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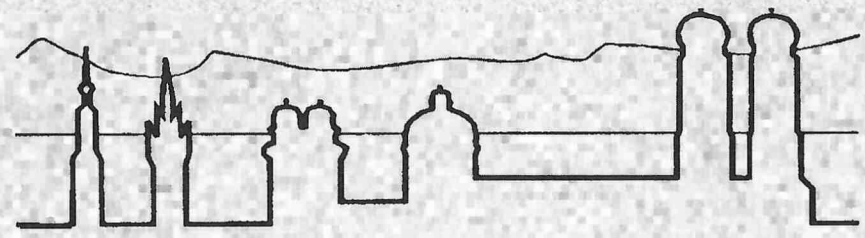

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Relationship between Nm23 expression and human gastric cancer both stage and survival

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SUMMARY

Nm23 expression and its relationship with the metastatic potential of cancer was investigated in a number of tumours. It was proposed that nm23 has a possible role in cancer evolution; studies concerning various human cancer have been performed with conflicting results.

Our study's purpose was to confirm the inverse relationship between nm23 expression and survival or clinical outcome in patients resected for gastric cancer. We examined retrospectively the paraffin-embedded specimens of gastric tumour using an anti-nm23 protein polyclonal antibody. The immunochemical findings were compared with tumour's histotype, local extension (T), regional lymph node metastasis (N) and patient's survival.

INTRODUCTION

In 1988, Steeg and Coll [1] first described nm23 protein and pointed out its relationship with tumoural metastatic process in experimental studies. Low levels of nm23 mRNA in murine melanoma cells were associated with an increased metastatic potential of the tumour.

The nm23 expression in various human tumours has been analyzed without unanimous conclusion. A small number of studies concerned gastric cancer and the relationship between nm23 protein expression and the fate of pàtients who underwent curative surgery.

Our aim was to verify retrospectively how nm23 expression correlates with local aggressiveness of gastric cancer, lymph node regional metastasis and survival after curative resection of gastric cancer.

MATERIALS AND METHODS

From 1983 to 1993 in the Clinica Chirugica of the University of Florence 246 patients with gastric cancer underwent surgery. We had data for the outcome of only 93 patients (34 females, 59 males, mean age 63.7 years at surgery). We took into consideration: tumour location, Borrmann's type, depth of invasion (pT), limph node metastasis (pN), stage (WHO classification), histological type (Lauren classification) and survival.

Nm23 expression was analyzed on paraffin-embedded sections using an anti-nm23 rabbit's polyclonal antibody (streptavidin-biotin-peroxidase technique). Immunoreactivity was evaluated both in term of intensity of neoplastic tissue coloration and in term of rate of stained cells.

We noted 3 distinct groups: 1) no reactivity; 2) weak reactivity and 3) moderate-intensive reactivity. The last group was further divided into: 1) less than 10%; 2) 10-50%; 3) more than 50% of stained cells. The study of the samples was blindly performed.

We compared nm23 expression with pT, pN, stage, location, histotype and Borrmann's type and with patients' survival rate. Relationships were evaluated by multivariate and regression analysis while cumulative survival rates were analyzed by Kaplan-Meier product.

RESULTS

Tumours were located in the stomach: 42 in the lower third, 29 in the middle third and 13 in the upper third (7 were diffuse and 2 were of the stump). Borrmann type 1, 2, 3, 4 were respectively 50, 34, 4, 4. 51 of them were Lauren intestinal type and 34 diffuse type (4 weremixed and 4 unclassificable).

18 (19.4%) specimens were nm23 negative, 39 (41.9%) were intermediate. Of the 36 found positive (38.7%), 9 (25%) showed less than 10% stained cells; 20 (55.5%) showed 10-50%; 7 (19.5%) more than 50%.

No relationship was found among nm23 expression, pT, pN, stage, histology and location during statistical analysis.

nm23 positive patients showed a worse survival rate, like in neuroblastoma and pancreatic cancer.

DISCUSSION

nm23 function has not been clearly understood yet. Various hypothesis have been formulated: 1) structural and functional relationship with "NDP Kinases", that are proteins involved with the intracellular messengers [2,3]; 2) homology with PuF (purine binding Factor), which is a protein capable of binding a specific site of the proto-oncogene *c-myc* and determinating the activation of transcription at least in vitro [4]; 3) autophosphorylation of an acid-resistent serine related to metastatic potential of nm23-transfetted [5]; 4) cytokine-like activity; 5) function in binding some proteins on the cell surface.

The nm23 gene deletion has been found in different human tumours, but an increased incidence of metastasis has been demostrated only in a few.It was impossible to determine if this was really due to nm23's loss. On the other hand, in some cancers the gene mutation or the protein change resulted in a locally more aggressive behaviour.

Studies concerning the role of nm23 in human tumours have been mostly achieved regarding breast cancer [6,7] a few concerned uterine cervix carcinoma[8], colorectal cancer [9,10], lung adenocarcinoma [11], epatocarcinoma [12], melanoma [13], gallbladder carcinoma [14], prostate cancer [15], neuroblastoma [16] and pancreatic cancer [17]. Conflicting results were found regarding different neoplasms and even in studies of the same tumour.

Nakayama [18] looked for gene deletion in gastric cancer and he evaluated mRNA expression and the tissue protein amount. Gene deletion was found in 8% of the tumours. 85% of the primitive tumours expressed higher levels of nm23 mRNA than non neoplastic mucosa. No data concerning nm23 protein was reported. Our cumulative percentage of positive and intermediate nm23 protein expression compare well with Nakayama data.

Kodera [19] studied 31 patients who underwent gastric resection for cancer. No significant difference on the mean nm23 expression in the tumour and in the healthy mucosa was found. A significant down-regulation of the gene existed in tumours with serosal invasion and in those with limph node metastasis. An inverse relationship between protein expression and negative prognostic elements was demonstrated.

In Livingstone's study [20] nm23 protein expression prevailed in Japanese patients in advanced stages, compared with European patients.

In our experience nm23 protein expression seems to be independent from all the prognostic features of gastric cancer. Our data suggests that nm23 protein could be an important negative prognostic index of gastric cancer.

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