FACTORS IN THE CAUSE OF DEATH IN CARCINOMA
OF THE CERVIX

A Study of Fifty-Seven Cases Coming to Necropsy

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This study is based upon 57 consecutive cases of carcinoma of the cervix in which autopsy examinations were performed. Thirty-one of these were studied at the University Hospitals. The remaining 26 were taken from the autopsy records in the Department of Pathology at the University of Minnesota. Microscopic sections were studied except in a few instances in which they could not be obtained. An attempt has been made to determine the immediate lethal factors and the frequency with which they occur. No attempt is made to determine the efficacy of the treatment.

URETERAL STRICATURE

Stricture of the ureters with consequent hydronephrosis and hydroureters was the most striking and constant autopsy finding in this series of cases, being present in 42 cases, or 75 per cent. This is in accord with the observations of others. Ernst Holzbach in 48 carcinomas of the cervix coming to autopsy found 31 bilateral and 10 unilateral strictures. Sampson found that the factors responsible for strictures were external pressure of a mass of carcinoma around the ureters as a result of parametrial extension and lymphatic metastasis, and added infection and edema. Carson states that metastasis may occur to the lymphatics of the ureters. Constriction by metastatic processes was not, however, very common in our series. It occurred only three times and was located in the midportion of the ureter.

In this series both ureters were constricted in 30 cases (52 per cent); one ureter in 13 cases (21 per cent). Of the unilateral strictures 7 were on the right and 5 on the left.

UREMIA

That uremia is a common cause of death in cancer of the cervix has been known for some time. Beatty, whose report before the Dublin Pathological Society, in 1854, is one of the earliest records on this subject, described 3 cases with death in uremia. Saxinger in 1864 reported 62 cases, in 28 of which marked evidences of uremia were present prior to death and post-mortem examination showed constriction of the ureters. Both writers deplored the fact that so little attention was paid to this cause of death.

Nineteen or 33 per cent of our patients died of uremia. In these cases there were clinical symptoms of uremia as well as definite increase in blood
metabolites. In 14 cases the blood metabolites were determined one or more times. In the remaining 5 the clinical course and symptoms were such as to exclude the possibility of any other cause of death. Of the 19 patients, 11 had marked bilateral hydronephrosis, 1 moderate right and 1 moderate left hydronephrosis. In every instance in which the output of urine was recorded there was oliguria.

Infection of the Urinary Tract

Urinary tract infection is a frequent occurrence in carcinoma of the cervix, and follows in the wake of obstructive hydronephrosis. Bell states that the most important complication of hydronephrosis is infection. In 13 of our cases (22 per cent) there was definite infection in the kidney and pelvis. Pyonephrosis occurred in 6 cases and pyelonephritis in 12. Infiltration of the bladder with carcinoma occurred in 9 cases, vesicovaginal fistula in 4, gangrenous cystitis in 4, chronic cystitis in 10, and edema in 3. Hydronephrosis was present, with its attendant stagnation, in 75 per cent, and in nearly every case the cervix was necrotic and infected.

Two cases in our series were of considerable interest, as the immediate cause of death could be ascribed to pyelonephritis in both instances. One of these patients (Case 22), a woman of forty-two, had daily chills with a temperature range from 101 to 103°F, pyuria, rapid pulse, and pain in the abdomen and back. Autopsy showed bilateral pyelonephritis. Microscopically the kidney showed multiple abscesses. The other patient (Case 45), aged forty-five, had chills and fever. Autopsy showed bilateral cortical abscesses and bilateral gangrenous inflammation of the bladder.

Faerber in 150 autopsied cases of carcinoma of the cervix found gangrenous necrotic cystitis in 26, hemorrhagic cystitis with ulcers in 13, edema in 4, purulent nephritis in 3, and vesicovaginal fistula in 68 cases (45 per cent). Pyonephrosis was present in both kidneys in 14 cases pyelonephritis and pyelitis in 19 cases, kidney abscess in 3, and perirenal abscess in 1.

