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PROGNOSTIC VALUE OF *c-myc* PROTO-ONCOGENE OVEREXPRESSION IN EARLY INVASIVE CARCINOMA OF THE CERVIX.

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The prognostic effect of *c-myc* oncogene overexpression was assessed in a multivariate analysis of 93 patients with invasive carcinoma of the cervix stage Ib, IIa, and IIb proximal. The treatment consisted of brachytherapy followed by colpohysterectomy and lymphadenectomy. C-*myc* gene expression was analyzed by Northern and slot blot hybridization techniques. C-*myc* overexpression (ie. levels at least 3 times the mean observed in normal tissues) was present in 33% of the tumors. The proportion of carcinomas with c-*myc* overexpression significantly increased with the size of the primary tumor ($p = 0.04$). No relationship was found between c-myc overexpression and the other clinical and histological parameters, including the nodal status. The relative risk of relapse (overall, pelvic failure, distant metastases) was analysed in a Cox's proportional hazards model. Three factors were significantly related to the risk of overall relapse when the multivariate analysis was performed, namely the tumor size, the nodal status, and c-*myc* expression. A combination of c-*myc* expression and the nodal status provided a very accurate indication of the risk of relapse. Indeed, patients with negative nodes had a 3-year disease-free survival rate of 94% (95% confidence interval CI, 79-98%) when c-*myc* was expressed at a normal level, whereas this rate was only 51% (95% CI 26-63%) when c-*myc* was overexpressed (log-rank test, $p = 0.017$). In addition, in the subgroup of patients with positive nodes, this rates was 44% (95% CI 25-77%) and 14% (95% CI 4-49%) when c-*myc* gene was expressed at normal level, or overexpressed, respectively. Finally, c-*myc* gene overexpression was, in the multivariate analysis, the first factor selected by the model regarding the risk of distant metastases.

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INTERFRACTION INTERVAL IS MAJOR DETERMINANT OF LATE EFFECTS, BUT NOT ACUTE EFFECTS OR TUMOR CONTROL, WITH HYPERFRACTIONATED IRRADIATION (HFX) OF CARCINOMAS OF UPPER RESPIRATORY AND DIGESTIVE TRACTS (URDT)

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A prospective, randomized, multi-institutional, phase I/II trial of HFX was conducted between 1983 and 1987. Patients with histologically proven, inoperable squamous cell carcinoma of the URDT, stratified by site, nodal status, and performance status, were assigned to one of three arms, 67.2 Gy, 72.0 Gy or 76.8 Gy. Fractions of 1.2 Gy were given twice daily, 5 days per week: intervals of 4 to 8 hours were permitted between fractions. After acceptable rates of acute normal tissue effects were found, the randomization was changed to evaluate a new higher total dose, 81.6 Gy. Of 479 patients entered, 447 were analyzed, 63 on 67.2 Gy, 129 on 72.0 Gy, 117 on 76.8 Gy, and 138 on 81.6 Gy. The treatment arms were well balanced with respect to pretreatment characteristics. Acute reactions consisted almost entirely of pseudomembranous inflammation. "Severe" (grade 3) acute reactions were reported in 33% to 41% of patients, with no difference in frequencies among the 4 arms; grade 4 reactions were found in 0 to 3%, with no differences among the 4 arms. Toxicities which developed or persisted beyond 90 days after 1st treatment (408 patients evaluable >90 days) did not differ among arms: grade 3+ reactions occurred in 10% to 14%, and grade 4+ effects (necroses) were reported in 5% at 67.2 Gy, 3% at 72.0 Gy, 7% at 76.8 Gy, and 2% at 81.6 Gy. Interfraction intervals ≤4.5 hrs were associated with higher frequencies of grade 4+ late effects in all 4 arms, 8% of 197 patients ≤4.5 hrs vs 1% of 211 patients >4.5 hrs. Estimates of late toxicity at 1,2, and 3 years were 5.5%, 9.8%, and 15.4% with intervals ≤4.5 hrs, vs 1.7% at all 3 periods for >4.5 hrs (p=.006). Local-regional control at 2 years was 25% for the assigned dose of 67.2 Gy compared to 43% to 45% for the 3 higher doses (p=.01), but a similar comparison for survival showed no significant difference (p=.35). There was no evidence for an effect of interfraction interval on either local-regional control (p=.38) or survival (p=.28). The sparing of normal tissues associated with HFX using interfraction intervals >4.5 hrs despite high total doses achieved, and the dissociation of acute effects and tumor control from late effects, support the comparison of 81.6 Gy HFX, using the longer intervals, with standard fractionation in a phase III trial.