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INVASIVE SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX

VI. Prediction value of non-keratinizing, parakeratotic and orthokeratotic cell forms and clinical staging

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Several attempts have been made to adapt the treatment modalities to the histopathologic classification of tumour biopsies. Monofactorial systems based on cell differentiation have been used together with clinical staging, which for some time has proven to be of superior prognostic value. However, the additional information, if any, should be identified. According to REAGAN et coll. (1957), WENTZ & REAGAN (1959) and REAGAN & WENTZ (1967), invasive squamous cell carcinomas can be divided into large cell non-keratinizing, large cell keratinizing and small cell carcinoma. This classification has been adopted by the WHO (POULSEN et coll. 1975). The keratinizing large cell carcinomas were supposed to be derived from the squamous epithelium of the portio, large cell non-keratinizing carcinomas from metaplastic epithelium within the junctional zone and the small cell carcinomas from the reserve cells (WENTZ 1966). A significantly higher survival rate has been reported in patients with large cell non-keratinizing compared with large cell keratinizing or the small cell tumours. The latter had the poorest survival rate of all. These results from the group of REAGAN & WENTZ were confirmed by others (FINCK & DENK 1970, SIDHU et coll. 1970, NG & ATKIN 1973, SWAN & RODDICK 1973, VAN NAGELL et coll. 1977, HARDT et coll. 1982) both for irradiation and surgical treatment. This was in contrast to the results of FIELD et coll. (1964), GUNDERSEN et coll. (1974) and GOELLNER (1976). Except for a preliminary report presented by STENDAHL et coll. (1979) reports from Scandinavia (LINELL & MÅNSSON 1952, NØDSKOV-PEDERSEN 1971, JOHANSSON et coll. 1976, BEECHAM et coll. 1978) have not shown any difference in survival after sub-grouping into cell types. The contradictory results reported by using the definitions of REAGAN & WENTZ might be explained by deviations from the original definitions. The aim of the present report is: a) to discuss the definitions of the different cell types of cervical carcinoma, b) to relate them to the 10-year lethality rate (lethality/lethality + survival), c) to discuss the different keratinizing cell forms such as single cell keratinization, parakeratotic and orthokeratotic forms in a context of a continual spectrum of keratinization rather than special cell forms.

Material and Methods

The material consisted of 432 consecutive patients stages IB–IV with invasive squamous cell carcinoma of the uterine cervix classified and treated at the Department of Gynecologic Oncology, University Hospital, Uppsala, during the years 1967 to 1971. In the final analysis 3 patients were omitted due to revised diagnosis and 4 because of unsuitable biopsy material. Thirty-two patients died from inter-

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Table

Lethality rates within stages and cell types among 393 patients with carcinoma of the uterine cervix. Per cent within parentheses

Cell type	Stage				Total
	I	II	III	IV	
1. Large cell non-keratinizing	10/61 (16)	15/53 (28)	7/7 (100)	4/4 (100)	36/125 (28)
2P. Large cell parakeratotic	4/35 (11)	30/75 (40)	7/13 (54)	4/4 (100)	45/127 (35)
2K. Large cell keratotic	5/23 (22)	33/63 (52)	21/26 (81)	12/13 (92)	71/125 (57)
3. Small cell	1/10 (10)	2/5 (40)	– –	1/1 (100)	4/16 (25)
Total	19/128 (15)	78/196 (40)	35/46 (76)	21/22 (95)	156/393 (40)

current diseases. Thus 393 patients were included in the series. The age varied between 22 and 82 years. All patients were kept under observation until death or for at least 10 years. Staging was done according to the FIGO classification (1971).

Treatment. Intracavitary irradiation was carried out according to a modified Stockholm-method (KOTTMEIER 1964) with separate intrauterine and vaginal irradiators in two sessions at an interval of 3 weeks. The mean dose was 7500 mgh. External irradiation was given to two opposite pelvic fields with 8 MV roentgen rays (linear accelerator), 33 MV roentgen rays (Betatron) or ^{60}Co photons. The majority of patients received a parametrial dose of 40 Gy (mean dose) in 20 fractions usually over a period of 4 weeks (5 irradiations/week) and with central shielding. Individual dose planning was done for each patient. A detailed description of treatment modalities has been given previously (STENDAHL et coll. 1981). The treatment in all cases was thus similar and did not differ significantly between stages.

Histopathology

The estimations of histopathologic parameters were performed retrospectively on pretreatment biopsies and without knowledge of treatment and further course of the disease. The original slides were re-examined twice at an interval of at least 3 months. The result of the last examination was used. At the re-examination new sections, 5 μm thick, were cut of the paraffin blocks. Both van Gieson and Hematoxylin-Eosin stained slides were used depending on the technique applied at the initial classification.

