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# Proliferation indices and p53-immunocytochemistry in uterine mixed mullerian tumors

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**Summary.** Mixed mullerian tumor (MMT) is a biphasic malignancy of elderly women. It, including both a carcinomatous and a sarcomatous component (CC and SC), is regarded as a female genital tract carcinosarcoma (FGTCS). Since current methods to grade CC and SC are not still univocal, the authors estimate mitotic index (MI) and MIB 1-immunolabeling index (MIB 1-LI) as common prognostic indices for the MMT components. They also compare above prognostic indices with p-53 immunocytochemistry, in MMTs. The present study thus points out that: (a) MI of CC and SC areas is consistent with the respective conventional tumor grades; (b) MI averages of CC are higher than those observed in the SC areas; (c) MI and MIB 1-LI of the CC-tumor cells correlate reciprocally in a very significant fashion; (d) A diffuse strong p53 nuclear immunostaining (>50% cells) is often patent where the highest MI and MIB 1-LI are found. In conclusion, the authors propose MI and MIB 1-LI as two complementary useful indices to assess prognosis of MMTs. They also suggest p53 nuclear immunolabeling should be regarded as an independent biomarker of unfavourable MMT behaviour.

**Key words:** Mixed mullerian tumor, Proliferation indices, Mitotic index, MIB 1-labeling index, p53 tumor biomarker

## Introduction

Mixed Mullerian Tumor (MMT), in the past was regarded as a malignant «collision neoplasm» (Macasaet et al., 1985), mostly affecting post-menopausal women (Gagne et al., 1989). Now it is ascribed to the female genital tract carcinosarcomas (FGTCS) (Silverberg et al., 1990; deBrito et al., 1993; Costa et al., 1994), which often arise inside the fundic endometrium, spread into the cervical canal, and infiltrate the miometrium (Larson et al., 1990; Schweizer et al., 1990). Both lymphatic and blood-vessel metastases occur early (George et al., 1995; Rosai, 1996). MMT-light microscopy displays a biphasic feature, because of the admixture of dominant carcinomatous component (CC), serous or endometrioid type adenocarcinomas, and of a sarcomatous component (SC) (Sreenan and Hart, 1995; Prat, 1996). The latter characterizes «homologous» and «heterologous» MMT variants, relating to the appearance of either endometrial sarcoma-like or soft tissue-like malignancies (Gompel and Silverberg, 1994; Zaloudek and Norris, 1994; Mount et al., 1995). Histoprognostic assessment of MMTs implies different approaches for CC and SC grading, on account of their putative dual clonality (Larson et al., 1990; Costa et al., 1993).

Epithelial histogenesis of MMTs has lately been perspected by the «conversion/metaplasia» theory, expecting CC to be the true malignancy and SC a consequence of either CC divergent differentiation (Wick and Swanson, 1993) and metaplasic tumor-change (Costa et al., 1994; Mount et al., 1995; Sreenan and Hart, 1995; Costa and Walls, 1996). In this way, previous immunohistochemical reports agree on cytoskeleton typing (Bitterman et al., 1990; Meis and Lawrence, 1990; Costa et al., 1991; George et al., 1991; deBrito et al., 1993), mutant p53 cell accumulation (Costa et al., 1994; Mayall et al., 1994), and p185 (erbB-2)-over-expression (Costa and Walls, 1996), in CC- and SC-cells of MMTs. To date, an interesting question arises to point out common prognostic tools for both the components of MMTs.

The present study was then performed to quantify and compare each other mitotic index (MI) and MIB-1 labelling index (MIB 1-LI) in variously differentiated CC and SC areas of MMTs, joining to p53 cell-immunostaining.

## Material and methods

The surgical specimens of endometrial lesions from ten elderly women (average age 71.7 years), were cut in slices of 10x10x5 mm, fixed for 24 hours with 10% neutral buffered formalin, dehydrated and paraffin-embedded. Twelve 5-µm thick sections were then obtained and mounted two by two on silane-coated (3-aminopropyltriethoxy-silane; Sigma Chemical Co., St.

