

PROGNOSTIC EVALUATION IN UTERINE CERVIX CARCINOMA IN RELATION TO THE LYMPHOPLASMACYTE INFILTRATE AND TO THE CYTO-HISTOLOGIC TYPE

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SUMMARY

The prognostic import of the lymphoplasmacyte infiltrate and of the cyto-histologic type have been evaluated in 109 cases of uterine cervix carcinoma, treated with various types of radical surgery or radiant or combined therapy, chosen every time, with the method of personalization.

The lymphoplasmacyte infiltrate resulted the most significant parameter, in the cases studied, for the prognostic evaluation: the survival rate after 5 years increased with the raise of the infiltrate intensity and, when this appeared in a high degree, it resulted significantly higher than in the other groups.

The survival rate showed, on the contrary, statistically significant variation in relation to the cyto-histologic type.

For what concerns the relation between the two examined morphological parameters and between them and the survival rate, we observed that the infiltrate of high level is significantly more frequent in the keratinizing carcinoma, where also the largest survival rate was found. On the other hand it results that the infiltrate of high level has the lowest frequency in the adenocarcinoma, where the survival rate is the lowest we found.

A precise personalized prognostic evaluation of neoplasias, taking into account numerous factors as, on one side, the conditions of the patients, and on the other side the histological type of tumor, is until now not possible.

In the research for other significant elements of the evolutive possibilities of the neoplasia, the attention was directed during the last years towards the study of the reaction of the host organism against the neoplastic cells with antigenic specifications unknown to the immune system of the host itself, and expressed by the intra and/or peritumorous lymphoplasmacyte infiltrate.

Many Authors, who conducted research on different organs as the stomach⁽²²⁾, the larynx⁽¹⁹⁾, the mammae^(15, 16, 17), the endometrium⁽¹⁴⁾, the cervix uteri^(2, 6, 7), showed that generally, the more the infiltrate is marked, the more favourable the prognosis for the patient is.

The purpose of our study is to verify further the prognostic meaning of the lymphoplasmacyte infiltrate in the cervix uteri-carcinoma, evaluating also the eventual relations between the infiltrate and the cyto-histologic type of neoplasia.

MATERIAL AND METHODS

The research has been conducted on 109 patients affected by cervix-uteri-carcinoma with ages ranging between 24 and 69 (average age 49 years) recovered at the Clinic of Obstetrics and Gynecology of the University of Padua, from January 1971 to December 1972.

All patients were submitted to a personalized therapy, deciding each time, according to the general health conditions of the patient, the cyto-histologic type and the clinical stage of the tumor, both the extension of surgical removal, and the eventual association and modality of complementary radiotherapy.

The parameters taken into consideration and compared to each other were:

- the cyto-histologic type of tumor;
- lymphoplasmacellular infiltrate;
- survival after 5 years.

The cyto-histologic type and the infiltrate were defined during this study reviewing the histologic preparations of the pre-operating bioptic drawings and of the operative piece at the Institute of

Table 1. — *Distribution of the cases according to the clinical stage.*

Clinical stages	No.	%
I	54	49.55
II	49	44.95
III	3	2.75
IV	3	2.75
Total	109	

Anatomy and Pathological Histology of the University of Padua.

To define the cyto-histologic type we retained, for what concerns the epidermoid carcinoma, the Wentz-Reagan ⁽²³⁾ classification, which considers the following types:

- a) keratinizing carcinoma;
- b) carcinoma with large cells;
- c) carcinoma with small cells.

To these three sub-types the adenocarcinoma and the adenosquamous carcinoma are added.

We meant immune type infiltrate the presence of lymphocytes and/or plasmacytes in the stroma that encloses the non-necrotic tumorous tissue, organized or not in follicular structures with or without germinative centers; occasionally, mixed with eosinophilic granulocytes and macrophagy.

The intensity of the stromal reaction has been evaluated according to the following scheme in:

- *marked*, when the lymphoplasmacytes delimit clearly the tumor tissue from the healthy surrounding tissue, or when around the neoplastic buds, lymphatic follicles are present;
- *moderate*, when lymphocytes and plasmacytes number is smaller, but they can surround with sufficient regularity the tumorous tissue;
- *minimal* or absent, when such cells are not present around the neoplastic buds, or if present, they limit them in a discontinuous way.

