

PATHOLOGIC-HISTOLOGY AND PROGNOSIS OF CANCER OF THE UTERINE CERVIX

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In this series of Uterine Cervical Cancers 1955-1958, the five-year survival rate for adenocarcinoma was lower than that for epidermoid carcinoma. The survival rate was about equal in both when the lymph nodes were free of tumour cells whereas in the presence of lymph node metastasis the survival rate for adenocarcinoma was much lower. The incidence of lymph node metastases was also higher with adenocarcinoma. From a review of the literature and our personal experience the authors feel that the present forms of treatment are ineffective for adenocarcinoma of the cervix and propose that future treatment should be: Surgery followed by chemotherapy for adenocarcinoma and chemotherapy and/or irradiation followed by surgery for small cell carcinoma.

Several factors influence the prognosis of carcinoma of the uterine cervix. It is evident that the prognosis of the disease depends largely on the extent of spread. The type of therapy may have some influence but strict comparison between the two main avenues of therapy namely surgery and irradiation, cannot be maintained and there have been few reports which can fulfill the rigid requirements of controlled study in which patients should be randomly assigned to surgery or irradiation. Twombly and Taylors¹³ work is almost ideal in this respect, but those of Masubuchi, Kubo, Tenjin and Kimura⁹ cited as close to the ideal is in fact, far from it as post-operative irradiation is performed on all cases. Apart from this, variations in techniques, equipment, skill of individual surgeons, and facilities available in institutions will influence the results of the two main therapeutic measures. Our clinical experience with cases where immediate generalised metastases or recurrence occurred after complete extirpation of an early disease, and the infrequent 5-year survivals in cases with extensive lymph node metastases or stage III and

stage IV cases, indicate the important role played by host tumour relation in the prognosis of the disease. In view of the early dissemination of the cancer cells into the systemic circulation, we are rather inclined to think that if there had been no immunity of the host's tissue against cancer cells to withstand CANCEREMIA at or immediately after operation, there would not have been such good end results obtained hitherto by several pelvic surgeons. What will then be the factors for a certain case to survive without metastases or recurrence, while others died from metastases or recurrence? We know very little in this field, but the number of cancer cells in the blood stream, host resistance against the cancer cells and the malignancy of the cancer cells may be the most important factors. While the attention of most investigators have been focused on the immunological aspects, the consideration to variations in the malignancy of the cancer cells seem to have been rather neglected. An attempt is made in this paper to re-evaluate the significance of cell malignancy in relation to the prognosis of the disease.

TABLE I

Surgical Results in Adenocarcinoma of the Uterine Cervix as Compared With Those in Squamous Carcinoma

	Number of Cases	Positive Nodes	Number	Cured	Author
Adenocarcinoma	27	10 (37%)	15	8 (53%)	Liu and Meigs
Squamous carcinoma	317	78 (25%)	178	125 (70%)	Liu and Meigs
Adenocarcinoma			93	40 (43%)	Limburg
Adenocarcinoma			35	17 (49%)	Hepler et al.
Adenocarcinoma	31	Positive Nodes 9 (29%)	9	22 (22.22%)	64.51%
		Negative Nodes 22 (71%)	22	18 (81.81%)	
Squamous carcinoma	193	Positive Nodes 35 (18.1%)	35	14 (40.0%)	75.13%
		Negative Nodes 158 (81.9%)	158	131 (82.91%)	

(A) ADENOCARCINOMA

(a) Review of literature:

The response of adenocarcinoma to irradiation has been questioned.^{1,7} However, data⁷ from such centre like John Hopkins, Columbia, New York, Boston and Radium Hammet, indicate equal salvage rates for adenocarcinoma and squamous carcinoma of the uterine cervix. At the Radium Hammet⁷ the relative 5 year cure rate of 3,000 case of stage I to III, was 54.1% for squamous carcinoma and 54.8% for adenocarcinoma. Because of the supposed radioresistance of adenocarcinoma, surgery has been suggested as a better method of treatment. Surgical results in adenocarcinoma are however, poorer than squamous carcinoma. In their recent paper Masubuchi et al⁹ reported that while pure adenocarcinoma especially the well differentiated adenocarcinoma showed comparatively poor response to irradiation, the mixed type (adeno plus squamous) carried a better response. This fact deserves some attention. (see Table I)

(b) Results in our series 1955-1958

From 1955-1958, thirty-one cases of invasive adenocarcinoma of the uterine cervix were subjected to radical panhysterectomy with pelvic lymphadenectomy.

