrasound (GF-UM 20, Olympus, Hamburg, Germany), abdominal sonography, and computed tomography of the abdomen.

A follow up endoscopy was performed 48 hours after PDT to determine the initial therapeutic effect. Subsequent endoscopies with extensive biopsies (2-10) were performed after four weeks, two, three, six, nine, and 12 months, and thereafter at six monthly intervals. Endoscopic ultrasound was scheduled after three, six, and 12 months.

### PHOTOSENSITISER AND PHOTODYNAMIC THERAPY

*Meso*-tetrahydroxyphenylchlorin (mTHPC; Foscan, Scotia Pharmaceuticals Ltd, Guildford, UK) was used as a photosensitiser in a dosage of 0.075 mg/kg. The compound was injected intravenously 96 hours prior to laser irradiation. After injection patients were kept in slightly darkened rooms for five days. The reduced dose of mTHPC was chosen according to animal data and first clinical

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Table 1 Patient data

Patient no	Age (y)	Sex	Histology	Endoscopic classification	Tumour size (cm)	EUS	Remission	Follow up (months)	Comments
1	77	M	T1/G2*	I	2.5	uT1	CR	30	
2	88	M	T1/G2*	Iib	2.0	uT1	PR	24	No further treatment
3	76	F	T1/G1*	I	2.5	uT1	CR	18	Local recurrence
4	82	F	T1/G1*	Iic	2.5	uT1	CR	18	
5	60	M	T1/G1*	Iic	0.7	uT1	CR	16	
6	74	F	T1/G3*	Iia	1.5	uT1	CR	14	
7	84	M	T1/G2*	Iia	3.0	uT1	CR	13	
8	87	M	Tis/G1*	I	1.2	uT1	CR	12	
9	84	F	T1/G2*	Iic	1.8	uT1	CR	24	
10	56	M	T1/G2*	Iib	1.2	uT1	CR	5	
11	60	M	T1/G2*	Iia	3.2	uT1	PR	7	Patient died postoperatively
12	89	M	T1/G2*	Iia+Iic	4.0	uT1	CR	12	
13	75	M	T1/G2*	Iia	2.8	uT1	CR	10	
14	72	M	T1/G2*	Iia	2.6	uT1	CR	10	
15	82	F	T1/G1*	Iia	1.5	uT1	CR	9	
16	76	F	T1/G2*	Iia	1.7	uT1	CR	3	
17	71	M	T1/G3†	Iia	2.5	uT1	PR	8	No further treatment
18	81	M	T1/G3†	Iib	2.0	N	PR	6	Gastrectomy
19	56	M	T1/G3†	Iic	1.5	uT1	PR	6	Gastrectomy
20	80	M	T1/G3†	Iia	1.2	uT1	CR	20	
21	70	M	T1/G3†	Iic	1.8	uT1	CR	8	Patient died of kidney failure
22	70	F	T1/G3†	Iia	1.4	uT1	CR	3	

G1, well differentiated; G2, moderately differentiated; G3, undifferentiated. \*Intestinal type according to Laurén; †diffuse type according to Laurén. I, protruded type; Iia, elevated type; Iib, flat type; Iic, depressed type. N, normal EUS; uT1, endosonographic tumour stage uT1N0M0. EUS, endoscopic ultrasound; CR, complete remission; PR, partial remission.

experiences.<sup>9-11</sup> After application of mTHPC vital signs were taken daily, and complete blood cell counts and blood chemistry studies were performed until the patients were discharged from hospital.

After a retention time of 96 hours PDT was conducted with conventional endoscopes (Olympus Video-Gastroscope Evis 100) (fig 1). Endoscopy was performed with topical anaesthesia and intravenous sedation with 1–10 mg midazolam. A KTP pumped dye laser (KTP/YAG XP 800, Laserscope, San José, California, USA) delivered light with a wavelength of 652 nm through a 600 µm quartz fibre inserted through the biopsy channel of a flexible video endoscope.

