A ratio of apoptosis to mitosis, proliferation pattern and prediction of radiotherapy response in cervical carcinoma

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The prognostic significance of apoptotic (AI) and mitotic (MI) indices, and the ratio of these parameters (AI/MI), MIB-1 labeling index (MIB-1LI) and proliferation pattern was studied in 130 (FIGO stage IB–IIIB) squamous cervical cancer patients before radiotherapy. Also the influence of the patients age and tumors pathological features (stage, grade, degree of keratinization) and DNA ploidy on the biological parameters were analysed. AI and MI were assessed on histological sections stained with hematoxylin and eosin, and the MIB-1LI on specimens stained with rabbit anti-human Ki-67 antibody (DAKO Ltd). Sections stained with MIB-1 antibody were used for assessment of the tumor proliferation pattern. The median age of the patients was 55 years (29–80). The median values for MIB-1LI, AI, MI, AI/MI, were: 52.3%, 1.1%, 1.5, and 0.9, respectively. In the univariate analysis median values for cut-off points were used for MIBLI, and AI, however, for other parameters significant cut-off points have been chosen. For MI it was 2.6 and for the AI/MI ratio 0.7. The median time of follow-up was 29 months, with a range of 2–145 months. The univariate analysis showed that tumor stage (p=0.7009), grade (p=0.6660) and AI (p=0.9378) had negligible influence on patients survival. However, MI >2.6 (p=0.0442), AI/MI ≤ 0.7 (p=0.0190), and random or mixed type of proliferation (p=0.0163) were significant prognostic factors. Cox multivariate analysis showed that MI, AI/MI, degree of keratinization and type of proliferation were significant prognostic factors for cervical cancer patients treated with radiotherapy.

Key words: Apoptosis, mitosis, proliferation pattern, cervical carcinoma.

Many tumor biological parameters are associated with tumor control in cervical tumors. Therefore, there is interest in the possible role of these parameters in tumor response. The most important parameters in cervical cancer include: tumor proliferation rate, intrinsic radiosensitivity, vascular density, hemoglobin level, and apoptotic index. It was shown that high proliferative potential of the cervical tumors [11, 19, 30], high intrinsic radiosensitivity [27], high tumor vascularity or high hemoglobin level [12, 22, 25], might be significant prognostic factors. Contradictory opinion comes from Tsang et al [26] and Cooper et al [8] studies. Apoptosis can be induced following irradiation of tumors and it has been reported that an acute apoptotic response after irradiation may be a feature of radioresponsive tumors and the pre-treatment apoptotic levels correlate with those seen after irradiation [17]. Therefore, there is interest in the possible role of apoptosis as an indicator of response to radiotherapy. In Levine et al [16] and Wheller et al [28] studies AI pretreatment below the median value was associated with higher rates of patients' survival. These was in contradiction with Chung et al [7] and Sheridan et al [24] studies, where it was shown that a higher level of spontaneous apoptosis in cervical cancer is a significant prognostic factor. Therefore, Potten suggestion [21] concerning the way of apoptosis measuring seem to be very adequate. The difference in the results of apoptosis may differ, because AI is expressed as a ratio or percentage of all cells present or all cells counted. The denominator in the AI measurement contains cycling cells and also quiescent populations, connective tissue, infiltrating non-cycling differentiated cells and any dead and dying cells not clearly recognisable as dead. Therefore, considering the ratio of AI to MI, (or