1. Incidence of lymph node involvement.

The overall incidence of lymph node involvement was 29% which was significantly higher than that in epidermoid

TABLE II

Incidence of Lymph Node Involvement in Adenocarcinoma of the Uterine Cervix

Stage	No. of Cases	No. of Cases with Positive Node	Per cent
I	25	3	12
II	5	5	100
III	0	0	0
IV	1	1	100
Total	31	9	29

TABLE III

A Comparison Between Incidence of Lymph Node Involvement in Adenocarcinoma and Epidermoid Carcinoma of the Cervix

Stage	Percentage of Involvement in Adenocarcinoma (1954-1962)	Percentage of Involvement in Epidermoid Carcinoma (1955-1958)
I	12	4.29
II	100	12.37
III	—	62.07
IV	100	60.00
Total		18.13

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TABLE IV

Lymph Node Involvement According to Histological Type of the Tumor (Modified After Nogales & Botella-Llusia, 1965)

Stage	Basal cell carcinoma	Spindle cell carcinoma	Adeno-carcinoma
I	6.5	25.0	50.0%
II	7.2	54.1	92.4%
III	9.5	60.0	92.9%
IV	—	—	—
Total	8.0	51.8	84.8%

carcinoma. In another series, being analysed at present, there is a much higher incidence of lymph node involvement. This may be due to a thorough microscopic examination of all lymph nodes removed. (see Table II to III)

2. Survival rate

Our 5-year survival rates according to the International clinical staging is shown in table V.

The 5-year Survival for Stage I was 80% but for cases of stage II and IV none survived the five following surgery. Death from recurrence usually occurred

TABLE V

Survival Rate of Adenocarcinoma of the Cervix Operated on at Provincial Taipei Hospital from 1954 to 1962 According to Clinical Staging

Stage	No. of Cases operated on	No. of Cases lost to study	No. of Cases living	No. of Cases dead	Survival Rate
0	1	0	1	0	100
I a	0	0	0	0	80
b	17	0	15	2	
c	8	0	5	3	
II a	2	1	0	1	0
	3	0	0	3	
III	0	0	0	0	0
IV	1	0	0	1	0

TABLE VI

A Comparison Between Survival Rates for Adenocarcinoma and Epidermoid Carcinoma of the Cervix

Stage	Adenocarcinoma 1954-1962	Epidermoid carcinoma 1955-1958
I	80	87.14%
II	0	71.91%
III	—	58.62%
IV	0	60.00%

TABLE VII

Cure Rate for Adenocarcinoma of the Uterine Cervix to the Presence or Absence of Regional Lymph Node Involvement

Stage	Cases With Positive Node				Cases With Negative Nodes				Total	
	No. of Cases	Meta-stasis	No. of Cases Cured	% Cured	No. of Cases	No. of Cases Cured	% Cured	No. of Cases	No. of Cases Cured	% Cured
I	5	100	0	0	22	18	81.81	25	20	80.0
II	5	100	0	0	0	0	0	5	0	0
III	0	0	0	0	0	0	0	0	0	0
IV	1	100	0	0	0	0	0	1	0	0
Total	9	29	2	22.22	22	18	81.81	31	20	64.51

TABLE VIII

Correlation Between the Number of Positive Node and the Five-Year Survival Rate

No. of Positive Nodes	No. of Cases	Adenocarcinoma			Epidermoid Carcinoma	
		No. of 5-Year Survivals (Hsu)	Cure Rate	Mitani's Series, 5-Year Survival Epidermoid	Hsu	
1	3	1	33.3%	51.6%	54.2%	
2	4	1	25.0%	27.56%	22.2%	
3	1	0	0	50.00%	62.3%	
4	1	0	0	25.00%	0	
5	0	0	0	0	60.0%	
6	0	0	0	0	100.0%	
7	0	0	0	0	0	
9	0	0	0	0	0	
12	0	0	0	0	0	
30	0	0	0	0	100.0%	

very early; 6 died within one year and 4 within 2 years. When the 5-year survival rates of the various stages of adenocarcinoma and epidermoid carcinoma are compared, marked contrast is apparent. (see Table VI)

The cure rate according to the presence or absence of lymph node involve-

ment is shown in table VII.