The definitions of REAGAN et coll. (1957) were carefully followed apart from additional sub-grouping into parakeratotic and orthokeratotic large cell keratinizing cell forms as follows:

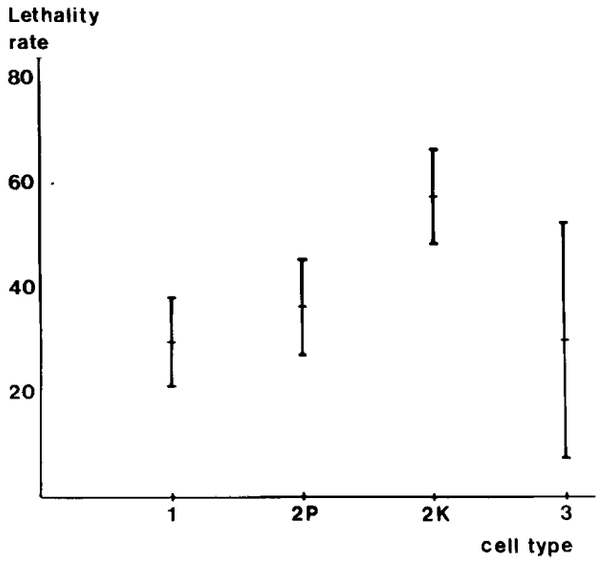
Type 1. Large cell non-keratinizing squamous carcinoma. No keratin production or single cells with intracytoplasmic keratin are referred to this group. A single superficial layer of parakeratosis can also be accepted in this group.

Type 2. Large cell keratinizing squamous carcinoma. 2P. Parakeratotic form: Keratinization without pearls, but with different amounts of remaining nuclei, often confined to the superficial area of the carcinoma and composed of several cell layers. 2K. Orthokeratotic form: All cases with light large cells and keratin pearls of both orthokeratotic and parakeratotic forms are referred to this group as are thick orthokeratotic desquamating types confined to the superficial area of the cancer.

Type 3. Small cell carcinoma. Small dark cells with an increased nuclear/cytoplasmic ratio and organophilic cytoplasm.

Results

The results appear in the Table. The lethality differed significantly between patients with type 3



Lethality rates for different cell types. Confidence limits are given for the 95 per cent level.

and type 2K ($p \leq 0.05$), which was higher in 2K. Corresponding figures for type 2K and type 1 were ($p \leq 0.001$) and for 2K and 2P ($p \leq 0.001$), respectively. No differences were found between cell types 1, 2P and 3. The confidence limits (95 per cent level) are given in the Figure. In patients with cell type 3 the small number of patients (16) gave a confidence interval between 0.07 and 0.52. Thus no firm conclusions can be drawn with respect to clinical outcome in that group.

Within the same stage there were no differences between types 2K and 3 (in contrast to the total material), nor between 1 and 2P. Between types 1 and 2K a significant increase ($p \leq 0.001$) in lethality rates was found in stage II. No such tendency was observed in stages I, III and IV.

Significant differences in lethality rates were found between clinical stages, and these were greater than those derived from cell type differentiation. Thus, clinical staging cannot be supplanted by this classification. After inclusion of clinical staging, cell typing is of additional prognostic value only in stage II. Possible causal connections between cell type differentiation and stage cannot be established in the present series.

Discussion

It is difficult to group according to the definitions of REAGAN & WENTZ. In spite of the precise definitions given, 10 to 20 per cent of the patients will fall outside the 3 groups (GUNDERSEN et coll.). The difficulties of evaluation become obvious when 2 or 3 different cell types are present within the same biopsy. REAGAN & WENTZ classified according to the most differentiated component while FINCK & DENK did the opposite. BEECHAM et coll. used the predominant cell type and GUNDERSEN et coll. tried both the latter alternatives. It is not surprising that the results have been most varying. Both orthokeratotic and parakeratotic cell forms occur together with or without horn pearl-formation and single cell-keratinizing, thus providing for numerous combinations. It is often not possible to attain definite knowledge, in different reports, regarding how these intermediate forms have been grouped even when elaborate definitions have been given (NG & ATKIN, GUNDERSEN et coll.).

The normal cervical mucosa is not keratinized and in agreement with WENTZ & REAGAN the non-keratinizing large cell carcinoma was considered the most differentiated one because of its resemblance to the mature cells of normal stratified squamous mucosa. Keratinized cells are considered to represent an abnormal differentiation, producing only keratin fibers, a process ending up with the cells being unable to divide and consequently dying off (GLÜCKSMANN 1956). True cornification is rare in carcinoma of the cervix (LINELL & MÅNSSON), but as a rule the keratinization is associated with the development of a stratum granulosum, at least in isolated foci (BURGHARDT 1973, NG & ATKIN, BEECHAM et coll.). STÜPER (1953) differentiated the keratinizing horn pearl forming type from the parakeratotic one, the latter being often superficial and with only a keratinizing tendency. The parakeratotic form has also been differentiated from horn pearl forming types by SCHRÖDER (1922), MARTZLOFF (1923), CORDUA (1926), HUEPER & SCHMITZ (1927) and LAHM (1927). REAGAN & WENTZ were of the same opinion as GUNDERSEN et coll., that only a few pearls are required to classify a tumour as a keratinizing squamous cell carcinoma.