Laser irradiation was carried out antegrade using a microlens with a 10 mm focus developed by our group; if necessary, several fields were irradiated.<sup>12</sup> The power output delivered by our applicators was measured with a calibrated integrating sphere (Labsphere Inc., New Hampshire, USA) immediately before and after PDT. A special integrated fibre detector developed by our group<sup>13</sup> helped to detect variations in the laser output power, defects of the fibre, or changes in the medium surrounding the fibre tip during laser treatment. The wavelength of 635 nm was cross checked using a hand monochromator (PTR Optics Corp., Waldham, USA). The light dose was calculated as J/cm<sup>2</sup> of tissue and was derived from the time of exposure, the power delivered by the diffuser, and the exposed area of the tumour. An energy density of 20 J/cm<sup>2</sup> was selected; the power density was 100 mWatt/cm<sup>2</sup>, and the homogeneity of light application at the aperture of the microlens was over 95%.

All patients received 20–80 mg omeprazole daily until all therapeutic lesions were healed.

STATISTICAL EVALUATION AND ETHICAL ASPECTS  
Statistical analysis yielded patient data and values which are given as means and ranges.

The study was approved by the Ethics Committee of the University of Erlangen-Nuremberg in accordance with the good clinical practice regulations.

## Results

Of the 22 patients, 16 exhibited a histologically proven Lauren's carcinoma of intestinal type; in the remaining six, the carcinoma was diffuse. Histological grading showed with one exception only well or moderately differentiated adenocarcinomas (G1–G2) of the intestinal type; for the diffuse type only undifferentiated carcinomas with signet ring-like cells were observed. The superficial extension of the carcinomas of the intestinal type varied from 7 to 40 mm, and that of the carcinomas of the diffuse type from 12 to 25 mm. The endoscopic classification according to the Japanese Endoscopic Society<sup>15</sup> of the carcinomas of the intestinal type was as follows: three patients had type I, seven type Iia, two type Iib, three type Iic, and one type Iia and Iic. The macroscopic classification of the carcinomas of the diffuse type was as follows: three patients had type Iia, one type Iib, and two type Iic. According to the TNM classification, all patients were assigned to the endosonographic uT1N0Mx stage (table 1).

Maximum necrosis of the tumour was observed three days after PDT. Mucosal healing and complete reepithelialisation took an average of three weeks under antiacid treatment with omeprazole 2 × 20 mg daily. Complete remission could be achieved in 13/16 (80%) patients with early cancer of the intestinal type. The mean follow up period was 12 months (range 3–30 months). An average of 1.8 treatment sessions was required; carcino-

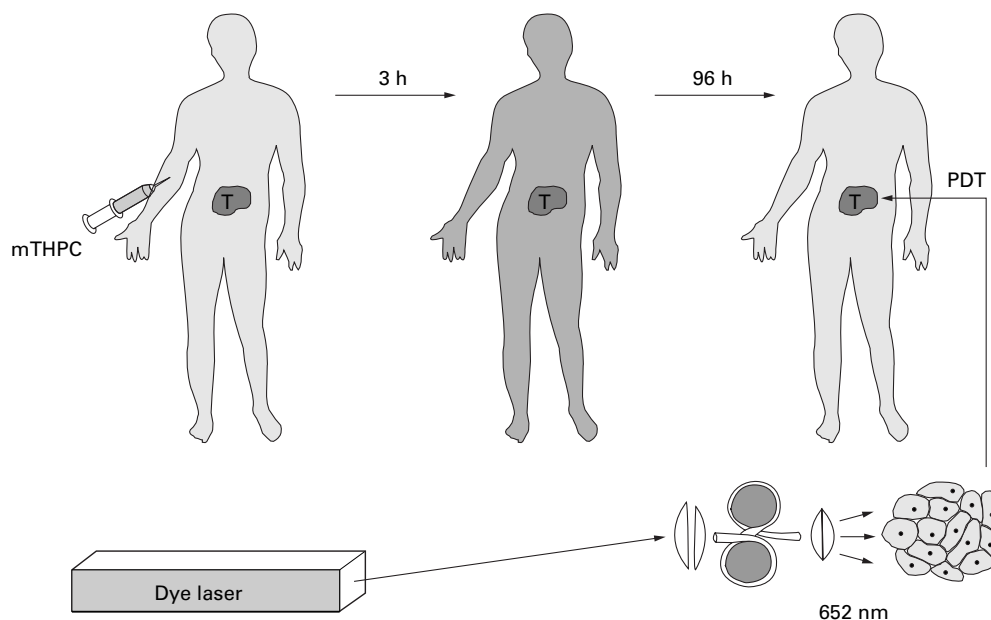


Figure 1 Principles of photodynamic therapy and the laser system.

