Clinical Management of Patients with Invasive Cervical Cancer Following a Negative Pap Smear

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Among 535 patients with invasive cervical carcinoma seen between January 1975 and June 1986, 26 were found to have developed the disease within six months (65 percent), 35 within 12 months (88 percent), 37 within 13 months (93 percent), and three developed the disease within 17 months after a negative Pap smear. Eighty-eight percent of these 40 patients were under age 40 at diagnosis. Rapidly progressive cancers are highly resistant to radiation therapy. Seven stage IB patients treated only with radiation died within nine to 29 months after initial therapy. By contrast, 15 patients treated by radical hysterectomy and four by radical hysterectomy and post-surgical radiation were alive with no evidence of disease from six to 109 months after surgery (median, 30 months). Six of nine patients with stage II to IV disease treated with radiation have died; the remaining three are alive. One patient is well 14 months after therapy, but two others have developed metastases seven and 12 months after treatment. Surprisingly, 37 of 40 patients had symptoms of pain, bleeding, and discharge at the initial diagnosis, but their physicians had a false sense of security because of a recent negative Pap smear. Early biopsy diagnosis and radical hysterectomy with bilateral pelvic lymphadenectomy is the most effective management for this cancer.

INTRODUCTION

The report of a cytological technique for the diagnosis of pre-invasive or occult cervical carcinoma by Papanicolaou and Traut in 1941 led to the assumption that cervical cancer could be eliminated [1]. As early as 1952, however, clinical studies of women screened by Pap smear indicated that invasive cervical cancer is not in all cases preceded by in situ lesions [2]. This finding suggested that there may be two forms of cervical cancer, biologically and clinically distinct, one of which is rapidly progressive and not detectable by routine Pap smear examination [3,4]. This paper will report on the clinical management and survival of 40 young women diagnosed to have invasive cervical cancer within a relatively short time interval from their last normal Pap smear. It is assumed that these patients have what has been characterized as a rapidly progressive form of cervical cancer, which shall be referred to as such in this paper. Clinical, epidemiological, and tumor characteristics will be presented.

MATERIALS AND METHODS

During the period from January 1, 1975, through April 30, 1986, 40 patients who developed invasive cervical cancer within 17 months of a negative Pap smear were seen...

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at Yale-New Haven Hospital, New Haven, Connecticut. They were identified as having the rapidly progressive form of disease. In the first six years of this study period, 11 cases were identified. Twenty-nine additional cases were observed during the latter six years of the study period.

The series of 40 patients included 33 white women, five blacks, one Indian, and one Vietnamese. This racial distribution is similar to that found in Connecticut. Patients ranged in age from 20 to 54 years old, with the great majority (88 percent) less than 40 years old. Figure 1 illustrates the age distribution of the 40 patients in our series, together with the age distribution for all patients with invasive cervical cancer seen at Yale-New Haven Hospital during the same period.

Table 1 lists the symptoms experienced at time of diagnosis by patients with the rapidly progressive disease. The most frequent symptoms were irregular bleeding (65 percent), pain (48 percent), and discharge (38 percent). Included under "irregular bleeding" were any unusual types of bleeding, whether related to amount or timing. Post-coital bleeding was noticed in 25 percent of women belonging to the sexually active age group. Two of three women asymptomatic at the time of diagnosis were found to have invasive cervical cancer by routine Pap smears.

The interval in months between diagnosis of invasive cervical cancer and last Pap smear reported to be negative for cancer (class I or II) is illustrated in Fig. 2 for the 40 patients studied. The disease developed within six months of a negative Pap smear in 26 patients (65 percent); within 12 months in 35 patients (88 percent), and within 13 months in 37 patients (93 percent). For three patients, the disease developed within 17 months after a negative Pap smear. Whenever possible, records were reviewed and the physical findings at the time of the last negative Pap smear were discussed with the physician. No patient was reported to have a visible lesion present at the time of the last negative smear prior to the diagnosis of cervical cancer.