Distant Metastases

In the earlier literature, especially texts dealing with the subject, distant metastasis of cervical carcinoma is often dismissed with the following statement: “Distant metastasis in carcinoma of the cervix is rare.” We were struck to find in many of our post-mortems, extensive metastasis to the liver, lungs, kidneys, and elsewhere.

Winter (1886), in 255 cases of carcinoma of the uterus, at autopsy found metastases to the liver in 9 per cent and to the lungs in 7 per cent. In 1893 Albers-Schönberg in 564 cases of uterine carcinoma found the highest percentages of metastasis in the liver, 13.7 per cent, and in the peritoneum, 7.44 per cent. Feilchenfeld found organ metastasis in 28.2 per cent, the lungs being affected in 15.4 per cent of his cases. Riechelmann in his Inaugural Dissertation in 1902 presented 86 cases of carcinoma of the cervix, 49 of which had metastases. Of these, 15.1 per cent occurred in the liver and 4.6 per cent in the lung. Williams, in 79 necropsies of cervical carcinoma, found
that dissemination had taken place in 16 or 20.2 per cent. MacCormac reported 241 patients with carcinoma of the cervix admitted to the cancer wards in the Middlesex Hospital from 1904 to 1908. Autopsies were performed in 107. Of these cases, 48 or 44.85 per cent had secondary deposits either in the lymph nodes or in the viscera.

<table>
<thead>
<tr>
<th>Author</th>
<th>Liver</th>
<th>Lung</th>
<th>Pleura</th>
<th>Peritoneum</th>
<th>Kidney</th>
<th>Bones</th>
<th>Spleen</th>
<th>Stomach</th>
<th>Intestines</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter, 1886: 255 cases</td>
<td>9.0</td>
<td>7.0</td>
<td>—</td>
<td>—</td>
<td>3.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Albers-Schönberg, 1893: 564 cases</td>
<td>13.7</td>
<td>4.07</td>
<td>1.95</td>
<td>7.44</td>
<td>1.77</td>
<td>.85</td>
<td>1.24</td>
<td>.17</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Feilchenfeld, 1902</td>
<td>—</td>
<td>15.4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>28.2</td>
</tr>
<tr>
<td>Riechelmann, 1902: 86 cases</td>
<td>15.1</td>
<td>4.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2.33</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Andriezen and Leitch, 1906: 187 cases</td>
<td>13.5</td>
<td>6.0</td>
<td>1.4</td>
<td>5.0</td>
<td>2.6</td>
<td>1.9</td>
<td>—</td>
<td>—</td>
<td>.9</td>
<td>20.4</td>
</tr>
<tr>
<td>Williams, 1908: 79 cases</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20.2</td>
</tr>
<tr>
<td>MacCormac, 1909: 107 cases</td>
<td>13.0</td>
<td>4.6</td>
<td>1.0</td>
<td>3.7</td>
<td>2.8</td>
<td>1.0</td>
<td>6.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Wertheimer, 1921: 104 cases</td>
<td>19.0</td>
<td>13.0</td>
<td>5.0</td>
<td>13.0</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>—</td>
<td>1.0</td>
<td>58.0</td>
</tr>
<tr>
<td>Ford, 1930: 24 cases</td>
<td>—</td>
<td>54.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>58.0</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Faerber, 1931: 150 cases</td>
<td>20.0</td>
<td>11.0</td>
<td>6.0</td>
<td>—</td>
<td>14.0</td>
<td>1.3</td>
<td>.7</td>
<td>1.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pearson (present report), 57 cases</td>
<td>19.0</td>
<td>9.0</td>
<td>5.0</td>
<td>5.0</td>
<td>2.0</td>
<td>7.0</td>
<td>3.5</td>
<td>—</td>
<td>—</td>
<td>25.0</td>
</tr>
</tbody>
</table>

A high percentage of distant metastasis was reported by Wertheimer, 58 per cent. The figures of others range from 20.2 per cent (Williams) to 28.2 per cent (Feilchenfeld). In our series distant metastasis had taken place in 25 per cent. The liver seems to be involved most frequently, varying from 9 per cent (Winter) to 19 per cent (present series and Wertheimer) and 20 per cent (Faerber). The low figure for metastasis to the lung is 4.07 per cent (Albers-Schönberg) and the high figure 54 per cent (Mayo Clinic). We have been unable to find as high a percentage of metastasis as reported by Ford anywhere else in the literature. Metastasis to the bones is quite variable, the figure averaging from 1 to 2 per cent. In our series we found 7 per cent. The low figures reported for most series are probably to be accounted for by the fact that few patients are completely x-rayed. The high figure in the Mayo Clinic series, 58 per cent, is striking.

