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*Perspectives and Commentaries*

# Changing Histology in Malignant Tumors: Diagnostic and Therapeutic Significance

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(A COMMENT ON: Hoon DB, Wang H-C, Ramshaw IA. Increased metastatic ability and bone formation of a mammary adenocarcinoma *in vivo* after *in vitro* passaging. *Eur J Cancer Clin Oncol* 1984, **20**, 1517-1526.)

THE ARTICLE by Hoon *et al.* [1] raises interesting questions concerning the heterogeneity of human and animal tumors. In human tumors, in particular, one asks what is the diagnostic and therapeutic significance of this changing morphology?

Hoon *et al.* report that after more than 50 *in vitro* passages, the histology of the rat mammary adenocarcinoma converted to fibrosarcoma and finally osteosarcoma, with enventual loss of all glandular elements. Chromosomal abnormalities and a metacentric marker chromosome were identified in tumor cells after 90 passages. The morphologic changes were associated with more rapid tumor growth and a greater potential for metastases. We feel that although this transformation from epithelial to stromal neoplasia is theoretically possible, it is likely that the conversion is related to cell contamination or a new tumor (sarcoma) arising at the site of inoculation of carcinoma cells, as the result of a tumor cell-host interaction. The cytogenetic evidence (altered chromosome numbers and the appearance of the marker chromosome) supports the impression that the sarcoma is of a different origin from the adenocarcinoma. Metaplastic foci of cartilage and bone have been described in human mammary carcinomas, but the epithelial nature of the tumors has not been in doubt [2].

Although the heterogeneity of tumors to be discussed in this article refers either to light microscopic diversity in morphology and/or transformation from one cell type to another, it seems pertinent to note that the heterogeneity of tumors is also observed in their variable antigenic expressions; functional or biochemical peptide hormonal properties; cytogenetic abnormalities; and ultrastructural characteristics [3].

Tumor heterogeneity may be observed at diagnosis, may occur spontaneously over time or may be elicited by chemotherapy and/or radiotherapy treatment modalities. It is possible to summarize only briefly these tumor types and changes. Impressions on the diagnostic and therapeutic significance of altered tumor morphology will be based on small cell lung cancer (SCLC).

## TUMOR HETEROGENEITY AT DIAGNOSIS

Heterogeneous tumors which may be appreciated by light microscopy at diagnosis include:

1. Germ cell tumors of the gonads, mediastinum or other sites. Such tumors arise from totipotential germ cells and are capable of differentiating to ectodermal, mesodermal and/or entodermal structures as well as gonadal or extraembryonic trophoblastic or yolk sac elements.
2. Mixed tumors. These tumors presumably arise from one germ layer and show variable epithelial and stromal differentiation. Included in this group are the mixed tumors (pleomorphic adenoma) of salivary glands, Wilm's tumor, mixed mesodermal tumors, blastomas and carcinosarcomas arising from any site. While the origin of blastomas and carcinomasarcomas is unknown, they may arise from elements of more than one germ layer, since major organs receive contributions from two or all three germ layers.

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Biphasic tumors which, by definition, show at least minimal epithelial and stromal differentiation are also in this category. Such neoplasms include mesotheliomas, synovial sarcomas, meningiomas and melanomas.

3. Epithelial tumors from a multiplicity of sites show variable differentiation, such as adenosquamous carcinomas or transitional cell carcinomas with squamous and glandular components.

## TUMOR HETEROGENEITY WITH TIME

Changing morphology over time or following therapeutic intervention has been noted in a number of tumor sites. The most impressive of these include:

1. Germ cell tumors. Following chemotherapy/radiotherapy, tumors may mature to adult teratoid elements. Such maturation is associated with loss of marker substances (AFP/HCG) and prolongation of life.

2. Neuroblastomas. Rare spontaneous regressions or spontaneous differentiation to ganglioneuromas have been reported, associated with a more prolonged survival.

3. Alterations in lymphomas. These include: (a) Indolent nodular lymphomas. Whether treated or not, these tumors may convert in time to aggressive malignant lymphomas, most frequently of a diffuse large cell type [4]. Nodular large cell lymphomas as well as diffuse mixed cell types have been reported in these conversions. (b) Cutaneous T cell lymphomas (mycosis fungoides/Sezary syndrome). Over a prolonged period, these cutaneous tumors may terminate with widespread visceral disease. At this end point, there may be loss of T cell markers. The accompanying monomorphic or blastic transformation morphology resembles diffuse malignant lymphoma, large cell type, cleaved, non-cleaved or immunoblastic sybtype [5]. Some cutaneous lymphomas are associated with a markedly pleomorphic lymphoid infiltrate that closely resembles and may be difficult to distinguish from nodular sclerosing Hodgkin's disease. (c) Hodgkin's disease. Alterations in morphology of Hodgkin's disease usually reflect an absolute or relative increase in the number of tumor cells and stroma and a relative or absolute decrease in the number of lymphoid and inflammatory elements.

