

## **Tolerability of endobiliary photodynamic therapy in non-surgical Klatskin tumour patients**

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## Aims and objectives

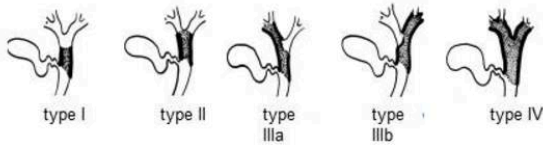
Cholangiocarcinoma is the second most common primary malignant tumor of the liver. Klatskin tumor or hilar cholangiocarcinoma represents more than 50% of all biliary tract cholangiocarcinomas [1]. The natural history of Klatskin tumors is dramatic. The median survival without interventions reaches three months, and it may be prolonged by drainage from four to ten months [2]. The patients die mainly due to jaundice, cholangitis, liver failure, complications of portal hypertension and cachexia. The majority of patients are not surgical candidates, so other therapies are required to increase their survival and improve the quality of life ( [Fig. 1](#) on page 3 ).

Endobiliary photodynamic therapy (EPDT) - is a binary tumor destruction procedure implying more or less specific accumulation of intravenously injected agent named photosensitizer by proliferative cells and inflammatory tissue following by intraductal laser irradiation ( [Fig. 2](#) on page 3 , [Fig. 3](#) on page 4 ). According to the literature the treatment of cholangiocarcinoma with endobiliary PDT is associated with an increased survival benefit, an improved biliary drainage, and a better quality of life ( [Fig. 4](#) on page 5 ). Varying intraductal light delivery equipment, irradiation regimen and light doses as well different photosensitizers using for EPDT may impact its safety. Identification of factors influencing EPDT tolerability in non-surgical Klatskin tumor patients is the purpose of the paper.

## Images for this section:

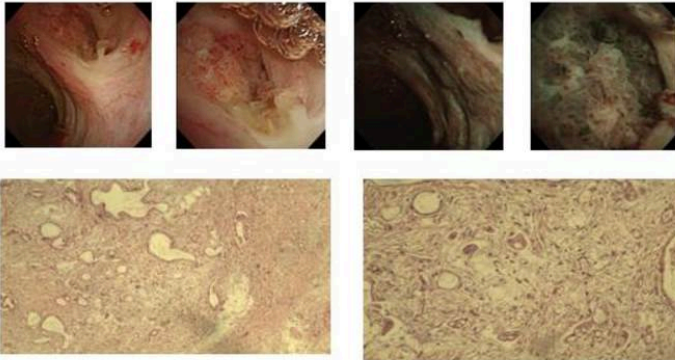
### Klatskin tumor

#### Bismuth-Corlette classifications



Park J. et al.  
Natural History and Prognostic Factors of Advanced  
Cholangiocarcinoma without Surgery, Chemotherapy, or  
Radiotherapy: A Large-Scale Observational Study //  
Gut Liver. 2009 Dec;3(4):298-305.

127 patients,  
Median survival **5.9 +/- 10.1 месяцев**



Cholangiocarcinoma...  
characterized by **dense desmoplastic stroma**  
**rich in cancer-associated fibroblasts (CAFs)**  
(Zhang XF et al., 2017)

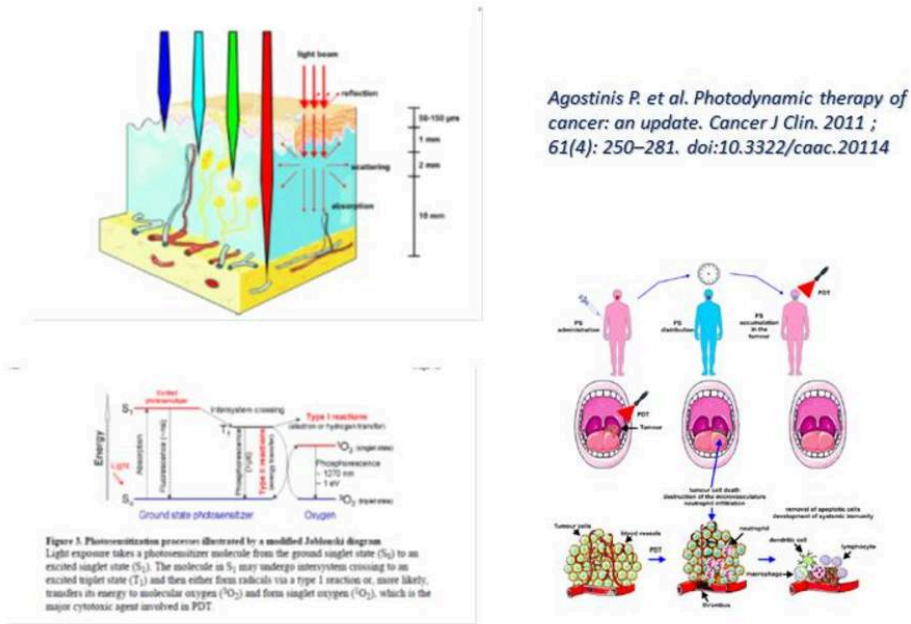
Resectability 30-50%;

