First Clinical Experience with δ-ALA Assisted Photodynamic Diagnosis of Bladder Cancer

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ABSTRACT

Visualization of early stage bladder cancer is considerably improved using 5-Aminolevulinic acid (ALA) as tumor marking agent. This is due to an intracellular accumulation of fluorescing Protoporphyrin IX (PP IX) in tissue following intravesical instillation of ALA in a pH-neutral solution.

ALA induced fluorescence was studied in 68 patients with bladder cancer. Tumors were detected endoscopically with naked eyes by fluorescence in the red spectral range. Histological examination of nearly 300 biopsies taken from fluorescing and nonfluorescing areas gave a specificity of 84% and a sensitivity of 100% up to now.

INTRODUCTION

Recurrence of bladder cancer, following conventional therapeutic procedures is clearly related to the presence of precancerous lesions and carcinoma in situ in the remaining mucosa. Fluorescence of systemically applied photosensitizing agents are suited to detect these optically insoluble tumors (1). Although tumor visualization was demonstrated the procedures are affected with considerable disadvantages. Large scale and highly sensitive detection devices are necessary to present acceptable fluorescence images for clinicians during cystoscopy.

As a new approach ALA has been intravesically instilled in bladder tumor patients. ALA is a precursor in the heme biosynthetic pathway and induces intracellular accumulation of endogenous PP IX if provided exogenously in large excess (2). On the basis of animal experimental results which show a fluorescence contrast of more than an order of magnitude first clinical application of fluorescence cystoscopy has been performed (3).

MATERIAL AND METHODS

ALA administration. 1,5g 5-Aminolevulinic acid hydrochlorid (Merck, Darmstadt, FRG) is soluted in 50 ml NaHCO₃. The pH-neu-
tral solution is applied intravesically via a French single use catheter. The initial incubation time in the bladder varied from 15-360 min. Time from ALA instillation to fluorescence cystoscopy ranged from 60-570 min with a median of about 180 min.

**Fluorescence cystoscopy device.** ALA assisted fluorescence detection of early stage bladder cancer has been judged by a correlation of fluorescence contrast with histology of biopsies. For that purpose a device is used as shown schematically in Fig. 1. A 21 French standard cystoscope with a flexible forceps and a 26 French continous flow instrument with a rigid forceps was used, respectively.

![Schematic diagram of the fluorescence detection device](image)

**Fig. 1:** Scheme of the fluorescence detection device including video presentation and documentation

Fluorescence of ALA induced porphyrins was excited in situ by violet light of a Kr⁺-laser. The laserlight was coupled into a 500 μm plastic fiber with a biconic shaped tip. The laser output power at the end of the fiber was about 200 mW. Biopsies were taken from fluorescing and non fluorescing areas during cystoscopy. The corresponding endoscopic findings of the mucosa were judged by white light view. The fluorescence contrast between tumor and adjacent tissue has been quantitatively determined with use of an optical multichannel analyzer (OMA). Fluorescence images in the red spectral range at wavelengths above 600 nm are taken via the cystoscope by an image intensifying camera. By means of a movable mirror the image under white light illumination can be switched alternately to a color camera.

**RESULTS**

Stimulation of the synthesis of highly fluorescing PP IX by ALA has been successfully performed in 68 patients. PP IX generation situ has been proven by an analysis of biopsy samples with HPLC.