4. Small cell lung cancer. The morphologic heterogeneity of SCLC is implied in the multiplicity of subtypes (i.e. fusiform, polygonal, lymphocyte-like type and 'others') and the occurrence at diagnosis of small cell tumors combined with adenocarcinoma or squamous cell carcinoma recognized in the 1967 WHO Lung Cancer Classification [6]. In the 1981 WHO classification, the fusiform, polygonal and 'other' subtypes were segregated from the lymphocyte-like type and classified as 'intermediate' [7]. It seems clear to us that the classic SCLC has fusiform or polygonal morphologic characteristics and that the hyperchromatic, so-called oat-cell/lymphocyte-like appearance of many SCLC tumors represents hypoxic and/or degenerative effects. This impression is reaffirmed by the cytology and morphology of SCLC in cell cultures and nude mouse heterotransplants. The majority of these tumors are 'intermediate' in appearance. Rarely is the 'lymphocyte-like' form expressed in these experimental models [8]. The presence of a few squamous nests or tubules within an SCLC tumor (the 'others' of the 1967 WHO classification) does not appear to effect response to therapy or survival of patients with these tumors. It is difficult to estimate the incidence of small cell carcinoma combined with squamous cell and/or adenocarcinoma. Such tumors are usually identified in surgical resections and probably represent less than 1% of SCLC tumors.

Although the occurrence of combined small cell-large cell carcinomas of the lung is recognized in the revised 1981 WHO classification [7] there is little acceptance of the concept or agreement on diagnostic criteria in the pathology community. In this tumor multiple clusters of cells with abundant cytoplasm and prominent nucleoli are dispersed throughout an otherwise typical small cell neoplasm. It is estimated that 6–10% of SCLC may be associated with non-small cell lung cancer elements (NSCLC) at diagnosis [8]. Following remission and relapse from chemotherapy and radiotherapy, the likelihood of identifying NSCLC elements increases markedly. At autopsy, over one-third of cases may show focal or complete alteration to non-small cell morphology [9, 10].

At the NCI — Navy Medical Oncology Branch, no significant difference in behavior or response to therapy has been identified in the classic SCLC subtypes (lymphocyte-like or intermediate). In contrast, patients identified prospectively as having combined small cell-large cell tumors have a worse prognosis and poorer response to therapy [8].

Variant tumors have also been identified in cell culture and nude mouse xenografts. Some of these variants retain a classic SCLC appearance, lose the majority of their neuroendocrine markers, including dopa decarboxylase, bombesin-like peptide and neurosecretory granules, but retain high levels of neuron-specific enolase and the CK-BB isoenzyme [11]. Most of these cultures were initiated from combined small cell-large cell

carcinomas and reflect alterations that had occurred or commenced *in vivo*. In a few cases, similar changes have occurred *in vitro* or in SCLC xenografts. The variant cells show atypical growth characteristics in cell culture, have shorter doubling times and higher cloning efficiencies. These variant lines (which are believed to be the *in vitro* equivalent of the small cell-large cell carcinomas) have greatly amplified levels of the *c-myc* oncogene [12] and are relatively radioresistant [13].

This experience with SCLC suggests that its progenitor cell is capable of and possibly programmed to differentiate in alternate directions, following prolonged time or chemotherapy/radiotherapy intervention. We speculate that the large cell component with prominent nucleoli identified in small cell tumors are either progenitor cells programmed to neuroendocrine differentiation or arise secondarily from SCLC cells as a result of oncogene amplification.

## CLINICAL AND THERAPEUTIC IMPLICATIONS OF TUMOR HETEROGENEITY

Temporal alterations in the histology of a neoplasm may have important clinical and therapeutic implications.

1. Embryonal/germ cell tumors following therapy may mature to adult ectodermal, mesodermal or entodermal components (mature teratoma). Metastatic nodules in the lung or primary mediastinal tumors may convert to these elements and be removed by surgical intervention.

2. Some multiphasic tumors, such as Wilm's tumor of the kidney, respond to therapy and cures are considered possible. Other mixed or biphasic tumors appear to respond less well to therapy.

3. Indolent nodular neoplasms have a 60% actuarial risk of conversion to aggressive lymphomas within 8 years of diagnosis [4]. Median survival after this conversion is less than 1 yr, in spite of the fact that some complete responses to therapy may be obtained.

4. Patients with mycosis fungoides/Sezary syndrome who terminate with widespread disease may show minimal response to therapy and have a median survival of 6-8 months [14].

5. From 10 to 20% of all patients with SCLC, presenting with limited disease survive over 2 yr. Median survival of all SCLC patients is 10 months. The median survival of patients with mixed small cell-large cell carcinoma is approximately 6 months, regardless of performance status or extent of disease.

## SUMMARY

Morphologic heterogeneity frequently occurs in a wide range of tumor types. It may be present at the time of diagnosis or develop with time. Perhaps as a result of therapy, such heterogeneity may be associated with a greater or lesser degree of differentiation or with simultaneous expressions of multiple forms of differentiation. Many forms of tumor heterogeneity have important diagnostic, clinical and therapeutic implications.

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