RESULTS

The distribution of the studied cases, depending on the clinical stage, the survival rate, the cyto-histologic type and the presence of the lymphoplasmacyte infiltrate, is reported in table 1, 2, 3 and fig. 1.

For what concerns the clinical stage, we observed (table 1) that stage I contains nearly half of the studied cases (49.55%); stage II follows with 44.95%; stage III and IV have both a frequency of 2.75%. It must be underlined that the frequency of stages I and II altogether, reaches 94.50%. The rate of survival after 5 years (fig. 1) considering the 109 cases without distinction of stage results in 77.10%; survival rates relative to stages I and II are respectively of 87% and of 71.40%.

For what concerns the cyto-histologic type (table 2) the most frequent carcinoma is the epidermoid with large cells with an incidence of 43.1%, followed by the epidermoid with small cells (35.8%) and the keratinizing epidermoid (11%). Altogether epidermoid carcinoma reaches a frequency of 89.9%. The remaining 10.1% includes the adenocarcinoma (6.4%) and the adenosquamous carcinoma (3.7%).

For what concerns the lymphoplasmacyte infiltrate (table 3), we can notice how, in about half of the cervix-uteri-carcinoma (50.5%), its degree is minimal or null, while it is moderate in 22% and high in 27.5%.

The survival in relation to the two morphological parameters taken into consideration (cyto-histologic type and stromal infiltrate) has been reported in tables 4, 5, and in figs. 2, 3, 4, 5.

For what concerns the cyto-histologic type (tab. 4, figs. 2-3) the highest survival

Table 2. — *Distribution of the cases according to the cyto-histologic type.*

Cyto-histologic type	No.	%
Keratinizing epidermoid carcinoma	12	11
Epidermoid carcinoma with large cells	47	43.1
Epidermoid carcinoma with small cells	39	35.8
Adenocarcinoma	7	6.4
Adenosquamous carcinoma	4	3.7
Total	109	