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**Table 1.** Clinico-pathological background of the MMT study cases, relating to conventional types and grades of both the CCS and SCs.

| PATIENTS | AGE (yrs) | MMT HISTOLOGIG VARIANT | CC | | SC | |
|---|---|---|---|---|---|---|
| | | | Type | Grade | Type | Grade |
| 1 (T.G.) | 81 | Homologous | Clear cell carcinoma | High | Endometrial stromal sarcoma | High |
| 2 (S.F.) | 66 | Heterologous | Serous papillary carcinoma | Low | Spindle cell sarcoma | Low |
| 3 (R.A.) | 75 | Heterologous | Endometrioid carcinoma | High | Rhabdo-myosarcoma | High |
| 4 (F.L.) | 63 | Homoglogous | Adenosquamous carcinoma | High | Endometrial stromal sarcoma | Low |
| 5 (C.M.) | 61 | Homologus | Endometrioid carcinoma | High | Endometrial stromal sarcoma | High |
| 6 (R.I.) | 72 | Heterologus | Poorly differentiated carcinoma | High | Leyo-myosarcoma | Low |
| 7 (L.D.) | 68 | Homologous | Serous papillary carcinoma | High | Undifferentiated sarcoma | High |
| 8 (P.G.) | 76 | Heterologous | Endometrioid carcinoma | High | Chondrosarcoma | High |
| 9 (B.C.) | 71 | Homologus | Endometrioid carcinoma | Low | Endometrial stromal sarcoma | Low |
| 10 (L.R.) | 84 | Homologous | Serous papillary carcinoma | High | Endometrial stromal sarcoma | High |

Louis, Mo. USA) glass slides. Two slides for each tumor-specimen were lightly stained with Haematoxylin-Eosin for both the diagnostic purpose and counting of mitotic figures (MFs). The study cases were classified according to the histological typing and low or high conventional grading of the CC (Costa et al., 1993) and SC areas (Silverberg et al., 1990; Costa et al., 1991).

### *Immunohistochemical techniques*

Two pairs of slides were air-dried, heated at 60 °C for 1 hour, deparaffinized, and brought to deionized water. They were microwave-irradiated twice at 100 °C for 5 min. in pH 6 citrate buffer and allowed to cool (Taylor et al., 1994). After treatment with 3% hydrogen peroxide and rinsing in deionized water, the slides were placed in phosphate buffered saline (PBS) and incubated in a humid chamber with horse normal serum (Vector Laboratories, Burlingame, Ca. USA) in PBS containing 1% bovine serum albumin (BSA) for 30 min at room temperature. The slides were utilized two by two for the antibody applications (pair A) and corresponding negative controls (pair B). The purposed immuno-reactions were carried out by the following primary monoclonal antibodies (MAbs): 1) MIB 1 MAb (Amac Inc., Westbrook, Me. USA), diluted 1:100; 2) DO7 anti-p53 MAb (Novocastra Laboratories, Newcastle, UK), diluted 1:80, recognizing both the wild and mutant forms of the p53 protein (Vojtesek et al., 1992). The pair B of slides (negative controls) were processed by omitting the primary MAb incubations. All the slides were rinsed in PBS and treated for 30 min. with biotinylated horse anti-mouse Ig diluted 1:200, as secondary Ab (Vector Lab.). After PBS bath, the slides were incubated again with Avidin-Biotin Complex (ABC) (Vector Lab.) for 30 min, developed by 3,3'-diaminobenzidine-HCl (Sigma Chem. Co.), as chromogen substrate, counterstained with 1% methylgreen, dehydrated, and cover-slipped with a synthetic mounting medium.

Nuclear positive immunoreactions were recorded separately in the CC and SC cell-lines, and graded as strong (++) or weak (+) staining. The MIB 1-labeling nuclei showing a strong, homogeneous staining were recognized as positive. For p53 expression, only tumor cells with a distinc nuclear labeling were regarded as positive. Their focal (<50% cells) or diffuse (≥50% cells) patterns were specified (Costa et al., 1991, 1994; Costa and Walls, 1996).