The FIGO clinical stage, histology, and grade of the patients' tumors are given in Table 2. There were 28 patients with FIGO stage IB (70 percent): 23 squamous (82
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TABLE 1
Symptoms at Diagnosis for 40 Patients with Rapidly Progressive Cervical Cancer

| Symptoms                        | Number | Percentage |
|---------------------------------|--------|------------|
| Irregular bleeding              | 26     | 65         |
| Pain (suprapubic, abdominal, lower back pain) | 19     | 48         |
| Vaginal discharge               | 15     | 38         |
| Post-coital bleeding            | 10     | 25         |
| Weight loss                     | 3      | 8          |
| Urinary incontinence            | 1      | 3          |
| Asymptomatic                    | 3      | 8          |

percent), four adenocarcinomas, and one adenosquamous carcinoma. All five patients with stage IIB disease had squamous carcinomas. Among the five patients with stage IIIB cancer, there were four squamous and one adenosquamous carcinoma. One patient with a stage IVB tumor had a small-cell squamous carcinoma, and the other had an adenosquamous carcinoma.

Tumors were histologically graded according to three groups, as illustrated in Table 2: grade 1 represented low-grade, i.e., well-differentiated cancers; grade 2, moderately well-differentiated carcinoma; and grade 3, poorly differentiated malignancies and anaplastic carcinomas. Initial treatments included six different modalities: type III radical hysterectomy and bilateral pelvic lymphadenectomy, radiation only, type III radical hysterectomy with bilateral pelvic lymphadenectomy followed by radiation, radiation and simple hysterectomy, simple hysterectomy and radiation, and chemotherapy with radiation. For each stage, histology, and grade of tumor, the treatment modality and the vital status at follow-up are also indicated in Table 2. Among stage IB patients, a total of 15 patients underwent type III radical hysterectomies and bilateral lymphadenectomies; seven were treated with radiation alone, four with type III radical hysterectomies with bilateral pelvic lymphadenectomies and radiation, one with radiation and simple hysterectomy, and another with simple hysterectomy and radiation. Radiation only was the treatment given to all stage IIB, IIIB, and IVB patients except in three cases. In two of these instances, simple hysterectomy and radiation was the treatment as the patients had had recent negative Pap smears and

FIG. 2. Interval in months between diagnosis of invasive cervical cancer and the preceding negative Pap smear.
TABLE 2
Tumor Characteristics, Initial Therapy, and Follow-Up Status for 40 Patients with Rapidly Progressive Invasive Cervical Cancer

| Stage | Histology       | Grade | Radical Hysterectomy | Radiation | Radical Hysterectomy and Radiation | Radiation and Hysterectomy | Hysterectomy and Radiation | Chemotherapy and Radiation |
|-------|-----------------|-------|----------------------|-----------|------------------------------------|----------------------------|---------------------------|---------------------------|
| IB (28) | Squamous        | 1     | 1                    |           |                                    |                            |                           |                           |
|       | (23)            | 2     | 7                    | 3\(^a\)   |                                    |                            |                           |                           |
|       |                 | 3     | 3                    | 3\(^b\)   |                                    |                            |                           |                           |
|       | Unknown         | 1     | 1                    |           |                                    |                            |                           |                           |
|       | Adenocarcinoma  | 2     | 2                    |           |                                    |                            |                           |                           |
|       | (4)             | 3     | 1                    |           |                                    |                            |                           |                           |
| IIB (5) | Squamous        | 1     | 1                    |           |                                    | 1\(^b\)                    |                           |                           |
|       | (5)             | 3     | 1\(^a\), 1\(^c\)     |           |                                    |                            |                           |                           |
| IIB (5) | Squamous        | 2     | 1\(^b\)              |           |                                    |                            |                           |                            |
|       | (4)             | 3     | 2\(^b\)              | 1\(^c\)   |                                    |                            |                           |                           |
|       | Adenosquamous   | 2     | 1\(^b\)              |           |                                    |                            |                           |                           |
|       | (1)             |       |                      |           |                                    |                            |                           |                           |
| IVB (2) | Squamous        | 3     | 1\(^b\)              |           |                                    |                            |                           |                           |
|       | small-cell      |       |                      |           |                                    |                            |                           |                           |
|       | (1)             |       |                      |           |                                    |                            |                           |                           |
|       | Adenosquamous   | 3     | 1\(^b\)              |           |                                    |                            |                           |                           |

*1. Type III radical hysterectomy with bilateral pelvic lymphadenectomy
2. Radiation only
3. Type III radical hysterectomy with bilateral pelvic lymphadenectomy followed by radiation
4. Radiation and simple hysterectomy
5. Simple hysterectomy and radiation
6. Chemotherapy with radiation
\(^a\)Deceased
\(^b\)Documented metastases
were not recognized pre-operatively to have cervical cancer, and in one case the patient received chemotherapy and radiation.

