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

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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].

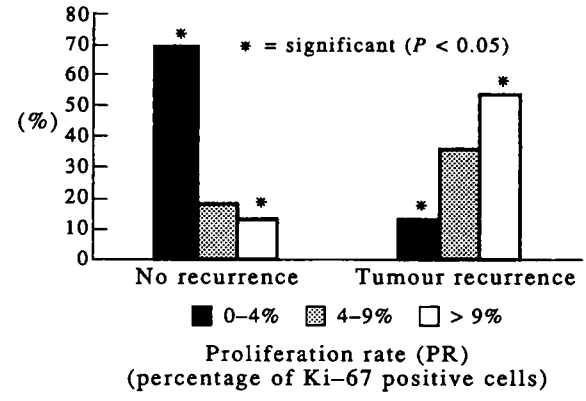

Fig. 1. Proliferation rates (PR) of 89 RCC patients in comparison to the incidence of tumour recurrence during long-term follow-up.

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).

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Myeloprotective Effect of Medroxyprogesterone Acetate (MPA)

Paolo Pedrazzoli

IN A RECENT paper published in *The European Journal of Cancer* Amadori *et al.* [1] evaluate the myeloprotective effect of medroxyprogesterone acetate (MPA) by looking at bone marrow granulocyte–macrophage progenitor cell (CFU-GM) growth in patients with head and neck cancer receiving chemotherapy alone or in combination with the progestin. They conclude that "the myeloprotective effect of MPA is due to its capability to induce mitotic rest in the stem cells which are thus protected from the action of chemotherapeutic drugs", but what they state is not clearly supported by data presented.

Their conclusion relies mainly on results comparing the number of progenitors before and after 2 weeks of MPA treatment; a reduction in CFU-GM growth was observed at day 14 in 7 out of 10 cases. Despite the fact that no statistical significance is reached, they do not give an explanation on the 3 cases in which the number of progenitors increases on day 14. In addition, their conclusion is not supported by any cell cycle analysis.

Further support for a protective role of MPA on bone marrow progenitors comes, in this study, from results comparing CFU-GM growth before and 14 days after chemotherapy. In 8 out of 10 cases of the MPA-treated group an increase of CFU-GM was observed on day 14, while in chemotherapy-alone group there was a reduction of CFU-GM at the same time. However, the authors did not point out and discuss that before chemotherapy the number of progenitors was significantly lower in MPA-treated patients and it was very close in the two groups—101.3 (6.0–187.2) vs. 95.0 (36.7–178.5)—on day 14.

As far as clinical results are concerned, they report 3 cases of grade 1 leukopenia and thrombocytopenia in MPA-treated patients as compared to 4 cases of grade 1 leukopenia and 3 cases of grade 2–3 thrombocytopenia in chemotherapy-alone group. This is, in my opinion, too little to state that "we observed lower haematological toxicity in the peripheral blood stream in arm B" (MPA). Furthermore they did not specify whether the two groups were matched for age, sex, previous myelotoxic therapy, etc.

Our and other experiences [2, 3] have failed to demonstrate a direct *in vitro* effect of MPA on bone marrow progenitor cells. Amadori *et al.* [1] have used a different and interesting approach to study this issue, but their data are not sufficient to draw any conclusions.

In the era of haemopoietic growth factors, the use of MPA to reduce chemotherapy-related myelotoxicity seems unrealistic, although the drug clearly remains an important tool in other oncological settings.

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Myeloprotective Effect of Medroxyprogesterone Acetate (MPA)

D. Amadori

PEDRAZZOLI'S CRITICISM of our paper [1] stems from the statement that the authors' conclusions "rely mainly on results comparing the number of progenitors before and after 2 weeks of medroxyprogesterone acetate (MPA) treatment".

Our conclusions were, on the contrary, based on the comparison of the behaviour of bone marrow activity in each subject, evaluated by counting the colony forming unit granulocyte–macrophage (CFU-GM) before and after a cycle of chemotherapy (CT), in patients treated with MPA (arm B) and in those not treated with MPA (arm A).

Pedrazzoli's main criticism is based on the observation that "before chemotherapy the number of progenitors was significantly lower in MPA-treated patients and it was very close in the two groups −101.3 (6.0–187.2) vs. 95.0 (36.7–178.5) — on day 14". We cannot accept this criticism for the following reasons:

(a) The two randomised groups are comparable in terms of absolute number of CFU-GM before each treatment (day 0 in cases not treated with MPA and day −14 in those treated with MPA). The number of progenitors in the two groups was not, in fact, statistically different at that time

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