### *Counting procedures*

CC and SC growth fraction was assessed separately by two of the authors in 20 HPFs (x400 magnification with a field area of 0.188 mm), relating to MF-count and tumor cellularity (Woosley, 1991; Simpson et al., 1992). MI was computed as ratio of MFs to the total of 1,000 malignant cells, by a quantitative simple method (Simpson et al., 1992). The MIB 1-LI, however, was expressed as percent strongly positive nuclei of 2,000 counted tumor cells, according to recent appraisals (Ostrowski et al., 1995; Langford et al., 1996; True, 1996)

### *Statistical analysis*

Correlations of the CC- to SC-mitotic indices, and of CC-mitotic index to CC- MIB 1-LI were calculated by a standard regression-line testing (Microcal Origin version 3.0 - Software, Inc. Northampton, Ma. USA). Probability (p) values lower than 0.05 were considered to be significant.

## Results

### *Light microscopy*

Six homologous and four heterologus MMTs were detected, of either the low or high conventional grade (Table 1). The homologous MMTs included an adenosquamous carcinoma (case 4), clear cell- (case 1), or papillary serous carcinomas (cases 7, 10), with associated endometrial stromal- (cases 1, 4, 5, 9, 10) or undifferentiated type - (case 7) SCs. In the heterologous MMTs, endometrioid - (cases 3 and 8), serous papillary - (case 2), or poorly differentiated - (case 6) CCs were observed, while SCs showed spindle cell (case 2), rhabdo- (case 3), leymyo - (case 6) or chondrosarcoma (case 8) dominant appearances. In all the instances, focal necrosis and haemorrhages were found, with few tumor-infiltrating lymphocytes (TILs). Easily identified MFs

**Table 2.** MI (‰) and MIB 1-LI (%) means in both CC and SC areas of the MMTs, as compared to respective percent of the p53-labeled nuclei (> or < 50%).

| MMT CASE | HISTOLOGIC VARIANT | CC | | | SC | | |
|---|---|---|---|---|---|---|---|
| | | MI (‰ cells) | MIB1-LI (%cells) | p53 (% cells) | MI (‰ cells) | MIB1-LI (%cells) | p53 (% cells) |
| 1 | Homologous | 17.3 | 46.4 | >50 | 9.4 | 27.4 | >50 |
| 2 | Heterologous | 17.2 | 38.4 | 0 | 8.5 | 10.2 | 0 |
| 3 | Heterologous | 14.3 | 19.2 | <50 | 9.6 | 9.8 | <50 |
| 4 | Homologous | 12.1 | 24.8 | 0 | 2.7 | 12.4 | 0 |
| 5 | Homologous | 10.0 | 19.2 | <50 | 9.4 | 8.6 | <50 |
| 6 | Heterologous | 18.4 | 38.7 | >50 | 4.2 | 11.3 | >50 |
| 7 | Homologous | 10.3 | 22.3 | 0 | 5.4 | 29.4 | 0 |
| 8 | Heterologous | 18.2 | 24.6 | >50 | 9.7 | 16.3 | <50 |
| 9 | Homologous | 3.8 | 9.2 | 0 | 0.63 | 4.1 | 0 |
| 10 | Homologous | 20.3 | 53.8 | >50 | 11.2 | 38.6 | >50 |

were counted and a complete agreement between the two observers was obtained.

By the use stereological estimation, MI showed a range from 10.0 to 20.3 (out of a thousand) in the high-grade CCs, but it was 3.8 in a low-grade endometrioid type CC (case 9). However, MI was restrained between 0.63 (case 9) and 11.2 (case 10) in the SCs of MMT, irrespective of their type and grade. Therefore, a significant correlation between the CC- and SC-mitotic indices could be proved by the scatterplot linear regression (Fig. 1).