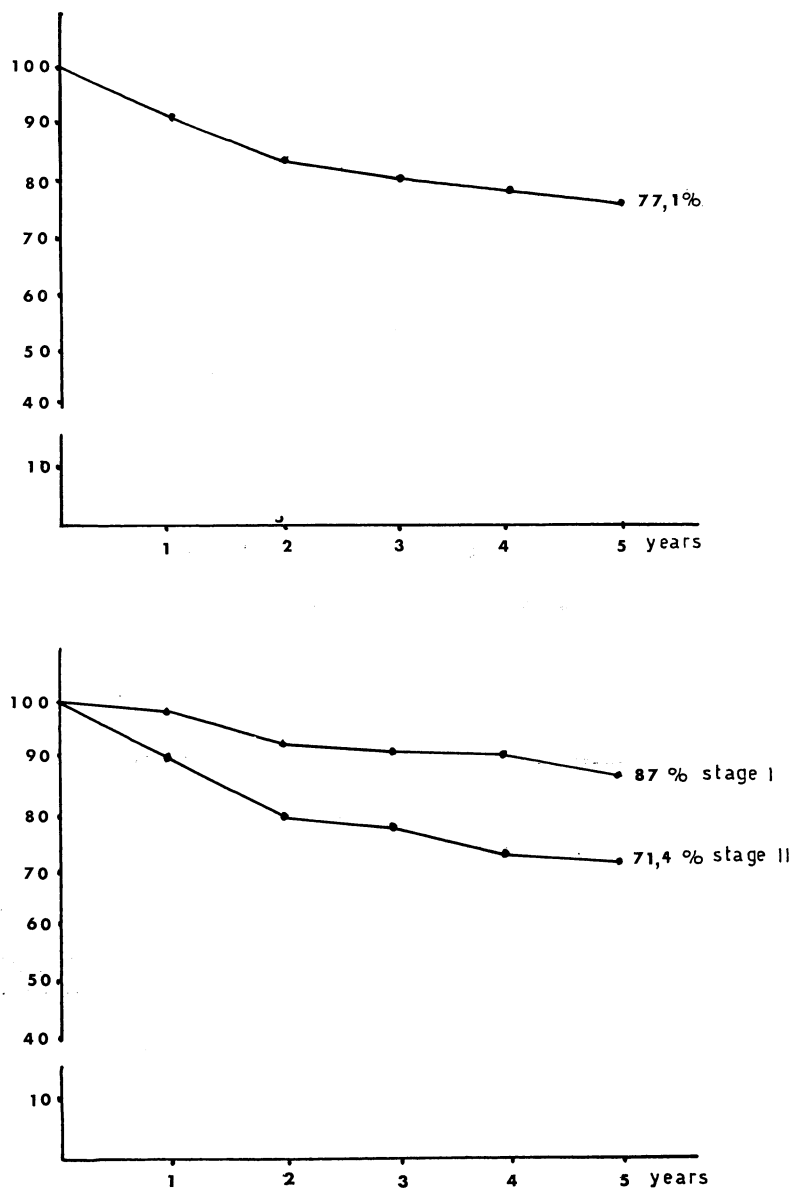


Fig. 1. — a) Five years survival according to clinical stages. b) Five years survival according to clinical stages I and II.

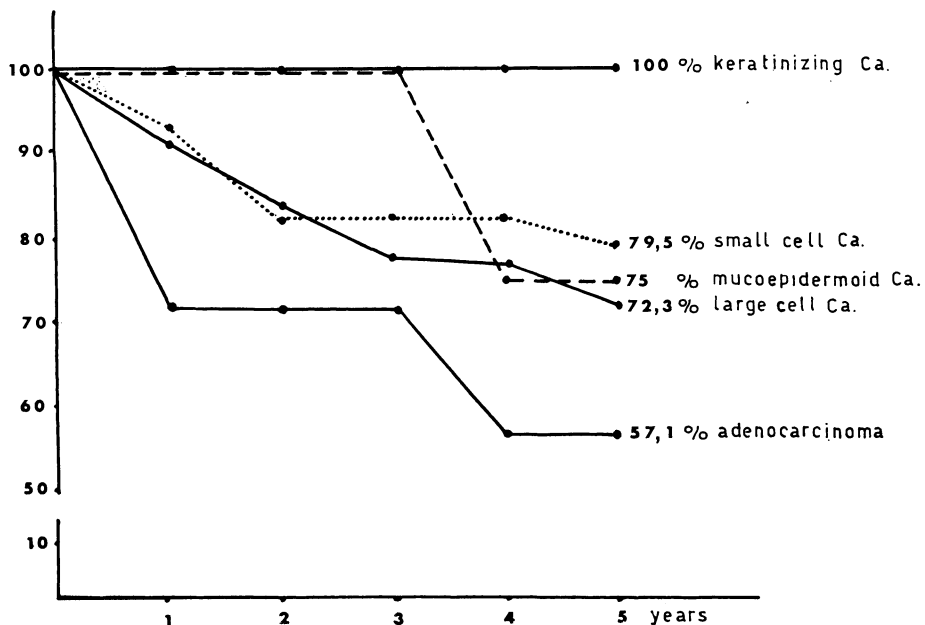


Fig. 2. — Five years survival according to cyto-histologic type (all stages).