Although epidemiologic information was limited on these patients, it was noted that 23 patients (57.5 percent) were smokers or ex-smokers and 17 (42.5 percent) had never smoked. Birth control pills had been taken by 20 women (50 percent) for various lengths of time, and another nine women (22.5 percent) reported having never been on the pill. For 11 women the information was lacking (27.5 percent).

There were a total of 78 pregnancies prior to diagnosis (average 2.5) among 31 women with the rapidly progressive disease. Fifty-nine infants were born to 23 mothers, and 19 abortions were performed on 17 women.

RESULTS

The first ten patients' survival was previously reported [5] and is summarized below. Eight patients recognized to have invasive cancer were managed in a standard fashion, either with a type III radical hysterectomy and bilateral pelvic lymphadenectomy or with intracavitary and external beam radiation therapy. The former treatment modality was only routinely recommended at this institution for stage IB patients with small primary cancers (less than 2 cm maximum diameter), histologically well- or moderately well-differentiated, and with no evidence of vascular space infiltration. Two patients with more advanced occult disease underwent primary routine hysterectomies, as the diagnosis of cancer was not appreciated pre-operatively, followed by post-operative whole-pelvis radiation therapy. A subsequent review revealed nine of the initial ten patients to have died of cancer. The only survivor in this group was the one 20-year-old patient who underwent a type III radical hysterectomy and bilateral pelvic lymphadenectomy for a poorly differentiated squamous cell cancer 6 cm in diameter and was found to have microscopic metastases to both pelvic side wall lymph node chains. The latter patient received whole-pelvis external beam radiation therapy post-operatively.

These findings led us to modify our approach to patients with cervical cancer diagnosed within a short time period following a reportedly negative Papsmear. Each patient with a stage IB cervical cancer, regardless of size of the primary cancer or its histologic appearance, was recommended to undergo a type III radical hysterectomy and bilateral pelvic lymphadenectomy. Patients found to have metastases to pelvic lymph nodes or cancer microscopically encroaching on the surgical margins of resection in the hysterectomy specimens were recommended to receive post-operative radiation therapy to the whole pelvis. Patients with stage II to IV cancers were to receive radiation therapy as the primary mode of therapy.

The survival data for the entire series is summarized in Table 2, based on the stage and the initial therapy. Fifteen patients with stage IB cancer treated with a type III radical hysterectomy and bilateral pelvic lymphadenectomy are each alive and well eight to 54 months following diagnosis (median, 31 months). Four patients with stage IB cancers who underwent type III radical hysterectomies, bilateral pelvic lymphadenectomies, and post-operative whole-pelvis radiation therapy are alive and well 17 to 109 months following diagnosis (median, 25½ months); however, each of seven patients with stage IB cancer treated with radiation therapy alone has died from the cancer nine to 29 months following diagnosis (median, 15 months), as have the two remaining stage IB patients who underwent either pelvic radiation followed by a simple hysterectomy or a simple hysterectomy followed by radiation.
Twelve patients in this series had stage IIB to IVB disease. Six of nine patients treated with standard radiation therapy alone have succumbed to cancer three to 35 months (median, 29 months) following diagnosis. Of the remaining three patients in this group, one with stage IIB squamous lesions treated with radiation therapy is alive 15 months after treatment, but this patient has a documented liver metastasis. The second patient, also with stage IIB squamous carcinoma, treated with radiation, is alive 14 months after therapy. The third patient has stage IIIB squamous carcinoma and is alive 12 months after the onset of radiotherapy but with documented metastases to the lung. Two patients who underwent a routine hysterectomy with radiation (one preceding, the other following surgery) have died. The only patient who received chemotherapy followed by radiation died nine months after diagnosis.

In an attempt to correlate histologic features with clinical findings, especially pain, which was severe in many of these patients, a review of available surgical specimens was performed by a gynecologic pathologist (MJM) on tumors from 24 patients in our series. We were able to obtain slides from radical hysterectomies in 16 of 24 (66.7 percent) patients; in only eight cases was the slide review based solely on biopsy material.