### *Immunohistochemistry*

A strong nuclear MIB-1 immunostaining (++) was found more often in the CC-tumor cells, as unhomogeneous and focal pattern (Fig. 2). There, the MIB 1-LI ranged from 9.2 (case 9) to 53.8% (case 10), while fewer nuclei were MIB 1-labeled inside SC-areas, with a median MIB 1-LI of 16.8% (Table 2). Said indices in the high-grade CC- and SC-areas of MMTs reached greater values than those estimated in the low-grade ones. Statistical fitting of the MIs and MIB 1-LIs for the CC areas displayed a significant correlation ($r=0.85994$; $p<0.01$) between the two proliferation indices compared (Fig. 3).

p53 immunostain was found in six of the study lesions (60%), as a homogeneous, strong (++) nuclear labeling (Fig. 4) in more or less of 50% malignant cells of the CC- and SC-areas (cases 1, 3, 5, 6, 8, 10). A dominant percentage of p53-positive nuclei was objectivized in both the high grade CC and SC cellularity (Cases 1, 10), including a low grade leyomyosarcoma-type SC (case 6). In a high-grade heterologous MMT p53 expressing CC-cells were diffuse (more than 50%), while focal SC-cells (less than 50%) could be seen (case 8). A focal pattern was also observed in both CC- and SC-cellularity of two high-grade MMTs (cases 3, 5). Negative p53 immunoreactions, like negative ones, were obtained in four instances, including both high and low grade lesions (cases 2, 4, 7, 9).

## Discussion

The described tumors depict the typical biphasic appearance of FGTCS; the so-called MMT; they include wide CC- structures and SC-cells varying by shape and differentiation. Among the latter, nuclear atypias and MFs are always fewer than those observed in the former. Mitotic counting is still proven to be a basic approach to assess growth fraction and prognosis of malignant tumors (True, 1996), joining to conventional grading systems and biomarker quantitative immunocytochemistry (Baak, 1990).

In this way, Ki67/MIB 1-nuclear labeling correlates with percent of cells in G1, S, G2, and M phases of the cell cycle (Ostrowski et al., 1995; Langford et al., 1996).

Regarding the prognostic assessment of FGTCS, it was pointed out that their CC- and SC-areas have to be graded separately, depending on their different features and progression rate (Costa and Walls, 1996). Regarding the present results, MI estimation provided a close relation between the CC and SC growth fractions ($p<0.05$), despite the lower values of the latter. On the other hand, the MI of CC-cells is consistent with a dominant role of malignant epithelium (Bitterman et al.,