Wertheimer calls attention to the fact that there has been apparently an increase in metastasis, especially of the atypical forms. The question arises: does irradiation of cervical carcinoma disseminate and increase distant metastasis? If our efforts at radiation therapy heal the local process but disseminate the growth, they are worthless. Wertheimer's series from the University Woman's Clinic at Frankfurt, 1909 to 1920, included 104 post-mortem examinations of carcinoma of the cervix. Fifty of these patients were not irradiated and 32 had shorter or longer courses of irradiation. No apparent effect of radiation on the dissemination of tumor growth could be demonstrated. Jeanneney, Wangermez, and Rosset-Bressand collected 51 cases with diffuse metastases, in some of which the patient was irradiated and some
not. They found no essential difference between the irradiated and the non-irradiated groups in this respect.

**Local Spread**

Most of the work done on local spread of carcinoma of the cervix is the outcome of attempts to improve the efficacy of total extirpation of the uterus. Kundrat found among 80 operated cases that the parametrium and pelvic lymph nodes were free from carcinoma in 32. Baisch found the regional lymph nodes involved in 33 per cent of "operable cases" of cervical carcinoma. In autopsy material higher percentages are found. Scheib states that lymphatic involvement is present in from 43 to 73 per cent of patients coming to necropsy. Sampson, in his careful work on pelvic nodes and the parametria, found that the malignant process progressed both by the lymphatics of the parametrium and also by direct extension. The latter, he believes, is the most frequent route. Extension to the vagina is a frequent occurrence, being present, according to Leitch, in 87.5 per cent of 847 cases. Schottländer and Kermauner found the vagina involved in 36 per cent of their cases. Brunet found involvement in 43 per cent. *In our cases the vagina was involved in 13 cases, or 24 per cent, the pelvic nodes were involved in 34, or 59 per cent.*

When one considers the proximity of the cervix and uterus to the bladder and rectum, it is not surprising that these structures are frequently invaded. Williams found invasion of the bladder in 56 of 75 autopsies; in 26, vesico-vaginal fistulae had formed. Faerber found vesicovaginal fistulae in 10 of 150 cases. Blau states that 50 per cent of all the fatal cases have invasion of the bladder and 33 per cent have fistulae. In our series vesicovaginal fistulae occurred 4 times or 7 per cent.

Rectovaginal fistulae occur, according to Bekman, in 6 per cent of cases. Faerber found rectovaginal fistulae in 46 of 150 cases (30.7 per cent). In our series, it occurred in 8 cases, or 14 per cent.

**Peritonitis**

In 11 of our 57 cases, or 19 per cent, death was due to a generalized peritonitis. All these patients had signs and symptoms of a generalized peritonitis. Faerber attributed death to a purulent peritonitis in 2 of 150 cases.

Heimann found that the parametria were almost regularly infected with bacteria in ulcerating cervical carcinoma and not infrequently in non-ulcerating growths. Among 65 cases in which the parametrium was cultured, 36 showed streptococci, and the operative mortality in this group was 61.1 per cent. In 18 patients with negative parametria the mortality was 5.5 per cent. Heimann believes that this parametrial infection is responsible for the peritonitis which is not infrequently encountered postoperatively.

