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The Correlation of Proliferation Rates to Prognosis in Human Renal Cell Carcinoma

W. de Riese, E.P. Allhoff, S. Liedke, G. Lenis, C.G. Stief, M. Werner, J. Atzpodien and H. Kirchner

THE FRACTION of proliferating malignant cells strongly influences tumour growth and is believed to be a major parameter for prognosis and treatment selection [1, 2]. Ki-67 immunohistostaining is a practical, reliable and reproducible *in situ* method of determining individual tumour-specific proliferation rates (PR) directly in human malignancies [1–4]. The monoclonal antibody Ki-67 was first isolated and characterised by Gerdes and colleagues in 1983 [5]. Ki-67 binds to a human nuclear antigen which is only expressed in the G_1, S, G_2 and M phases of normal and malignant proliferating cells, but is absent in resting cells (G_0) [6]. Several studies on breast cancer and lung cancer have reported an additional prognostic value of this new tumour biological parameter in comparison to conventional parameters (staging, grading, lymph node status) [2–4, 7]. There are no data available comparing tumour-specific proliferation rates and prognosis in human renal cell carcinoma (RCC).

Since 1986, in a prospective ongoing study, *in vivo* proliferation rates in RCC patients were immunohistochemically determined using the Ki-67 assay. All patients entering the study had no evidence of metastatic disease at the time of nephrectomy (according to imaging techniques). Depending on the individual tumour size, several tissue samples are necessary to detect the intratumoral variability [8]. The immunostaining technique for Ki-67 and the evaluation of the slides are described in detail in other reports [1, 7, 9]. Statistical analysis was accomplished using the χ^2 test. P values of less than 0.05 were considered significant [9]. The tumour-specific proliferation rates (PR = percentage of Ki-67 positive cells) ranged between 1 and 23%, whereas normal renal tissue exhibited PR up to 2% only. No correlation between individual PR and tumour stage (pT) was found. However, a strong correlation between PR and low grade (G1) as well as high grade (G3) tumours was observed. These results have previously been published [8] and correspond to other studies on proliferation rates in different human malignancies [2–4, 7].

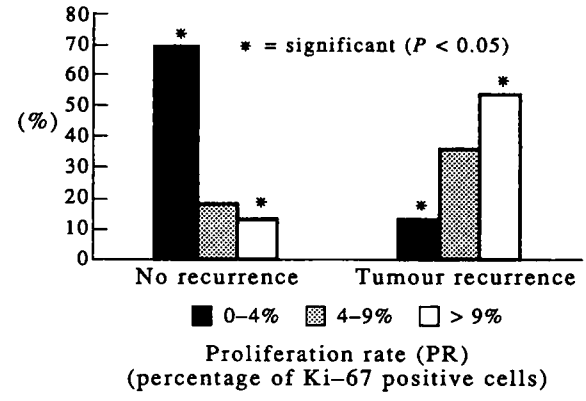

Fig. 1. Proliferation rates (PR) of 89 RCC patients in comparison to the incidence of tumour recurrence during long-term follow-up.

Table 1.

	PR: 0%–4%	4% < PR < 9%	PR > 9%
55 patients (61.8%) without recurrence	38 (69.1%)	10 (18.2%)	7 (12.7%)
34 patients (38.2%) with recurrence	4 (11.8%)	12 (35.3%)	18 (52.9%)

We here present the long-term follow-up of 89 (80.9%) out of 110 RCC patients, undergoing surgery between 1986 and 1990. The mean follow-up is 4.3 years (52 months), range of 26–75 months. 34 patients (38.2%) developed a local tumour recurrence or metastatic disease. Table 1 summarises the distribution of proliferation rates of the primary RCC tumours at the time of nephrectomy in comparison to the incidence of tumour recurrence. Patients with low proliferation rates (< 4%) had a significant lower recurrence rate during follow-up compared to those with tumours with high PR (> 9%). Primary tumours with a moderate proliferative behaviour (4% < PR < 9%) exhibited an intermediate risk for recurrence.

According to the data, the individual proliferation rate is an objective biological marker of tumour aggressiveness. This biological parameter of the tumour appears to be a relevant additional diagnostic index for detection of RCC patients at high risk, especially at early stages showing identical histological features (staging and grading).

Correspondence to W. de Riese.
W. de Riese is at the Department of Urology, Indiana University Medical Center – A 112, 926 West Michigan Street, Indianapolis, Indiana 46202-5250, U.S.A; E.P. Allhoff, S. Liedke, G. Lenis and C.G. Stief are at the Department of Urology; M. Werner is at the Laboratory of Cytogenetics and Immunohistochemistry, Institute of Pathology; and J. Atzpodien and H. Kirchner are at the Department of Hematology and Oncology, Hannover Medical School, Konstanty-Gutschow-Str. 8, 3000 Hannover 61, Germany.
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