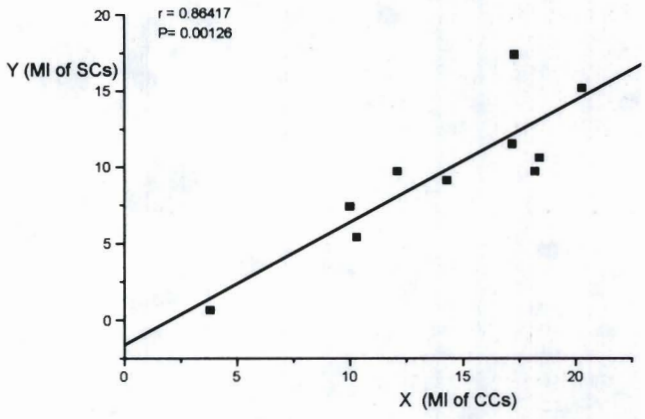
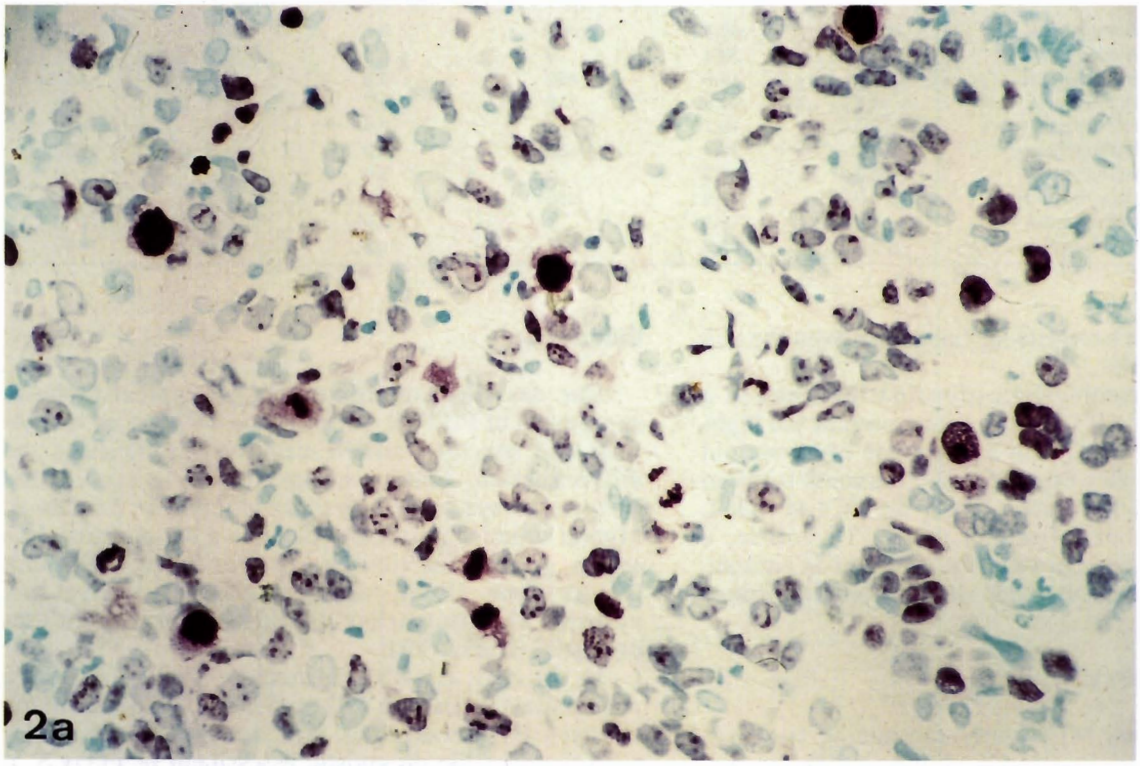



**Fig. 1.** Scatterplot of MI averages in the CC- (abscissa') and SC- (ordinate) areas. The regression line testing shows that CC and SC growth fractions are co-related ($p<0.01$).

1990; Sreenan and Hart, 1995; Costa and Walls, 1996), which spreads early and metastasizes (George et al., 1991; deBrito et al., 1992; Wick and Swanson, 1993), and is often accompanied by synchronous extrauterine carcinomas (Krigman et al., 1995).