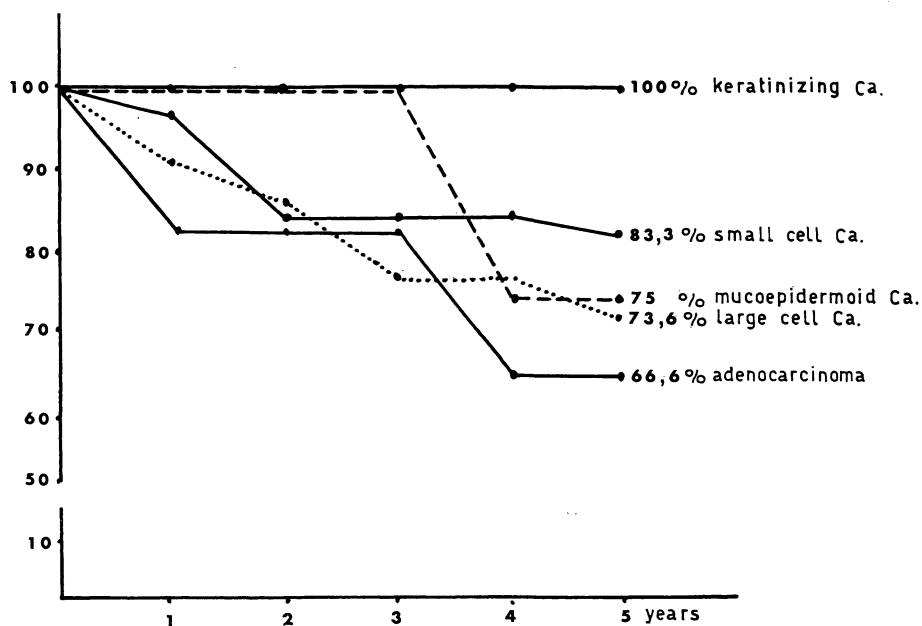


Fig. 3. — Five years survival according to cyto-histologic type (stages I and II).

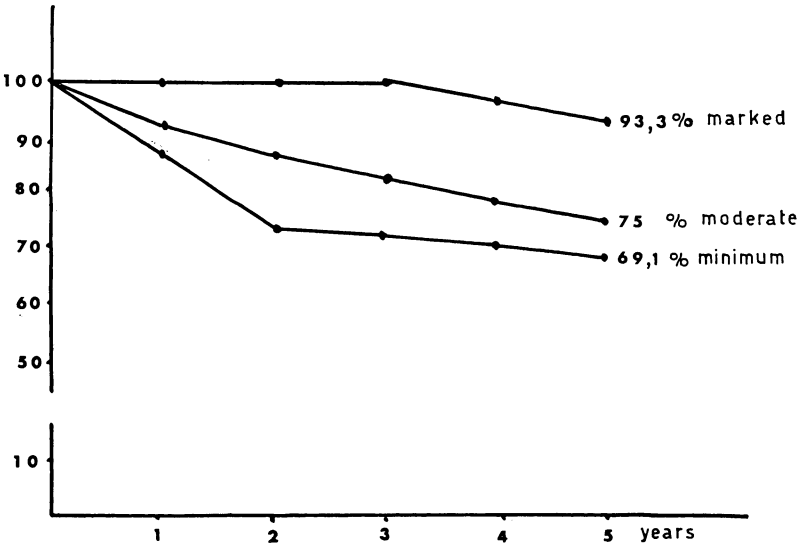


Fig. 4. — Five years survival according to lymphocytic infiltrate (all stages).

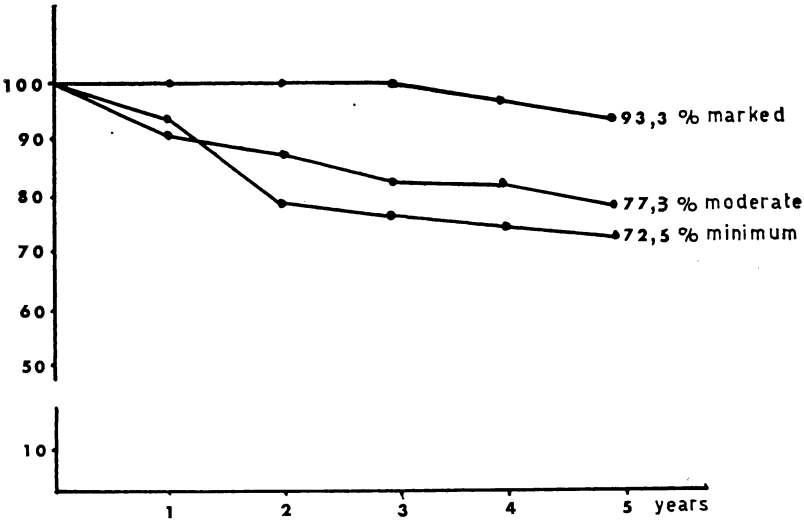


Fig. 5. — Five years survival according to lymphocytic infiltrate (stages I and II).