Local recurrence rate reaches 76% in 7 years. (Park J 2009 et al.; Molina V et al., 2015;  
Groot Koerkamp B et al., 2015; Jarnagin WR et al., 2003)

**Fig. 1**

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# Photodynamic therapy: basic principles



**Fig. 2**

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#### MECHANISMS OF PDT ACTION

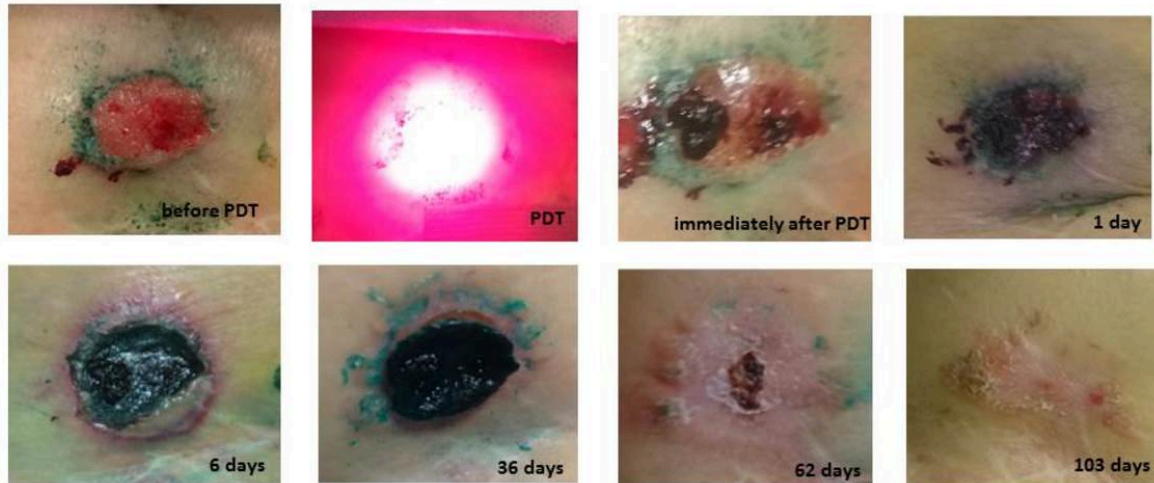
- Necrotizing (PDT per se)
- Immunological (immuno-PDT)
- Microbicidal (anti-microbial PDT)

## PHODYNAMIC THERAPY: basic principle



### TUMOR EVOLUTION AFTER PDT

cholangiocarcinoma implantation metastasis at the drainage site, fotoditazin 0.9 mg/kg 5 hours prior the procedure, 200 J/cm<sup>2</sup>



\*Pathologist findings: skin portion, covered by stratified squamous epithelium with ulceration showing moderately differentiated adenocarcinoma

**Fig. 3**

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## Эффективность ФДТ: данные литературы

Author	Year	Number of patients	Median survival	Results
Ortner M.E. et al. (Centre Hospitalier Universitaire Vaudois, Switzerland)	2003	19 – stenting only	98 дней	research discontinued for ethical reasons
		20 – stenting + PDT	493 дня	
Zoepf T. et al. (University Hospital Essen, Germany)	2005	11 – biliary drainage only	7 мес	PDT has the potential to result in a changeover of current palliative treatment of BDC
		11 – biliary drainage + PDT	21 мес	
Yi Lu et. al. (Shanghai Jiaotong University School of Medicine, China). A meta-analysis of 7 trials.	2015	266 – stenting + PDT  336 – stenting only		The palliative treatment of cholangiocarcinoma, with photodynamic therapy, is associated with an increased survival benefit, an improved biliary drainage, and a better quality of life.
Harsha Moole, et. al (University of Illinois College of Medicine, United States). A systematic review and meta-analysis	2017	402		Survival period in PDT and BS groups were <u>413.04</u> <u>d (95%CI: 349.54-476.54)</u> and <u>183.41 (95%CI:</u> <u>136.81-230.02)</u> respectively.