No previous studies have quantified proliferation



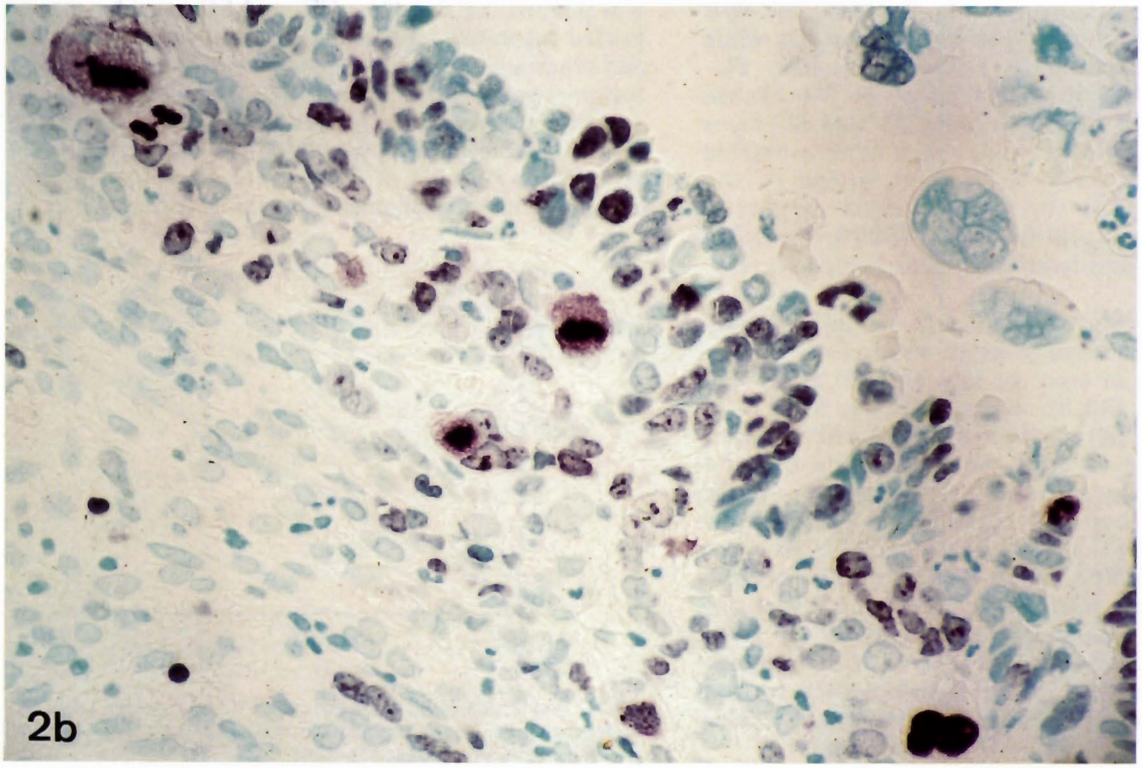




**Fig. 2. A.** Case 5 MMT: MIB-1 nuclear labeling among the admixed CC- and SC-tumor cells can be seen to a similar extent. **B.** Case 10 MMT: a deep MIB-nuclear positivity is patent as focal pattern. The MIB 1-reacting CC-cells are more than the SC-ones. MIB-1 MAB. x 400

indices in MMTs. Now, the parameters used to comparatively assess MI and MIB 1-LI in MMTs show that MI and MIB 1-LI are parallel proliferation indices, increasing as a function of the respective MMT grade. They also denote the lower growth fraction of SC, in agreement with histoprognostic criteria and recent reports on other-sited tumors (Kamio, 1996; Langford et al., 1996). A further prognostic trial for MMT classifying is represented by p53 nuclear immunostaining, the overexpression of which has to be ascribed to a mutant form of this tumor suppressor gene protein (Porter et al., 1992; Costa et al., 1994; Mayall et al., 1994). Comparative p53 immunolabeling supports the previously hypothesized role of mutant p53 for tumor progression (Papadaki et al., 1996) and monoclonality (Costa et al., 1994; Kamio, 1996).

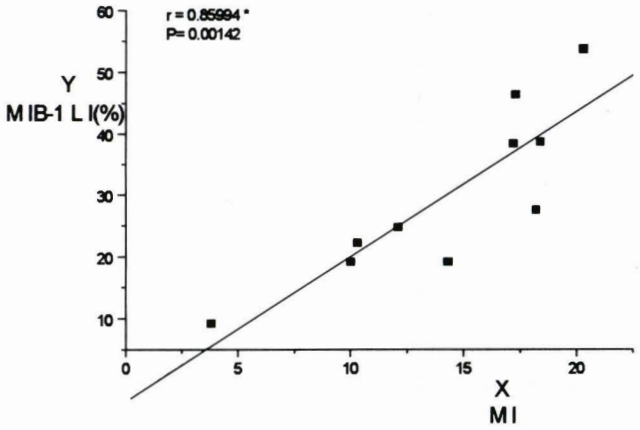



**Fig. 3.** Scatterplot of MI (abscissa), ranging from 3.8 to 19.0, and MIB 1-LI (ordinate), ranging from 9.2 to 53.8 in the CCs of the study-MMTs (n=10). The regression-line testing shows a significant correlation (*) between the two proliferation indices ($p < 0.01$).

