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## Hysterectomy—definitive therapy for carcinoma in situ?

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**H**YSTERECTOMY has long been the favorite treatment for carcinoma in situ of the uterine cervix. This operation has often been termed "complete therapy"<sup>1</sup> in contrast to conservative forms of treatment or "incomplete therapy." Many authors<sup>2-7</sup> have come to consider hysterectomy as definitive therapy for carcinoma in situ in the uterine cervix.

The operation does constitute definitive treatment, but only in so far as the cervix is concerned. Since carcinoma in situ is not a condition peculiar to the cervix, and may be found in numerous sites in the female lower generative tract, inferences in regard to the definitive nature of hysterectomy are not only groundless, but represent potentially dangerous thinking. To adhere to the concept that the operation is complete therapy often results in incomplete postoperative progress examinations, leaving the distinct possibility that recurrent disease will be overlooked.

For the last 14 years, we have been testing the theory that there is no single definitive treatment for carcinoma in situ. Treatment has been individualized and graded in accordance with the extent of the disease and its response to treatment.<sup>8</sup> This response has been judged on the basis of careful, periodic, pelvic examination, and repeated cellular studies.

Conization has constituted the primary mode of therapy for cervical carcinoma in situ. It has been the only surgical treatment required in 314 of 414 patients. Hysterectomy has been performed only on the basis of the following criteria: (1) results of cellular studies have been abnormal after coniza-

tion; (2) cervical stenosis after conizations has made results from cervical spreads unreliable; and (3) other pelvic disease is present and constitutes an indication for excision of the uterus. In the course of pursuing this study, we have observed and treated 10 patients in whom cervical carcinoma in situ has been associated with or followed by similar lesions in other sites in the lower generative tract. We have also studied and treated six other women in whom carcinoma developed in the vagina in from 3 to 27 years after they underwent hysterectomy. In each instance, the hysterectomy was reported to have been performed for a benign condition.

#### MULTIPLE SITES OF CARCINOMA IN SITU

Carcinoma in situ may occur in numerous sites, either simultaneously or sequentially (*Table 1*). This terminology is somewhat arbitrary, since the time relative to the duration of a specific pathologic lesion is difficult to establish. However, three women in this group each seemed to have lesions occurring simultaneously in two separate sites. Patient 1 was found to have carcinoma in situ of the cervix and on the anterior third of each labia majora. There was no visible cervical lesion, but a visible hyperkeratotic process affected the labia. Patient 2 had a 1-cm erythematous lesion in the anterior fornix of the vagina in addition to an invisible one in the cervix. Patient 3 had no evident vaginal disease when conization was performed to investigate abnormal findings in the cervical cellular study. Two months later, a diffuse leukoplakia of the upper third of the vagina was observed; biopsy revealed carcinoma in situ. We assume that invisible carcinoma in situ was present in the vagina when conization was performed.

Seven women have had multifocal disease diagnosed sequentially over a span of from 1 to 17 years. Only two (patients 5 and 7) were treated by us for the primary disease. The others consulted us after the primary diagnosis had been made and hysterectomy had been performed. Several of these patients are of particular interest.

Patient 4 underwent hysterectomy after carcinoma in situ of the cervix was diagnosed from the conization specimen. The uterus contained no detectable carcinoma in situ. One year later, the results of the first post-operative cytologic study were abnormal. At the apex of the vagina there was a slightly erythematous area 1.5 by 1.5 cm. An excisional biopsy specimen of this area disclosed carcinoma in situ. Results of subsequent cytologic studies were also abnormal, but there is no visible pathologic lesion. Further treatment, doubtless, will be necessary.

Patient 6 had incomplete surgical treatment for a cervical carcinoma in situ, as a fragment of cervix was inadvertently left intact when hysterectomy was performed. Three years later, the cervical fragment was the site of a mistaken diagnosis of invasive carcinoma, and radiation treatment was

**Table 1.**—*Clinical data of 10 patients with multiple foci of carcinoma in situ*

Patient	Age, years	Carcinoma in situ						Follow-up, time, status
		Primary site	Therapy	Interval, years	Secondary site	Therapy		
1	30	Uterine cervix	Conization	0	Vulva	Vulvectomy	3 years, negative	
2	60	Uterine cervix	Vaginal hysterectomy	0	Vagina	Partial vulvectomy	3 years, negative	
3	53	Uterine cervix	Conization	0	Vagina	Excision and cautery	6 years, alive	
4	64	Uterine cervix	Hysterectomy	1	Vagina	Excision	1 year, (?)	
5	38	Uterine cervix	Conization	1	Vulva	Excision	1 year, negative	
6	47	Uterine cervix	Hysterectomy	3	Cervical remnant	Irradiation		
7	73	Uterine cervix	Conization	15	Vagina	Cautery	5 years, negative	
8	47	Uterine cervix	Vaginal hysterectomy	5	Vagina	Irradiation	2 years, negative	
9	55	Uterine cervix	Hysterectomy	6	Vagina	Medical and surgical	4 years, (?)	
10	34	Right side of vulva	Hemivulvectomy	6	Vagina	Medical and surgical	3½ years, (?)	
				17	Left side of vulva	Vulvectomy		
				18	Dysplasia, cervix	None	3 years, (?)	