In our cases, perforation was demonstrated post mortem 3 times, twice probably as the result of radium necrosis with perforation and once as an external bowel fistula. In 6 of our cases, peritonitis followed radiation treatment in from two to five days. While we can not definitely state that the peritonitis was the result of irradiation, the sequence seems suggestive, as we
know that irradiation may stir up infections. Stacy has called attention
to this point in a report of 134 cases of inoperable carcinoma of the cervix.
She believes that the usual radiation reaction and pelvic cellulitis and peri­
tonitis are the most common complications following irradiation. In 24 of
her cases (17.9 per cent), complications followed immediately after radiation.
In 7 the evidence of pelvic peritonitis was severe enough for the treatment to
be discontinued entirely. In a series of 227 non-malignant cases treated by
radiation for menorrhagia during the same period, these complications oc­
curred in only 2.2 per cent. It would seem that radiation may be a factor
in stirring up latent infection in far advanced cases.

**Other Causes of Death**

Hemorrhage terminated the picture in 5 cases. In all instances the hemor­
rhage was massive.

Cachexia is a rather difficult term to define, but we have limited it to cases
in which the patient terminally went rapidly down hill and lost a great deal of
weight and in which post-mortem examination revealed only carcinoma. Five
such cases were studied. Two patients died in whom only generalized distant
metastases were present. In two cases nothing was found except the local
carcinomatous process in the pelvis. One patient had a severe secondary
anemia and post-mortem examination showed local pelvic carcinoma and
vesicovaginal fistula. In two cases the cause of death was probably cachexia.
Bronchopneumonia was directly responsible for one death in association with
cachexia.

Diffuse distant metastasis with polyserositis was present in one case which
gave no signs of local trouble and which was diagnosed chronic nephritis. A
second patient with diffuse distant metastasis went to a physician because of
swelling of the abdomen. One patient was brought into the hospital with signs
of intestinal obstruction. One patient died following operation for relief of
intestinal obstruction.

Lobar pneumonia was the immediate lethal factor in one case. One pa­
tient died following amputation of the leg for arteriosclerotic gangrene. One
patient with hypertensive heart disease died with symptoms of cerebral hemor­
rhage. In one case cerebral metastasis was suspected, but the brain was not
examined post mortem.

**Tabulation of Data**

The average duration for the whole group was nineteen months. The
youngest patient was twenty-seven years old and the oldest seventy-eight.

<table>
<thead>
<tr>
<th>Table I: Age and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Groups</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Average duration in months</td>
</tr>
</tbody>
</table>
TABLE II: Causes of Death in Carcinoma of the Cervix

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremia</td>
<td>19 (33 per cent)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>11 (19 per cent)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>5 (9 per cent)</td>
</tr>
<tr>
<td>Cachexia</td>
<td></td>
</tr>
<tr>
<td>(a) Secondary to generalized and distant metastasis</td>
<td>2</td>
</tr>
<tr>
<td>(b) Secondary to local carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>(c) Anemia, cachexia, vesico-vaginal fistula</td>
<td>1</td>
</tr>
<tr>
<td>(d) Unknown, probably cachexia</td>
<td>2</td>
</tr>
<tr>
<td>(e) Bronchopneumonia, secondary cachexia</td>
<td>1</td>
</tr>
<tr>
<td>Multiple distant metastases with polyserositis</td>
<td>1</td>
</tr>
<tr>
<td>Multiple distant metastases with ascites</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative intestinal obstruction</td>
<td>1</td>
</tr>
<tr>
<td>Lobar pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative amputation of leg</td>
<td>1</td>
</tr>
<tr>
<td>Hypertensive heart disease, cerebral accident?</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral metastasis?</td>
<td>1</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>2</td>
</tr>
</tbody>
</table>

TOTAL                         57

There were 19 deaths from uremia, constituting 33 per cent of the deaths. The average duration of these cases was twenty-nine months. Eleven patients died of peritonitis, a percentage of 19. The average duration of these cases was thirteen months.