The overall cure rate for cases with negative nodes was 81.8% while that for cases with positive nodes was only 22.2%. In the same series the 5-year survival rates for epidermoid carcinoma without node involvement was 82.91% and this dropped to 40% when nodes were in-

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TABLE IX

Outcome of 6 Cases of Small Cell Carcinoma

	1 LWLR	2 HCSL	3 YLYR	4 LWY	5 LZR	6 WCPY	
Parity	7	10	6	8	5	6	
Age	49	53	41	49	35	43	
Clinical	Staging	I	I	III	I	II	
	Cervix	plus	plus	plus	plus	plus	
Pathology	Corpus	—	—	plus	—	—	
	Parametrium	—	—	—	—	—	
	Vagina	—	—	plus	—	plus	
	Lymph nodes	—	-0/23	-0/20	19/56	-0/18	5/12
	Ureter, Kidney	—	—	—	plus	—	—
	Adnexae	—	—	—	—	—	
Postoperative	Lt. inguinal	—	—	—	Spine	Lung	
Metastases	nodes	—	—	—	—	—	
Local	Vagina	—	plus	—	—	+	
Recur	—	—	plus	—	plus	plus	
Rence Pelvis	—	—	—	—	—	—	
Chemotherapy	Mitomycin	—	Mitomycin	Mitomycin	Mitomycin	—	
	Endoxan	—	—	—	AF-2	—	
Irradiation Radium	—	—	4000 mgh.	—	—	—	
Co 60	6000 r	4800 r	5000 r	—	Incomplete	—	
Time of Death	—	—	—	—	—	—	
after Operation	13	15	15	18	9	6	
(Month)	—	—	—	—	—	—	

involved. When the correlation between the number of positive nodes and the 5 year survival is made the difference in 5-year survival between epidermoid and adenocarcinoma will be more evident. (see Table VIII)

In adenocarcinoma no survival was seen among those with node metastasis of more than 2, but in epidermoid carcinoma a good number of survivals were observed among those with node metastases of more than 5.

(c) Comments

From the above results, the 5-year survival rates for adenocarcinoma and epidermoid carcinoma in those cases without lymph node metastases were almost equal in contrast to the sharper drop of survival rates in the positive node group in adenocarcinoma than that in epidermoid carcinoma. This would indicate that lymph node metastases exert a graver influence on the prognosis in adenocarcinoma than that in epidermoid

carcinoma. The poorer prognosis of adenocarcinoma compared with epidermoid carcinoma is not only related to the higher incidence of lymph node metastasis in adenocarcinoma but also probably to the tumour behaviour of adenocarcinoma per se.

The overall 5-year survival rates in adenocarcinoma of the uterine cervix (64.51%) is apparently poorer than epidermoid carcinoma (75.13%). When only those with lymph node involvement are compared the sharper fall in the survival rates of adenocarcinoma (22.2%) in contrast to epidermoid carcinoma (40%) is well in accord with the results of Meigs. These results are still equal and somewhat superior to the results of several irradiation centres. Because of the differences in opinion among investigators on the irradiation response of adenocarcinoma (Graham, Bersjo, Masubuchi), surgery in our opinion has a place for the treatment of adenocarcinoma of the

uterine cervix but special adjuncts to surgery like postoperative chemotherapy should be carried out to prevent recurrence or metastases. Although adenocarcinoma constitutes 5% of carcinoma of the cervix, the form of therapy, the mode and kind of chemotherapy, and the mode of combine treatment has to be closely studied to improve the 5-year survival rates for the benefit of patients.

(B) SMALL CELL CARCINOMA

(a) Review of literature

There have been several attempts to correlate the prognosis of cervical cancer to the degree of anaplasia of the cancer cells. Marzcoff¹⁰ in 1923 published his system of grading cancer cells into 3 grades, namely:- "spinal", "transitional", and "fat-spindle". Broders⁴ in 1922 published his 4 categories of grading according to the degree of differentiation, namely: Grade I (more than 75% differentiated cells), Grade II (50-75% differentiated cells), Grade III (25-50% differentiated cells) and Grade IV (less than 25% differentiated cells). More recently, Wentz and Reagan¹⁵ and Wentz¹⁴ proposed a classification of 3 categories. "Keratinizing", "non-Keratinizing" and "small cell carcinoma", the latter being claimed to be the most malignant. The cells in this category are small, almost round and have a basaloid appearance and belong to a particular type of basal cell carcinoma that has been described by Broders.