given. When we first examined the patient, 15 years posthysterectomy, there was no visible cervix and the vagina appeared to be normal. A Papanicolaou test indicated the presence of abnormal cells. In the upper part of the vagina a 1/2-cm area did not stain with double-strength Lugol's solution, and biopsy confirmed the presence of carcinoma in situ.

Patient 7, aged 73 years, had persistent cytologic abnormalities after conization for cervical carcinoma in situ. She declined the recommended hysterectomy. Five years later, she returned because of vaginal bleeding, caused by a 2 cm by 3 cm, invasive, squamous cell carcinoma, in the left lateral vaginal wall, 2 cm from a normal cervix. Had hysterectomy been performed when originally advised, it is doubtful that the affected vagina would have been included in the operative specimen. Almost certainly, then, postoperatively the vaginal lesion would have become visible at the apex of the vagina and would have been considered to be due to incomplete excision of the abnormal tissue.

Patients 8 and 9 had almost identical problems. In each patient, multicentric vaginal carcinoma in situ developed six years after hysterectomy for the same disease. Each patient has been treated with various conservative methods, and is still being observed. Patient 10 is included, because carcinoma in situ developed on the right side of the vulva and then 17 years later developed on the left side. Since then, dysplastic cells have been found on cervical Papanicolaou testing, but thus far she has declined to undergo a diagnostic operation.

#### VAGINAL CARCINOMA—'REMOTE' HYSTERECTOMY

Six patients (*Table 2*) have been observed for whom carcinoma of the vagina was diagnosed within from 3 to 27 years after hysterectomy.

Patient 11 underwent excisional biopsy of a lesion in the vaginal vault, three years after a total abdominal hysterectomy. Upon microscopic examination, the vault specimen was diagnosed as carcinoma in situ. The patient returned one year later with a 3-cm invasive carcinoma in the same site; radical upper vaginectomy was performed. Pelvic lymph nodes showed no tumor. Three years later, an extensive, invasive, squamous cell carcinoma was found to constrict the rectum. The vagina was normal and a Papanicolaou-stained spread was negative. A combined abdominoperineal resection was performed, with removal of the entire posterior two thirds of the vagina. Eleven of 17 lymph nodes contained metastatic tumor. It is impossible to determine whether this course of events represents metastatic progressive disease, or perhaps two different primary lesions. The patient did not return for progress examinations between the surgical procedures.

Patient 12 underwent hysterectomy because of leiomyomas in 1957. Chronic cervicitis was present, and preoperative cytologic studies were negative for tumor cells. Four years later, vaginal cytology was abnormal,

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**Table 2.**—*Clinical data of six patients with vaginal carcinoma after hysterectomy*

Patient	Posthys- terec- tomy, years	Site of lesion	Age, years	Therapy	Follow-up time, status
11	3	Carcinoma in situ, vagina	43	Excision	
	4	Carcinoma, vagina	44	Radical surgery	
	7	Carcinoma, rectum	47	Posterior exenteration	3 months, recurrence
12	4	Carcinoma in situ, vagina	47	Excision and cautery	4 years, negative
13	15	Carcinoma in situ, vagina	65	Excisional biopsy	3 years, negative
14	20	Carcinoma in situ, vagina	58	Cautery	
	22	Superficial carcinoma, vagina	60	Irradiation with radon seeds	6 years, negative
15	27	Carcinoma in situ, vagina	67	Cautery and exci- sion	6 years, negative
16	12	Carcinoma in situ, vulva; and leuko- plakia, vagina	53	Vulvectomy	
		Carcinoma, vagina and vulva	55	Irradiation with radium	3 years, negative

but there was no visible lesion. Double-strength Lugol's solution was used to localize areas for biopsy. Multiple specimens were taken; they all demonstrated carcinoma in situ. Extensive vaginal cautery was performed and results of subsequent cytologic studies have been normal.

Patient 14 had a multicentric carcinoma in situ diagnosed 20 years after she underwent hysterectomy. The vaginal apex, the distal part of the sub-urethral area, and the upper posterior vaginal wall were all affected with grossly invisible carcinoma in situ; extensive cautery was performed. Fourteen months later, three regions of superficial carcinoma could be seen in these locations. Radon seeds were implanted, and for six years periodic cytologic examinations have been negative for tumor cells.