The histopathological findings are given in Table 3 for the 16 patients who underwent radical hysterectomies. Among these latter patients with slide review, pain was present in six and absent in ten of them. Three out of four patients with adenocarcinoma of the cervix in our total study were found in the group of patients without pain, as mentioned above. Perineural invasion was present in 17 percent of specimens from patients with pain and in 20 percent of those pain-free. Vascular and/or lymphatic space infiltration was noted in 100 percent and 70 percent of patients with and without pain, respectively. There was no apparent correlation between the presence of pain and the grade of the tumor.

Additionally, dysplasia was identified in ten out of the 16 patients and condylomatous changes were visible in eight of these patients (Table 3).

**DISCUSSION**

The finding that at least 7 percent of patients referred to this institution had negative Pap smears reported within a relatively short time prior to the diagnosis of cervical cancer and the strikingly rapid growth rate of these malignancies raises several important issues. Does the entity of rapidly progressive cervical cancer really exist or is it a reflection of false-negative Pap smear readings? What is the most effective treatment for this cancer? How does one recognize patients at high risk for this disease, so that clinicians can more rapidly diagnose and care for such patients? Finally, are there any significant histologic features that help to characterize these cancers?
Does the entity of rapidly progressing cervical cancer really exist? The presence of a rapidly progressive cervical cancer is surprisingly well documented in gynecologic and epidemiologic literature. Based on data from the British Columbia Cervical Cancer Screening Program [6], Albert [7], by using the mathematical modeling approach, estimated that each year between 1.7 percent and 9.7 percent of all new cervical cancers and about one-third of all new "occult invasive" cases are diagnosed within one year after a negative Pap smear, thus belonging to the rapidly progressive variety. While earlier studies reported that older women were the target of the rapidly progressive form of cervical cancer [2,3,4,8,9], more recent publications have reported that young women are more likely to be afflicted with this serious form of the disease [5,10,11,12,13].

In 1976, Laskey, Meigs, and Flannery [10] gave evidence for two classes of invasive cervical carcinoma based on the study of time trends in the Connecticut Tumor Registry data for the 1935 to 1973 period. These authors supported the views of Ashley in the U.K. [4] and of Pedersen et al. in Norway [14] and postulated that one class of cervical cancer was preceded by an in situ phase and developed slowly, while the other, undetectable by screening, had a short pre-malignant stage and progressed rapidly. They found this latter form in young women under 35.

In 1977, Rylander [11] reported that among 21 patients who were diagnosed, mostly at a young age, as having invasive cervical cancer during the 1968–1974 period, four (19 percent) developed their disease within one year and 11 (52 percent) within two years following a negative Pap smear. None of these women had symptoms or visible changes on the cervix at the time of cytological testing. Among the 21 patients, three developed adenocarcinoma of the cervix.

Yule in 1978 [12] reported an increase in the rapidly progressive form of disease among young women from the northwestern region of the United Kingdom. This observation was made despite the fact that, in this region, the largest increase in Pap smear testing had occurred in women under 35 years of age. He suggested that "the pre-invasive phase of carcinoma of the cervix may be shorter in younger women, leading more quickly to an aggressive invasive tumor which is less likely to be prevented by routine screening unless the interval between tests is short." He also suggested that screening programs may not be reaching the population at risk. Yule postulated that the early onset of sexual activity in the young and the increased use of non-barrier contraceptives, particularly the contraceptive pill and intrauterine devices which offer no protection against infectious agents, are likely to contribute to an increased risk of cervical cancer in young women. In these patients, the disease occurred without Pap smear findings of a pre-invasive stage.

Berkowitz and his colleagues [13] reported on 27 women under 35 with invasive cervical cancer, of whom 15 (55 percent) had negative or inadequate cervical smears within the previous two years. All 15 women complained of irregular vaginal bleeding or persistent vaginal discharge and were found to have clinically apparent cervical lesions. Fourteen were diagnosed as having stage IB, and one had stage IIB. Overall, among the 27 women in this study who were under 35 at diagnosis of invasive cervical cancer, abnormal cervical cytology was the precipitating factor leading to the diagnosis of cervical cancer in only ten (37 percent) of these young women.

With the advent of large population-based cervical cancer screening programs, data on rescreening of women previously found negative have become available. In a study in Memphis-Shelby County, Dunn [15] reported that the proportion of newly developing malignant cervical cancer cases was about one-third invasive and two-
thirds in situ during the early years of the rescreening program. This proportion still persisted after ten years of further screening [16]. Dunn concluded that two-thirds of invasive cancers are preceded by an in situ phase, while the remaining one-third progress rapidly to the invasive stage without an in situ phase.