Table 3. — *Distribution of cases according to the stromal infiltrate.*

Stromal reaction	No.	%
Minimum	55	50.5
Moderate	24	22
High	30	27.5
Total	109	

rate (100%) is correlated to the keratinizing carcinoma followed by the carcinoma with small cells (79.5%), by the adenosquamous carcinoma (75%) and by the carcinoma with large cells (72.3%). The adenocarcinoma has the worst prognosis between the various cyto-histologic types observed with a survival rate of 57.1%.

When stage III and IV carcinomas are excluded, the values related to the survival rate raise slightly, but the succession of the different cyto-histologic types remains inalterd (figs. 4-5).

The differences encountered are of no statistical value (X^2).

For what concerns the lymphoplasmacyte infiltrate of the carcinomas in the four stages (tab. 5, fig. 4) we pointed out that the survival rate raises with the increase of stromal reaction intensity: it changes from 69.1% for the minimal degree to 75% for the moderate degree and to 93.3% for the high degree. When the survival rate in carcinoma of stages I

and II (fig. 5) are separately observed, even if survival rates raise, the succession remains inalterd.

The differences noticed, resulted statistically significant (X^2), in particular the survival rate with the high degree infiltrate results significantly higher ($p < 0.05$) than in the other situations.

The relation between cyto-histologic type and intensity of the infiltrate (tab. 6) shows how, as to the epidermoid carcinomas, the most differentiated form is linked to a lymphoplasmacyte presence with an undoubtly high frequency (75%), unlike the others where in most cases an infiltrate with a minimal degree can be observed (51.1% in carcinoma with large cells, and 56.4% in carcinoma with small cells). Such differences are very significant with the X^2 calculation.

The highest incidence of minimal degree infiltrate (71.4%) is in the adenocarcinoma and of the four cases adenosquamous carcinoma, two showed a minimal stromal reaction, one a moderate one and one a marked one; the exiguity of the cases in these groups doesn't allow statistically valuable comparisons.

At last, we assembled and compared the data relative to lymphoplasmacyte infiltrate and cyto-histologic type to the data concerning the survival rate (tab. 7).

The exiguity of cases of some cyto-histological groups does not allow to take definitive and statistically valuable conclu-

Table 4. — *Survival rate behaviour in relation to the cyto-histologic type.*

Cyto-histologic type	Alive percentage		Death percentage		Total
	No.	%	No.	%	
Keratinizing epidermoid carcinoma	12	100	0	0	12
Epidermoid carcinoma with large cells	34	72.3	13	27.7	47
Epidermoid carcinoma with small cells	31	79.5	8	20.5	39
Adenocarcinoma	4	57.1	3	42.9	7
Adenosquamous carcinoma	3	75	1	25	4
					109

Note: Differences don't result statistically significant (X^2).

Table 5. — Behaviour of the survival rate in relation to the intensity of the stromal lymphoplasmacyte infiltrate.

Stromal	Alive perc.		Death perc.		Total
	No.	%	No.	%	
Minimum	38	69.1	17	30.9	55
Moderate	18	75	6	25	24
High	28	93.3	2	6.7	30
					109

Note: The difference between the minimum and the high results statistically significant ($P < 0.05$); the significance diminishes between the minimum and the moderate, considered together, and the high ($P < 0.1$).

sions, but we can mention that within the single groups, the general trend is observed for which the survival rate is higher in presence of high degree infiltrate.

CONCLUSIONS

On the basis of the results obtained in our study on the prognostic value of the lymphoplasmacyte infiltrate and of the cyto-histologic type in the cervix uteri car-

cinoma for 109 cases treated between 1971 and 1972, the cyto-histologic type does not seem to present significant data and prognostic criteria. In fact, though the keratinizing epidermoid carcinoma cases had the highest survival rate (100%), all other type rates range between 72.3 to 79.5% without any significant differences excepted the few cases of adeno carcinoma in which the survival rate after 5 years was of 56.3%. This trend confirms the bad prognosis of the adeno carcinoma, and, for what concerns the squamous type, the criterion that the minor differentiation should be always linked to a worse prognosis, does not seem confirmed; it does neither confirm Wentz and Reagan's observation that the keratinizing type, as it is due to an anomaly of the differentiation and not to a differentiation, would have a worse prognosis compared to the type with large cells.