Patient 16 underwent hysterectomy and bilateral salpingo-oophorectomy in 1950 because of chronic pelvic inflammatory disease. Pathologic examination of the cervix showed only chronic cervicitis. In 1962, diagnoses of carcinoma in situ of the vulva, and leukoplakia of the vagina, were made when simple vulvectomy and vaginal biopsy were performed. Two years later, we diagnosed invasive carcinoma in the vagina and in skin on the left side of the introitus, and incidental carcinoma in situ in the skin from the right side of the ostium vaginae. Radium treatment was administered, and there has been no evidence of recurrent disease in the last three years.

## DISCUSSION

The foregoing cases are presented to emphasize the fact that carcinoma in situ may be found in multiple sites in the female lower generative tract. We agree with the concept that carcinoma in situ is truly a regional disease<sup>9</sup> often associated with invasive carcinoma. In the past, the posthysterectomy recurrence of carcinoma in situ in the apex of the vagina generally has been attributed to inadequate surgical excision. The histories of patients 4 and 7 suggest that, at least in some instances, the disease is simply multicentric in origin.<sup>10</sup>

The group of cases here presented is small in relation to the total number of patients we have examined and treated for carcinoma in situ of the uterine cervix. This raises an interesting question: Is carcinoma in situ an extremely uncommon condition in the vagina and vulva, or have we simply been overlooking its existence?

Woodruff and Williams<sup>11</sup> indicated that the chance of "...anaplastic change occurring in the cervix is 120 to 150 times as great as that in the vagina, and 15 to 20 times as great as that on the vulva." They cited 20 instances of "multiple sites of anaplasia" in a 19-year review. In the succeeding four years, 17 more cases were reported.<sup>12</sup> This mounting evidence suggests that either the disease has been overlooked in the past or it is becoming more common. We suspect that both situations may be in effect.

Until just recently our cytologic screening technics have been directed toward the detection of abnormalities occurring in the uterine cervix. Until relatively recently, posthysterectomy study of cytology has not been routinely advised—an outgrowth of the concept that definitive treatment is provided by total hysterectomy. Before the advent of mass testing of women by cytologic technics, many women died of cervical carcinoma. Some of the "recurrent" or radioresistant carcinomas may well have been unrecognized new tumors occurring in the vagina.

In the last 20 years the indications for hysterectomy have been broadened considerably as a result of routine cytologic testing, improved anesthesia, and refinement of operative technics. In addition, total hysterectomy has come to be the usual, rather than the unusual, operation it was two decades ago.

If the uterine cervix is the primary site of predilection for the development of carcinoma in the female lower generative tract, the removal of the uterus probably does not eliminate the stimuli or factors favoring neoplasia. Considering all of the above factors, it is reasonable to conclude that vaginal and vulvar carcinomas may seemingly become more common, as greater efforts are made to detect these conditions.

The recognition of carcinoma in situ is a relatively new diagnostic development. As recently as 1961, two individual case reports were pub-

lished.<sup>13, 14</sup> Since then, there has been increasing concern over abnormalities found in routine vaginal cytologic studies.<sup>3, 4, 9, 12, 15</sup> Vaginal cytologic specimens should be obtained as a part of routine examinations on each woman who has had a previous diagnosis of invasive carcinoma or carcinoma in situ. Vaginal cytologic specimens should be obtained (perhaps every two or three years) from all women who have undergone hysterectomy, even when the pathologic findings at the time of hysterectomy are known to have been benign. Even when the cervix is present, a careful examination of the vagina should be made. Too often the examiner is preoccupied with the detection of cervical abnormalities. A Schiller's test of the entire vagina should be combined with conization and dilation and curettage in evaluating cytologic abnormalities.

There seems to be a singular lack of enthusiasm among surgeons for performing routine total vaginectomy, when a focus of carcinoma in situ is found in the vagina. No truly satisfactory treatment has yet been found for this condition. Cautery has been fairly effective in our experience. Two patients have been treated locally with 5-fluorouracil, but no conclusions in regard to effectiveness of this treatment can be made at present. A topical treatment, which will preserve a functional vagina, is most desirable.

#### SUMMARY AND CONCLUSION

There is no truly definitive treatment for carcinoma in situ, short of total extirpation of the uterus, vagina, vulva, perianal tissues, and urethral meatus. Since such radical treatment is unlikely to gain popular support, it is incumbent upon the physician to carry out careful, periodic examinations of all female patients, regardless of their medical or surgical history.

The true incidences of carcinoma in situ of the vagina and of the vulva are not known. Present cytologic screening technics are largely directed at the detection of uterine cervical lesions. The concept that hysterectomy constitutes definitive treatment for carcinoma in situ of the uterine cervix has insidiously resulted in inadequate postoperative cytologic progress examinations of a large group of women. Available evidence and logic suggest that carcinoma in situ of the vagina and of the vulva may be far more common than we formerly believed to be possible. These pathologic conditions actually may become more common in future years.

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