The complexity of the keratinizing process is not fully understood (ADAMS 1976, MATOLTSY 1976). A continual spectrum seems to exist from non-keratinizing to para-keratinizing to ortho-keratinizing epithelia rather than distinctly different cell types (CHEN & MEYER 1971, ADAMS). The amount of keratinization is reflected by the degree of packing and orientation of tonofilaments (ADAMS). Ribosomal and ly-

sosomal activity (MATOLTSY), persistence of gene function, DNA and RNA content (MATOLTSY, SUZUKI et coll. 1977), thickness of basal membrane (ADAMS), turn-over rate (HAMILTON & BLACKWOOD 1974) and mitosis rate (HALPRIN 1972) contribute. Enzyme levels and vitamin status (GLÜCKSMANN, WOLFF-SCHREINER 1977, KRUPP & FRINK 1978), oestrogen level (GLÜCKSMANN, LINDHOLM 1975), temperature (INDO & MIYAJI 1979) and the stromal component surrounding the malignant cells (ADAMS, GREEN et coll. 1977) also play a role. The water content of the cell (ADAMS), inflammation (HUGOSON et coll. 1971, ADAMS) and the natural degradation process which takes place within the keratocyte including keratohyaline activity and production of sulphur-rich proteins (MATOLTSY) may also interact.

The present series supports the thesis that the orthokeratotic cell type has the highest lethality rate and that the large cell non-keratinizing one has the lowest. As a single prognostic parameter the classification of REAGAN et coll. does not need to be changed with respect to definitions. However, if used clinically to predict the outcome for patients it has a limited value. In combination with clinical staging, it will have no additional value apart from a limited number of patients in stage II.

The reason why the keratinizing cell type of carcinomas has a worse prognosis compared with non-keratinizing large cell forms is obscure. Two main arguments have been put forward: 1) A real biologic difference exists (REAGAN et coll., WENTZ & REAGAN) with a different genesis and localization (WENTZ, VAN NAGELL et coll.). Several reports on patients treated with surgery support this view (HUEPER 1928, SCHÜLLER 1952, SIDHU et coll.). Others, however (GOELLNER, VAN NAGELL et coll.), could not find any difference in surgically treated patients. In this context the view of ADAMS, that keratinization is a question of degree of keratinization rather than separate cell types, should be mentioned. 2) According to GILMOUR et coll. (1949), REAGAN et coll., MILLER et coll. (1959), and GUNDERSEN et coll., radiation therapy does not influence the different cell types in a similar way. Following modern radiation therapy no differences in treatment results should occur between different cell types (SHERMAN 1961, SCOTT et coll. 1966, BOURNE & MEAD 1968, GUNDERSEN et coll.). In the present series the treatment given the various groups was similar. Considering the fact that these patients were followed for up to 15 years it should be pointed out that neither treatment modality nor results have changed significantly during the past two decades. The different survival rates may partly be explained by the fact that DNA, RNA and other sub-cellular structures are still susceptible to irradiation in the non-keratotic and parakeratotic cell forms. In contrast, these sub-cellular structures are sparser in the orthokeratotic cell form.

In a multifactorial histopathologic classification of invasive squamous cell carcinoma of the uterine cervix presented previously, the cell type was one parameter of eight. Several other parameters had more prognostic information with respect to survival, especially those parameters representing the tumour–host relationship (mode of invasion, stage of invasion, vascular invasion and host-cellular response; STENDAHL et coll. 1979, 1980, 1981). However, any additional information which can be obtained from a single parameter such as cell type differentiation is valuable but should be extracted and be compared with other predictive parameters. In the present series, cell type differentiation by itself had a prognostic value which was subordinate to that from clinical staging.

The difference in lethality rates between large cell orthokeratotic or horn-pearl forming, and large cell non-keratinizing in stage II, affected 32 per cent of all the patients. Although highly significant the difference in specificity will have little consequence with respect to treatment.

Before a new method is introduced into practice its clinical significance should be established (RINGSTED et coll. 1978).

SUMMARY

In 393 patients with invasive squamous cell carcinoma of the uterine cervix stages I to IV the predictive value of the histopathologic classification of REAGAN & WENTZ (differentiation into cell type) was analysed in relation to 10-year lethality rate. Patients with large cell horn-pearl forming and orthokeratinizing tumours had the poorest, and those with large cell non-keratinizing the best prognosis. Large cell parakeratotic tumours did not differ significantly in prognosis compared with the non-keratinizing cell form. When clinical staging was included the prediction value of the histopathologic classification disappeared except in stage II. From a clinical point of view this additional prognostic information will have little practical consequences.

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