F-18-Fluorodeoxyglucose (FDG) Positron-Emission Tomography of *Echinococcus multilocularis* Liver Lesions: Prospective Evaluation of its Value for Diagnosis and Follow-up during Benzimidazole Therapy


**Abstract**

**Background:** Long-term benzimidazole therapy benefits patients with non-resectable alveolar echinococcosis (AE). Methods to assess early therapeutic efficacy are lacking. Recently, AE liver lesions were reported to exhibit increased F-18-fluorodeoxyglucose (FDG) uptake in positron emission tomography (PET). To assess the value of FDG-PET for diagnosis and follow-up of AE patients.

**Patients/Methods:** Twenty-six consecutive patients with newly diagnosed AE were enrolled. Baseline evaluation included CT and FDG-PET. Thirteen patients (11 women; median age 50 years, range 40–76) were resected, the remaining 13 (8 women; median age 60 years, range 39–72) had non-resectable disease, were started on benzimidazoles, and CT and FDG-PET were repeated at 6, 12 and 24 months of therapy. Twelve consecutive patients with newly diagnosed cystic echinococcosis (CE) of the liver were also subjected to baseline FDG-PET.

**Results:** In 21/26 AE patients, baseline PET scans showed multifocally increased FDG uptake in the hepatic lesions’ periphery, while liver lesions were FDG negative in 11/12 CE patients. Thus, sensitivity and specificity of FDG-PET for AE vs. CE were 81% and 92%, respectively. In 5 of 10 non-resectable patients with increased baseline FDG uptake, the intensity of uptake decreased (or disappeared) during benzimidazole therapy, in 3 by $\geq 2$ grades within the initial 6 months.

**Conclusions:** FDG-PET is a sensitive and specific adjunct in the diagnosis of suspected AE and can help in differentiating AE from CE. The rapid improvement of positive PET scans with benzimidazole therapy in some patients indicates that absent FDG uptake does not necessarily reflect parasite viability.

**Abbreviations**

- *E. multilocularis*
- *E. granulosus*
- AE
- CE
- PET
- FDG

**Introduction**

The larval stage of the fox tapeworm *Echinococcus multilocularis* (*E. multilocularis*) causes in humans alveolar echinococcosis (AE), a disease primarily affecting the liver. *E. multilocularis* is prevalent throughout the northern hemisphere [1–3]. An annual incidence of AE of 0.2–1.4 per 100,000 population has been estimated in central Europe [2, 4].
Biologically, *E. multilocularis* behaves in the liver like a slowly, but invasively and destructively growing malignant tumor. Without treatment, >90% of patients die within 10 years of diagnosis [1, 2, 5]. Radical resection is the treatment of choice [3, 5, 6]. At diagnosis, however, only one third of AE lesions are still amenable to radical resection [4]. Long-term treatment with the benzimidazoles Mebendazole or Albendazole reduces 10-year mortality in non-resectable cases to less than 20% [2, 5]. While it is accepted that benzimidazoles are parasitostatic, i.e. inhibiting disease progression, the controversy remains unsettled whether benzimidazoles may be parasitocidal, i.e. curative, and may therefore safely be stopped after years of treatment in some patients. In a previously reported series of non-resectable AE, about one third of patients relapsed upon stopping long-term benzimidazole treatment, while the other two thirds did not [7, 8]. Moreover, parasite samples obtained from patients with long-lasting benzimidazole therapy proved still viable in an in vitro assay [5, 9]. Unfortunately, no clinical, laboratory or imaging marker has been identified for assessing the early therapeutic efficacy of benzimidazole therapy. This is largely due to the difficulty of predicting the parasite's viability in vivo.

In contrast to alveolar echinococcosis, treatment of cystic echinococcosis with an expanding growth and usually no invasion and destruction by cysts, should be reserved for symptomatic lesions or those affecting vital anatomical structures [3]. There have been no major clinical trials for any treatment modality in patients with cystic echinococcosis.

*E. multilocularis* liver lesions were reported to show increased FDG (fluorodeoxyglucose) uptake in PET imaging, possibly reflecting parasite viability [10, 11]. The purpose of this prospective study was therefore to determine the sensitivity and specificity of FDG-PET in the diagnosis of *E. multilocularis* liver lesions and to explore the evolution of FDG avid lesions during benzimidazole treatment.

**Patients and Methods**

The study was performed according to the declaration of Helsinki. The protocol was approved by the hospital ethics committee and written informed consent was obtained from all participants.

**Patients with Alveolar Echinococcosis**

From July 2000 to December 2004, patients (both genders, age 18 to 80 years) with AE were eligible for the study, provided they fulfilled the following criteria: a) newly diagnosed disease without previous treatment (n = 6) or benzimidazole therapy for less than two weeks (n = 3), or b) recurrence after radical surgery treated with benzimidazole therapy for less than two weeks (n = 3), or c) recurrence after radical surgery with benzimidazole therapy for less than two weeks (n = 3). Diagnosis of CE was based on morphological imaging studies (CT or MRI) and serological results as defined by WHO [1]. In one of these patients serology and further work-up revealed later no evidence for CE and the diagnosis of a simple, benign liver cyst was made (Table 2, #12).

In the CE patients, there had been evidence of active infections other than echinococcosis, except for one patient (Table 2, #11) who presented with symptomatic choleodocholithiasis and mild cholangitis.

**Follow-up Alveolar Echinococcosis**

Thirteen of the 26 patients with AE underwent radical resection followed by a 2 years course of benzimidazole therapy [1, 6]. In 5 of these 13 patients material from the *E. multilocularis* lesion was collected intraoperatively and subjected to viability testing using an animal model [9]. Twelve of the 13 resected patients survived and remain recurrence-free, one (Table 1, #9) died from multiorgan failure within the early postoperative period.

In 12 of the 13 non-resectable AE patients long-term benzimidazole therapy was started. One patient (Table 1, #20) with extensively calcified lesions and without detectable anti-*Echinococcus* antibodies was followed without therapy. Four hours post-ingestion Albendazol and Mebendazole serum levels were targeted to >1 umol/l and >250 nmol/l, respectively [5, 8].

Non-resectable AE patients were followed with physical exam, lab tests and imaging studies including CT and FDG-PET. One patient died 2 months after baseline examination from metastatic renal cell carcinoma (Table 1, #18).

**Viability Testing**

In vivo viability testing was performed in jirds (*Meriones unguiculatus*), as described [9]. In brief, 0.25 ml homogenate prepared in physiological saline from an intraoperatively collected portion of the *E. multilocularis* resection specimen was intraperitoneally injected in jirds (3–5 animals per specimen). After four to six months, animals were sacrificed and the abdomen macro- and microscopically examined for metacestode proliferation.

**PET and PET/CT**

A single baseline FDG-PET examination was performed in the patients with CE (n = 12) and in the patients with resectable AE...