NUCLEAR SIZE IN CARCINOMA OF THE CERVIX UTERI—ITS RELATION TO PROGNOSIS

by

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Size of cancer cells and their nuclei has engaged the investigators since long. But data regarding its clinical significance is limited. Work of Ehrich (1936), Hoffman (1953), Stich, *et al* (1960), Spriggs *et al* (1962) Hauschka (1963) and Atkin (1964) has stated that fundamental difference between normal and malignant tissue is eneuploidy of chromosomes. Atkin (1964) on the basis of DNA estimation of Feulgen stained smears and its comparison with nuclear size determination, drew conclusion that if the average diameter of nuclei exceed 10 micron it indicate ploidy, whereas less than 10 micron diameter is indicative of diploid or near diploid state. Tumour having large nuclei (or high model DNA content) have better prognosis.

In this preliminary study, mean nuclear diameter has been determined in cervical smears from squamous cell carcinoma of the cervix and the relationship of nuclear size has been correlated with the prognosis of these patients.

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Material and Methods

Nuclear size was measured in cervical smears (Papanicolaou stained) from 108 histologically proved squamous cell carcinoma of the cervix uteri, using a micrometer eye piece of 8x and scale of 0.1 mm, in two main axis of the nuclei. The cases were classified into two groups as having nuclear size less than 10 micron or more than 10 micron (after Atkin, 1964). In a small number of cases where there was regional or diffuse difference in nuclear size, intimate mixture of small and large nuclei were measured in almost equal proportions and mean was considered to group them. 80-120 nuclei were measured in each case. The results of nuclear size were correlated with different clinical stages and histological grades after Riotten and Christopherson (1973). The follow up data is collected from the files of Radiation Medicine Department. Follow-up of 2-5 years is available in only 69 cases and only these are analysed for prognostic significance.

Observations

Squamous cell carcinoma of the cervix having tumour nuclei of more than 10 micron are 55 (50.92%) while 53 (49.08%) have nuclear size of less than 10 micron. Table I shows the break up

TABLE I

Relationship Between Nuclear Size and Clinical Stages in Carcinoma of the Cervix

Clinical Stage	Nuclear size							
	<10 micron				>10 micron			
	Survival	Died	Lost	Total	Survival	Died	Lost	Total
Stage I (8)	3	-	1	4	3	-	1	4
Stage II (39)	10	2	6	18	7	6	8	21
Stage III (46)	16	-	10	26	8	4	8	20
Stage IV (12)	1	-	4	5	2	4	1	7
Stage unknown (3)	1	1	-	2	1	-	-	1
(108)	31	3	21	55	21	14	18	53

Figures in bracket indicate total number of cases in each clinical stage.

of two groups of the patients in different clinical stages and their follow-up data. Thirty-nine patients are lost to follow-up (21 in large nuclei group and 18 in small nuclei group). Statistically, there was no significant difference in survival between various clinical stages in either of the groups whether average nuclear diameter is more than ten micron or less than ten micron ($P > 0.01$).

Table II shows the distribution of these into various histological grades of squam-

TABLE II

Break up Between Various Grades of Squamous Cell Carcinoma in Relation to Follow-up

Squamous cell carcinoma histological cell type	Nuclear size							
	>10 micron				<10 micron			
	Alive	Died	Lost	Total	Alive	Died	Lost	Total
I. Carcinoma in Situ (3)	3	-	-	3	-	-	-	-
II. Keratinizing CA (25)	6	-	4	10	2	3	10	15
III. Large cell non-Keratinizing CA (46)	15	2	10	27	7	7	5	19
IV. Small cell non-keranizing (25)	2	-	6	8	10	4	3	17
V. Mixed group (9)	5	1	1	7	2	-	-	2
(108)	31	3	21	55	21	14	18	53

The figures in bracket indicate total number of cases in each histologic type.

Alive versus dead between nuclei of >10 micron vs <10 micron $X^2 = 7.43$ $P < 0.01$.

ous cell carcinoma along with their prognosis in each type. Statistically there is no significant difference between the prognosis of patients of group II vz group III in both the groups (Patients having nuclear size of more than 10 micron or less than 10 micron, P value being > 0.99 and > 0.01 respectively). When individual histologic type prognosis is compared according to the size of the nuclei, there was also no statistically significant difference. But when overall prognosis is compared between the two groups of nuclear size in terms of survival of two to five years—it was found to be highly significant statistically ($P < 0.01$) irrespective of clinical stage and histological type.

Discussion

Studies on the nuclear size in assessing the prognosis of these patients are limited. Higher survival in patients of large nuclei group is statistically significant ($P = < 0.01$) and is not related to degree of differentiation and clinical stage. These findings are corroborative with the findings of Atkin (1964), Sugimori and Gusberg (1969) and Sircky (1972).

Studies on the chromosomal pattern of tumours (Spriggs *et al.* 1962, Ishiharia *et al.* 1963, Lubs and Clarke, 1963, Jones *et al.* 1968, Richard and Ludwig 1969 and Jones *et al.* 1970) have shown that tumour cells are mostly aneuploid, varying from triploid, tetraploid or polyploid, resulting into giant nuclei. Why the tumours from same morphologic type and grade should have wide variation in DNA content as reflected in nuclear size is not clear. Whether this difference is due to endomitosis (Mittwoch, 1963, Wolman *et al.* 1964, Mittwoch, Lele and Webster 1965 a and b and Mittwoch, 1968) or due to triploid or tetraploid or polyploidy resulting into giant nuclei, is not clear and difficult to distinguish (Atkin, 1962). But it is found that tumours with DNA mode in hypotetraploid region having high basic chromosome number have more favourable prognosis in cervix than tumours with hypertetraploid DNA mode and stem cell line with lower chromosome number. The distinction between hypotetraploid and hypertetraploid tumour can be done only by cytogenetic studies but the observations of Atkin (1964), Sugimori and Gusberg (1969), Sircky (1972) indicate that patients with these two groups of tumour considered together have a better prognosis than those of near diploid state. The reasons for better prognosis at best remain speculative. However, with the available literature and findings of the present study, amply justifies the use of nuclear size as an independent parameter in assessing the prognosis of a patient of carcinoma of the cervix uteri. A long term follow-up study in a larger series may prove to be more profitable.

Summary

Nuclear diameter in Papanicolaou stained smears of 108 cases of squamous cell carcinoma of cervix uteri have been measured. 60.92% of carcinoma of the cervix have an average nuclear diameter of more than 10 micron and this indicate nuclear ploidy. 49.08% nuclei of carcinoma cervix have less than 10 micron nuclear diameter and represent diploid or near diploid state of nucleus. The follow-up study of 69 of these shows, 91.17% survival in carcinomas having larger nuclei as against 60 per cent survival in small nuclei group, independent of histological grade and clinical stage. It is suggested that nuclear size determination can be used as an independent parameter in as-

sessing the prognosis of the patients of carcinoma of the cervix.

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