(b) Small cell carcinoma in our series.

During the past five years we have encountered 6 cases of cervical cancer classified into the category of small cell carcinoma. It will be evident in Table IX that all our cases of small cell carcinoma died from metastases or recurrence within one and a half years regardless of absence

or presence of lymph node involvement at operation and whether irradiation or chemotherapy was instituted postoperatively.

(c) Comments

There were conflicting results in the literature with regard to small cell carcinoma. While Wentz and Reagan¹⁵ reported only 5% 5-year survival rates with small cell carcinoma, 33% and 45% for Keratinizing and non-Keratinizing carcinoma respectively; Field, Dockerty and Simmonds⁶ reported 88.3% 5-year survival rates for Stage I, 64.3% for Stage II and 53.8% for Stage III small cell carcinoma irradiated, although Field et al's criteria of diagnosis were consistent with those of Wentz and Reagans. Novak et al¹² think that the stage of the disease is much more important than the cell type. Nevertheless, the poor results with surgery from our limited experience led us to believe that the early invasion of surrounding tissues and veins by the anaplastic tumour cells is the main cause of the poor prognosis. The increase in mitosis, early invasion of surrounding tissues and veins with early dissemination is a characteristic of this type of tumour cells. In this type of cancer, handling and manipulation of tumour tissue during operations may well increase the risk of iatrogenic spread. Although it may be too premature to draw conclusions, small cell carcinoma should be better treated by irradiation and/or chemotherapy followed by radical surgery.

(C) MIXED ADENOSQUAMOUS CARCINOMA

Tumours composed of both adenomatous and squamous elements have been well recognised. When both elements are well differentiated, the diagnosis can be made with certainty. In some cases however the correct diagnosis cannot be made

before detailed examination is carried out on the operated specimen.

Glucksmann divided immature mixed tumours into two groups, namely: signet-ring and glassy-cell types. Pretreatment biopsy will enable one to identify this particular lesion with the help of mucin-carmin and PAS stain. Often the diagnosis can be confirmed when the cancer cells are forced to differentiate by irradiation which makes the features of the two elements clearer. Glucksmann related these types of tumour to pregnancy and considered the prognosis to be poorer than unmixed lesions. Metastatic lesions are frequently differentiated into one or the other i.e. adenocarcinoma in one node and squamous carcinoma in the other. The signet-ring cell type is characterised by a crescent shaped nucleus and cytoplasm with positive mucin carmin and PAS staining. The glassy cell type is the most anaplastic, staining pale blue with haematoxylin and presents a ground-glass appearance. In Glucksmann's series of 195 cases of mixed tumour which represents 5-8% of uterine cervical cancer, 51-65% of these were found to accompany pregnancy. Glucksmann is of the opinion that mixed tumours respond poorly to radiotherapy alone. In his series the mature type could have some salvage with radiotherapy plus surgery, while the signet-ring cell type showed poorer results and none of the glassy cell type survived for 5 years. At the seminar of the International College of Surgeons held in Chicago in April 1969, Way expressed a similar opinion.

In our series we have only two cases of adenoepithelioma who are doing well with radical surgery alone. However, with only two years of follow up and too limited a number of cases, we are not in a position to make any comments in this aspect.

(D) CONCLUSION

Apart from such considerations as extent of the disease, method of therapy and host tumour relationship; emphasis was placed on the significance of histological patterns of the tumour in evaluating the prognosis of uterine cervical cancer. In our series adenocarcinoma showed a poorer 5 year survival rate than squamous carcinoma, and none of the small cell carcinoma had a survival beyond 2 years. To increase the salvage rate surgery followed by chemotherapy for the former, while chemotherapy and/or irradiation followed by surgery was recommended for the latter. The 2 cases of mixed tumour surviving two years in our series do not warrant any comment for the present.

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