Following 25 years of cervical cytology screening experience in Memphis-Shelby County, Dunn [17] further reported that among 430 patients studied during the 1952–1978 period, 142 (33 percent) were cases of rapidly progressive cervical cancer. The age distribution at diagnosis for these women indicated a higher proportion of older women, as 84 (59 percent) were 39 and over while 58 (41 percent) were under this age. The average interval from the last negative cytologic finding to diagnosis was 2.6 years.

In a study of invasive cervical cancer in Alameda County, California, from 1960 to 1974, Dunn [18] reported that 29 percent of women who developed invasive cervical cancer during 1970–1974 had a history of a recently negative Pap smear. Over 70 percent of these women were diagnosed within two years of a negative cytologic report. In contrast to other studies, Dunn found this aggressive and rapidly progressive form of cervical cancer to occur at all ages.

One must consider the possibility that many of the so-called “rapidly progressive cervical cancers” represent nothing more than misread or false-negative Pap smears. Berkeley et al. [5] reviewed the Pap smears of the first ten patients in the present series and found that five patients had completely normal and adequate Pap smears (true negative) within a ten-month period prior to the diagnoses of invasive cancer, while the remaining five had changes requiring further investigation, i.e., false-negative Pap smears. To date, cytology specimens have been reviewed from 22 patients in this series. Twelve of the 22 cytology specimens were true negative Pap smears. Five patients had false-negative Pap smears. Five patients had inadequate Pap smears due to (1) no endocervical cells present, (2) scanty material, or (3) poor slide preparation.

Berkowitz et al. [13] reviewed so-called negative Pap smears from a group of ten young women with rapidly progressive cervical cancer and found three to be true negatives, five of the ten patients to have false-negative smears, and two others to have inadequate Pap smears. This study illustrated that there is an increased risk of false-negative Pap smears in cases of cervical adenocarcinoma that may lead to failure of diagnosis in the presence of mild symptoms [19]. Adenocarcinomas may arise in deeper layers of the endocervical cavity and be less accessible than most squamous cancers of the cervix. Cancers with a brief pre-clinical stage arising shortly after a negative Pap smear may not be detectable by the Pap smear technique. Biological variations in tumor and host factors may account for differences in cervical cell exfoliation [3,4,20,21].

False-negative rates for Pap smear vary greatly from 12.5 percent [22] to 20 percent to 45 percent [23]. Double sampling has been suggested in order to diminish the risk of failure in specimen collection [24]; however, a 25 percent disparity in results has been found between two slides obtained at the same time [25]. Thus, the practice of obtaining repeat smears for confirmation of cytologic findings is an unreliable method to search for cervical pathology when conclusive confirmation is needed. Sampling inefficiency had been thought to be the most important reason for false-negative Pap smears [11]. The authors recommend annual Pap smears for sexually active women. Patients must see their physicians promptly, however, for evaluation of any pelvic pain, vaginal discharge, or abnormal bleeding, regardless of the severity.
What is the most effective treatment for rapidly progressive cervical cancer? Radiation therapy has been employed at Yale-New Haven Hospital as standard therapy for cervical cancer when unfavorable histologic features (poorly differentiated cancers, lymphatic or vascular space invasion), bulky tumors, or advanced-stage disease was present. Most patients in the present series qualified for standard radiation therapy by these standards. A review of the first ten patients revealed nine of them to have died rapidly from the disease. The only survivor had undergone a type III radical hysterectomy and bilateral pelvic lymphadenectomy, was found to have microscopic metastases to each pelvic side wall lymph node chain, and received post-operative radiation therapy. Since that time, each patient with stage IB cancer has been recommended to undergo radical surgery regardless of the histologic appearance of the cancer or the bulk of tumor present in the cervix. Post-operative radiation therapy was offered to patients who had positive pelvic lymph nodes or cancer encroaching on the surgical margins of the hysterectomy specimen. All but one patient have followed these recommendations, and each of these patients is presently alive and well. The one patient who elected to be treated with radiation therapy had previously been successfully treated with a lumpectomy and radiation therapy for breast cancer and did not want to undergo "mutilating" surgery. That patient subsequently developed a metastasis of squamous cell cancer of uncertain origin to the left supraclavicular area and has died.