TABLE III: Changes in the Urinary System

Bladder
- Chronic cystitis: 10
- Infiltration of the bladder: 9
- Vesicovaginal fistula: 4 (7 per cent)
- Gangrenous cystitis: 4
- Edema: 3

Ureters and kidneys
- Hydronephrosis: 43 (75 per cent)
- Both ureters: 30 (52 per cent)
- One ureter: 13 (22 per cent) (right, 7; left, 6)
- Slight dilatation: 4
- Moderate dilatation: 20
- Marked dilatation: 19

Infections of the kidney
- Pyelonephritis: 12
- Bilateral: 11
- Unilateral, left: 1
- Pyonephrosis: 8
- Bilateral: 5
- Unilateral: 3 (right, 2; left, 1)

TABLE IV: Vaginal and Rectal Involvement

Vaginal involvement: 13 (24 per cent)
Rectal involvement including fistula: 23
Fistulous formation: 8 (14 per cent)
Rectal involvement without constriction: 7
Rectal involvement with constriction: 7
Fistula to the large intestine: 1
Among 7 cases with rectal involvement with stricture, colostomy was done in 3 because of symptoms of intestinal obstruction. One patient with long-standing intestinal obstruction died from this cause *per se*, coming into the hospital in a moribund condition.

**Table V: Distant Metastasis in Carcinoma of the Cervix (25 per cent)**

<table>
<thead>
<tr>
<th>Metastasis</th>
<th>Cases (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>11 (19 per cent)</td>
</tr>
<tr>
<td>Lungs</td>
<td>5 (9 per cent)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>3 (5 per cent)</td>
</tr>
<tr>
<td>Pleura</td>
<td>3 (5 per cent)</td>
</tr>
<tr>
<td>Kidney</td>
<td>1 (2 per cent)</td>
</tr>
<tr>
<td>Bones</td>
<td>4 (7 per cent)</td>
</tr>
<tr>
<td>Spleen</td>
<td>2 (3.5 per cent)</td>
</tr>
<tr>
<td>Psoas muscle</td>
<td>1</td>
</tr>
<tr>
<td>Supraclavicular node</td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
</tr>
</tbody>
</table>

Bone metastasis occurred in one patient to the right acetabulum, and in one patient to the 12th dorsal vertebra, causing a compression myelitis. The same patient also had metastasis to the right femur. One patient had metastasis to the spine. A fourth patient had metastasis to the left innominate bone.

Local metastasis to the pelvis occurred in 34 cases, or 59 per cent; distant metastasis in 19 or 25 per cent.

**Conclusions**

1. Fifty-seven cases of carcinoma of the cervix were studied. The average age was forty-seven years. The average duration of the disease was nineteen months. The youngest patient was twenty-seven and the oldest seventy-eight years.

2. The most striking post-mortem finding was stricture of the ureters, occurring in 43 patients (75 per cent), with its attendant hydronephrosis in varying degrees. These strictures occurred in most instances at the entrance of the ureters to the bladder.

3. Nineteen cases (33 per cent) terminated in uremic death. The blood metabolites were increased and clinical symptoms of uremia were present.

4. Infection of the kidneys was found in 13 cases (22 per cent). This was either pyonephrosis or pyelonephritis or both. Death could be ascribed to pyelonephritis in 2 cases.

5. Distant metastases were present in 25 per cent of the cases. The liver was involved in 19 per cent, and the lungs in 9 per cent. The bones were next with 7 per cent involvement. Irradiation is apparently not a factor in the development of distant metastases.

6. Local metastases to the pelvic nodes were present in 34 or 59 per cent of the cases. Rectovaginal fistula occurred in 8 cases (14 per cent) and vesicovaginal fistula in 4 (7 per cent).

7. Rectal involvement with definite stricture occurred 7 times. In 4 of these patients, symptoms of intestinal obstruction supervened. One died without colostomy. Three had colostomies; one died postoperatively. The constriction occurs at the floor of the pouch of Douglas.
8. Generalized peritonitis was the immediate cause of death in 11 cases (19 per cent). Deep x-ray therapy seems to be a factor in stirring up latent infection. Perforation was responsible for 3 deaths.

9. Hemorrhage was the immediate cause of death in 5 cases.

NOTE: The author wishes to express his thanks and appreciation to Dr. E. T. Bell and Dr. William A. O’Brien for their advice in the preparation of this paper. He is also indebted to Miss Rose Gillig for her technical assistance in the cutting and preparation of the numerous microscopic sections needed for this study.

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