The described p53-immunoreactions, for wild and mutant forms of the same protein, prove the p53 gene mutation to be a relatively common event in high grade CC and SC lines of MMTs. The percent of p53-labeling nuclei does not represent a proliferation index, even if it is consistent with the increase of MI and MIB 1-LI. P53 overexpression was equally found in CC- and SC- cells, so it can be regarded as an independent biomarker for a poor prognosis and rapid progression of MMTs.

The said tumor biomarker is not characteristic for MMT; in this malignancy, it is a predictor of unfavourable behaviour rather than a simple tester of growth rate.

In conclusion, MI and MIB 1-LI must be regarded as useful prognostic tools to classify both the components of MMTs, and to substantiate the prevalent growth fraction of CC. p53 nuclear immunostaining represents a biomarker of a frequent clonal mutation in the MMT components. It is a very significant parameter for prognostic worsening of the high-grade MMTs.

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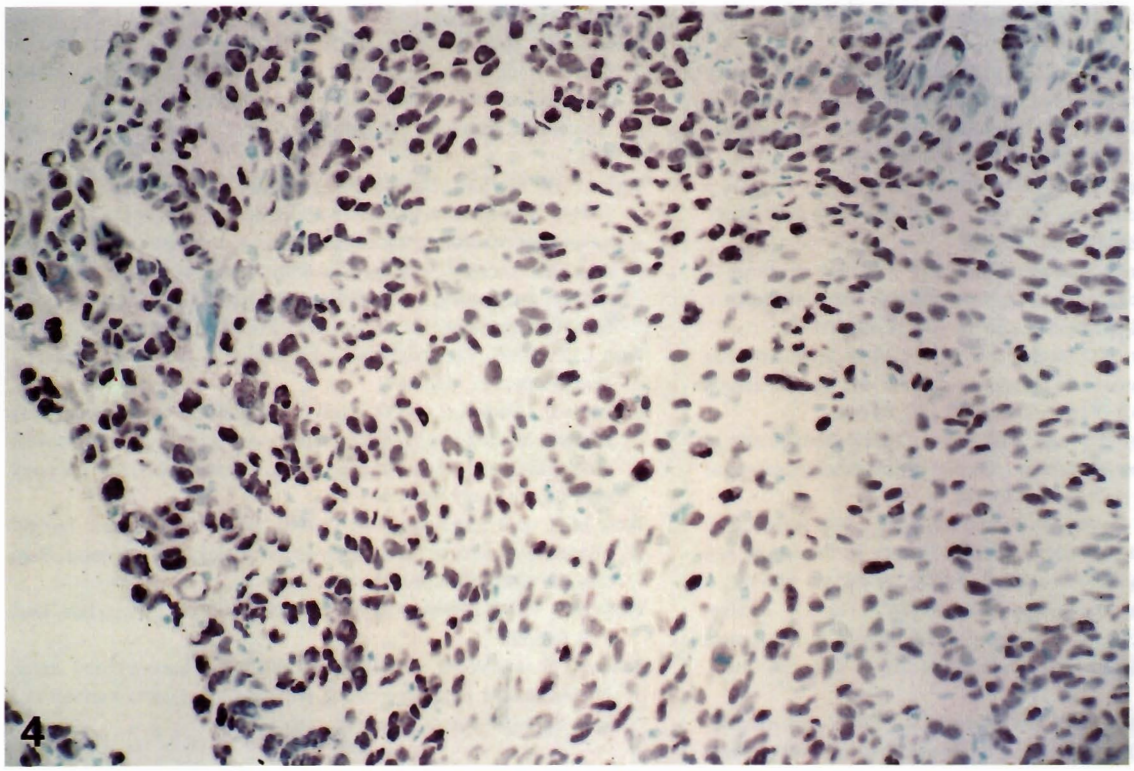


**Fig. 4.** Case 10 MMT shows a diffuse p53 MAb nuclear staining (>50% cells), in both the CC and SC tumor components (DO 7 MAb x 250)

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