We must not forget, however, that the survival rate of the group studied by us is rather high, and that various types of radiant and/or radical surgical therapy was used; in every time personalized method, and is known that one or another cyto-

Table 6. — Distribution of the lymphoplasmacyte infiltrate in relation to the cyto-histologic type.

Cyto-histologic type	Infiltrate						Total
	Minimum		Moderate		High		
	No.	%	No.	%	No.	%	
Epidermoid keratinizing carcinoma	2	16.6	1	8.3	9	75	12
Epidermoid carcinoma with large cells	24	51.1	15	31.9	8	17	47
Epidermoid carcinoma with small cells	22	56.4	6	15.4	11	28.2	39
Adenocarcinoma	5	71.4	1	14.3	1	14.3	7
Adenosquamous carcinoma	2	50	1	25	1	25	4
							109

Note: X^2

High infiltrate: significantly more frequent than the minimal one in the keratinizing carcinoma in regard to all the other ones ($P < 0.001$), and separately: carcinoma with large cells ($P < 0.001$), carcinoma with small cells ($P < 0.002$).

Infiltrate of minimum and moderate degree: significantly less frequent in keratinizing carcinoma in regard to all the other ones ($P < 0.002$) and separately: carcinoma with large cells ($P < 0.001$), carcinoma with small cells ($P < 0.005$).

Table 7. — *The survival rate in relation to the cyto-histologic type and to the stromal infiltrate.*

Cyto-histologic type	No.	Infiltrate		Survival rate		Total
		No.	%	No.	%	
Epidermoid keratinizing carcinoma . .	12	Minimum	2 16.6	2	100	12/12 100 %
		Moderate	1 8.3	1	100	
		High	9 75	9	100	
Epidermoid carcinoma with large cells	47	Minimum	24 51.1	18	75	34/47 72.3%
		Moderate	15 31.9	9	60	
		High	8 17	7	87.5	
Epidermoid carcinoma with small cells	39	Minimum	22 56.4	14	65.63	31/39 79.4%
		Moderate	6 15.4	6	100	
		High	11 28.2	11	100	
Adenocarcinoma	7	Minimum	5 71.4	3	60	4/7 57.1%
		Moderate	1 14.3	1	100	
		High	1 14.3	0	0	
Adenosquamous carcinoma	4	Minimum	2 50	1	50	3/4 75 %
		Moderate	1 25	1	100	
		High	1 25	1	100	
						84/109 77.1%

histologic type have differentiated answers to surgical or radiant therapy. The lymphoplasmacyte infiltrate, as an index of immune response of the host, resulted instead, in view of prognostic evaluations, more significant.

We noticed that the survival rate raises with the growth of the intensity of the infiltrate: in fact from 69.1% in presence of infiltrate of low degree, it passes to 93.3% in case of infiltrate of high degree, and this in all stages.

What seems to influence in a significant way the prognosis is the infiltrate of high degree (only present in 27.5% of the cases), being the survival rate of the moderate degree just a little greater than that of low degree.

From the evaluation of the existing relations between the two morphological studied parameters, and between these and the survival rate, it emerged that lymphoplasmacyte infiltrate of high degree has the maximum of the frequency in the keratinizing carcinoma that separates itself in a significant way from the others, and that also has the maximum of the survival rate, while it has the minimal frequency

in the adenocarcinoma where the survival rate is the lowest.

Anyway, in all groups, in presence of the infiltrate of high degree, the survival rate is superior to the average for this cyto-histologic type.

Practically, if the cyto-histological criterion, in case of personalized therapy, does not seem to settle the prognostic evaluation for the cervix uteri carcinoma, the lymphoplasmacyte infiltrate is without any doubt, when present in high degree, a favourable factor for the prognosis.

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