mas larger than 20 mm had to be treated up to three times. One patient who failed to achieve remission died after gastrectomy; the other patients did not receive any further therapy because of their reduced general state of health. A further patient suffered a local recurrence 18 months later, which was then photodynamically retreated.

In 3/6 patients with a carcinoma of the diffuse type (Lauren) bioptically confirmed complete remission was achieved with an average follow up time of 20 months; 2/3 patients without complete remission were treated by gastrectomy without complications, and in one patient with a poor general state of health treatment was discontinued.

Severe side effects were not observed. Four patients showed a slight reddening of the skin, two developed pronounced sunburn on the hands, and one patient sunburn with moderate development of blisters in the face. In both cases pronounced sunburn was due to the non-compliance of the patients; they exposed their hands or face to bright sunlight. Twelve patients suffered from epigastric pain after PDT for 1–10 days, which could be well controlled by medication.

### Discussion

In contrast to advanced cancers of the stomach, early cancers have a favourable prognosis.<sup>16–19</sup> Surgical resection (gastrectomy or two thirds resection) is the established standard therapy for early cancer in Western countries. In the larger studies the morbidity and mortality rates have been reported as approximately 20–40% and 4–10%, respectively.<sup>20–22</sup> Until recently, in Western countries endoscopic treatment of early carcinomas remained confined to patients who were either inoperable or who had refused treatment. Therefore, only limited experience has so far been reported in the literature from countries of the Western hemisphere.<sup>16</sup> Fur-

thermore, the qualitative significance of some of the published reports is partly diminished by the fact that patients were treated even though the depth of penetration of the carcinoma had not been determined by endoscopic ultrasound. Thus a reliable classification as to early or advanced cancers was not possible.<sup>17–19</sup>

In addition to reports on endoscopic mucosal resection (EMR) coming almost exclusively from sources in Asia,<sup>6 14 18 23–25</sup> there have been contributions concerning non-selective Nd:YAG-laser vaporisation and case studies on electro-surgical thermocoagulation of early cancer.<sup>7 16 26</sup>

The non-selective destruction of tissue by lasers or electrocoagulation is a definite disadvantage of these thermal techniques, but their implementation does appear justified for palliative purposes. A major advantage of EMR is that the resected specimen can be examined by the pathologist to establish the absence of tumorous tissue. Yet the technique bears the risk of stomach perforation and haemorrhage and cannot—for anatomical reasons, for example, at the minor curvature—always be carried out completely and in every patient.

In contrast, PDT allows largely selective tumour destruction in all visually accessible sections of the stomach. PDT makes use of the phenomenon that light can activate photosensitising compounds stored in tissue. In several reaction steps the light energy absorbed by the photosensitiser is transferred to oxygen molecules incorporated in the tissue, leading to tumour destruction through oxidation processes that affect specific cell structures (for example, the cell membrane, or endothelium of the tumour vessels).<sup>27 28</sup> For this purpose, laser light with a defined wavelength located within the relative absorption maximum of the applied photosensitiser is endoscopically delivered into the gastrointestinal tract through a flexible optical fibre and then used for topical irradiation of the sensitised malignant tissue.