Fig. 4

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## Methods and materials

The intraprocedural adverse events of 159 EPDT's performed in 62 biopsy confirmed non-surgical Klatskin tumor patients in a ten-year period were studied. The endobiliary light delivery was fulfilled through the previously inserted percutaneous transhepatic biliary drainage channels by means of a 600  $\mu\text{m}$  in diameter optical fiber with a 2 to 6 cm diffuser tip after prior 2 to 5 hours i.v. injection of chlorin photosensitizers ( [Fig. 5](#) on page 8 ). Intraprocedural adverse events included pain, hemodynamic disorders, shaking chill, nausea and vomiting. They were distributed into 3 grades: 1 - no or requiring medication only; 2 - requiring fluence rate reduction; 3 - requiring procedure cessation ( [Fig. 6](#) on page 9 ). Their dependence on total dose (range 64.6-3240 J), fluence rate (range 19,1 - 288 mW/cm<sup>2</sup>), power density (range 14,5-206,3 J/cm<sup>2</sup>), diffuser tip length (2,3,5,6 cm) , number of channels (range 1-4), photoexposure time (range 3-240 min), photosensitizing drug (Photolon, Fotoditazin, Radahlorin) and its dosage (0.6-2.0 mg/kg) was analyzed ( [Fig. 5](#) on page 8 ).



Images for this section:

**Results:**

*8 and 4 patients (5,4% and 2,7% per procedure) experienced intraoperative adverse grade 2 and 3 events, respectively.*

*No significant influence of total dose, fluence rate, power density, diffuser tip length, number of channels, photoexposure time has been demonstrated.*

*The grade 2 adverse events were frequently observed when Fotolon was used ( $p < 0,05$ , Fisher`s exact test).*

**Fig. 7**

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## Intraductal PDT: technique



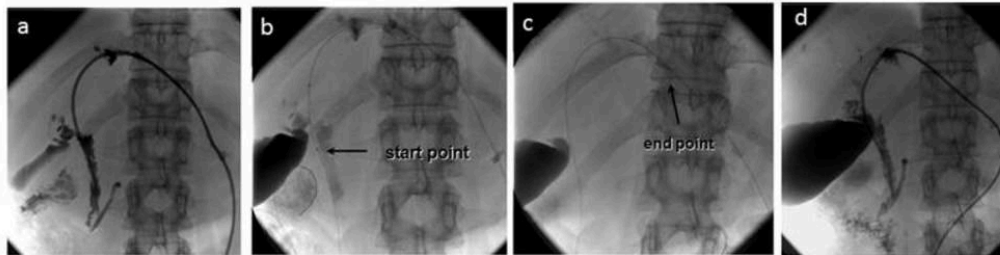
*62 patients, 159 PDT procedures*

**Step-by-step laser irradiation:**  
wavelength 662 nm, pulse mode

*Fluence rate 19,1 – 288 mW/cm<sup>2</sup>*

*Power density 4,64 – 206,3 J/cm<sup>2</sup>*

*Total dose 64,6 – 3240 J*



**Fig. 5**

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***Intraprocedural adverse events  
(pain, hemodynamic disorders, shaking chill, nausea  
and vomiting)***

<b><i>Grade 1</i></b>	<b><i>Grade 2</i></b>	<b><i>Grade 3</i></b>
<b><i>No or requiring medication only</i></b>	<b><i>Requiring fluence rate reduction</i></b>	<b><i>Requiring procedure cessation</i></b>

**Fig. 6**

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## Results

Eight and 4 patients (5,4% and 2,7% per procedure) experienced intraoperative adverse events grade 2 and 3 events, respectively. No significant influence of total dose, fluence rate, power density, diffuser tip length, number of channels, photoexposure time has been demonstrated. The grade 2 adverse events were frequently observed when Fotolon was used ( $p < 0,05$ , Fisher`s exact test), but further investigation are required due to small number of cases ( [Fig. 7](#) on page 12 ).

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## Conclusion

Endobiliary PDT is effective and well tolerated procedure. Small number of intraprocedural adverse events hampers identification of factors influencing EPDT tolerability.

## References

- 1) Suarez-Munoz M.A., Fernandez-Aguilar J.L., Sanchez-Perez B., PerezDaga J.A. et al. Risk factors and classifications of hilar cholangiocarcinoma. *World Journal of Gastrointestinal Oncology* 2013; 5: 7: 132- 138.
- 2) Park J. et al. Natural History and Prognostic Factors of Advanced Cholangiocarcinoma without Surgery, Chemotherapy, or Radiotherapy: A Large-Scale Observational Study // *Gut Liver*. 2009 Dec;3(4):298-305.