To date dihaematoporphyrinether/ester has been most frequently applied among the so called first generation photosensitisers.<sup>29</sup> However, only case based studies concerning the treatment of early stomach carcinoma have been reported.<sup>30-31</sup> This may be due to the fact that the first generation photosensitisers do not constitute a group of chemical substances with a specifically defined composition, but rather a mixture of compounds.<sup>32</sup> Furthermore, accumulation of the photosensitisers in the skin for several weeks can occur as a side effect, posing a substantial risk when patients are exposed to light. Ultimately, the first generation photosensitisers exhibit only a limited tumour selectivity.<sup>26</sup> More recent second and third generation photosensitisers with an exactly defined chemical composition—for example, 5-aminolaevulinic acid or mTHPC, can improve conditions for PDT.<sup>9, 33-34</sup> 5-Aminolaevulinic acid, which is usually administered orally, is converted to protoporphyrin IX via several enzymatic steps. Protoporphyrin IX is a potent photosensitiser with a high mucosal specificity and selectivity, especially in the stomach.<sup>35-36</sup> Due to the rapid endogenous generation and decay of porphyrin long lasting phototoxicity of the skin is not to be expected.<sup>13, 35-36</sup> Initial clinical applications of this compound have confirmed the experimental assumptions.<sup>13, 37</sup> A disadvantage of 5-aminolaevulinic acid is that because of its high mucosal specificity deeper layers of the stomach wall cannot be reached. Thus, it has been shown that  $\delta$ -aminolaevulinic acid is incapable of completely destroying the tumour in the case of Barrett's carcinoma of the oesophagus with a penetration depth of more than 2 mm. In individual cases, however, this was possible with a subsequent mTHPC treatment.<sup>8</sup> The higher photodynamic efficiency of mTHPC has been documented both in animal experiments and in a clinical experimental setting.<sup>9-11, 38</sup> The high photodynamic efficiency of mTHPC appears to be of major importance for clinical application, as this permits a significant reduction in the irradiation time and the use of substantially less expensive laser diodes and conventional light sources. The highly efficient low irradiation doses of 10–20 J/cm<sup>2</sup> allow the treatment time to be reduced by a factor of six to seven in comparison to the conventional haematoporphyrins, especially in areas that are difficult to visualise endoscopically and in which a light application system is difficult to position—as for example in the small curvature of the stomach and in large tumours. Variations in the distance between the applicator and tumour tissue can thus be minimised and more homogeneous application of light is possible.

Clinical results on the application of mTHPC in early stomach cancer are not available at present. Communications in the form of abstracts have been provided only for oesophageal applications.<sup>34-39</sup> Potentially severe complications such as perforation were observed in the reported cases, albeit under different irradiation conditions.

A modification of the treatment parameters used at 652 nm was therefore necessary in order to take advantage of the high photodynamic efficiency of mTHPC and at the same time to minimise the risk of perforation. Reducing the phototosensitiser dose by a half not only induces a lower phototoxicity in the skin, but also minimises the danger of perforation while simultaneously lowering the power density of the applied light. No local complications, and in particular no perforation or haemorrhage, occurred in our patients when our irradiation parameters—a reduced photosensitiser dose and a low power density—were maintained and the thickness of the stomach wall was taken into account. Although phototoxicity proved to be stronger than in the case of  $\delta$ -aminolaevulinic acid, only a small number of patients showed a slight skin reaction, and phototoxic effects lasted a maximum of four to five weeks. The reduced dose and the rapid bleaching of the photosensitiser, confirmed by animal experiments, must be regarded as the cause of the low level of phototoxicity in the skin.<sup>9</sup>

Our results show that complete remission can be achieved by PDT with mTHPC in up to 80% of patients with early carcinomas of the intestinal type. Due to the small number of documented cases, it cannot be conclusively determined at the present time whether the results for carcinoma of the diffuse type are comparatively worse or not. In view of the different metastatic spread—a much higher percentage of lymph node metastases must be anticipated in early diffuse carcinoma<sup>40</sup>—a more cautious approach is definitely advocated when local minimally invasive therapy is being considered for the diffuse carcinoma type.

Taking the high average patient age of 75 into account, the present results appear satisfactory, at least as far as the intestinal form of early cancer is concerned and especially in view of the perioperative mortality in this age group. The fact that the majority of our patients were multimorbid and inoperable, reinforces this conclusion.

In summary, it can be concluded that photodynamic therapy using mTHPC as the photosensitiser represents a safe and efficient method for local treatment of early cancer of the stomach, and especially of Lauren's intestinal carcinoma. If the preliminary results can be verified in a larger patient series and during long term follow up, local treatment of early cancers by means of photodynamic therapy could also be considered as a therapeutic option for selected patients.

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