Six of nine patients with stage II to IV cancer treated with standard radiation therapy have had rapid progression of disease and have died. One of the remaining three patients is alive and free of disease 14 months following diagnosis, while the second and third patients are alive but have developed metastases, one in the lung and the other in the liver, seven and 12 months, respectively, following diagnosis.

Berkowitz et al. [13] have reported on 27 patients under age 35, who had invasive cervical cancer, 15 of whom had recently reported negative Pap smears. Twenty-four of 25 patients with stage IB cancer were treated surgically, and each is alive and disease-free. Three patients received prophylactic post-operative radiation therapy because of metastases to pelvic lymph nodes and were free of disease at the time of the report. One patient with lymph node metastases did not receive prophylactic radiation therapy and developed a pelvic side wall recurrence six months later that responded to radiation therapy. Two patients with stage IIB lesions were treated initially with radiation therapy, and each developed pulmonary metastases, one while receiving radiation therapy and the other eight months following completion of radiation therapy.

The experience in the present series and the report of Berkowitz et al. support the role of surgery as the initial step in the management of rapidly progressive cervical cancer and subsequent post-operative radiation therapy if unfavorable histologic findings are present. Patients with advanced-stage disease do not appear to benefit from radiation therapy alone, and new strategies for management will have to be devised. These techniques might include systemic or intra-arterial chemotherapy with or without radiation therapy or surgery or primary exenterative surgery. Multi-institutional studies will be necessary to confirm our observations before new treatment strategies are to be attempted.

How are we to recognize patients at high risk for rapidly progressive cervical cancer, and how can we rapidly diagnose and treat such patients? Patients at high risk for rapidly progressive cervical cancer have yet to be characterized. Examining the
patients in the present series suggests that these patients are often under age 40, smoke, and have used oral contraceptives. Parity does not appear to be associated with this process. Additionally, most patients are symptomatic at presentation despite the fact that 75 percent are identified when the cancer is still confined to the cervix.

Symptoms experienced by 37 of the 40 patients in this study included irregular bleeding or abnormal menses (65 percent) and vaginal discharge (38 percent). We consider that the high frequency of pain in our patients (48 percent), whether abdominal, suprapubic, or lower back pain, is somewhat characteristic of the rapidly progressive form of cervical cancer and should alert the physician, since this complaint is not as frequently found among other patients with cervical cancer.

Epidemiologic studies have suggested that venereal diseases such as herpes simplex virus (HSV2), cytomegalovirus (CMV), and human papilloma virus (HPV) may play a role in the development of invasive cervical cancer [26, 27, 28]. Several studies have shown that HPV types 16, 18, and 31 are more likely to be associated with invasive cervical cancer, while types 6 and 11 are found and more readily identified in cases of dysplasia and carcinoma in situ [29]. Barnes and associates have recently presented data suggesting that HPV type 18 may be associated with rapidly progressive cervical cancer [30]. Condylomatosus changes were frequently found to be present histologically in patients with rapidly progressive cervical cancer (Table 3), but subtyping of HPV was not performed.

*Are any significant cytologic or histologic features present that could help to identify rapidly progressive cervical cancer?* A preliminary review of histologic material from patients in this study suggests that most cancers are histologically moderate or poorly differentiated squamous carcinomas. Perineural infiltration of cancer within the cervix itself has been noted in some radical hysterectomy specimens but not specifically associated with those patients presenting with pelvic pain (Table 3). Capillary space involvement was frequently observed, but no histologically distinguishing features have been noted to date. A more extensive histologic review will be performed as more histologic and cytologic materials become available.

A consistent finding in this study was the security that gynecologists placed on a reportedly negative Pap smear despite the frequent presence of visual lesions on the cervix. Discussions with gynecologists caring for these patients revealed a lack of knowledge that a patient who underwent routine Pap smear screening could develop invasive cancer less than one year from the last reported negative Pap smear.

The message has been clear to both physicians and patients that a positive Pap smear requires prompt evaluation; however, the corollary has yet to be demonstrated to be true. Taylor [1], in his discussion of Papanicolaou and Traut’s 1941 paper on the diagnostic value of vaginal smears in cancer of the uterus, stated that three steps must be taken for routine cytologic screening to be effective. The first was to demonstrate that a positive Pap smear meant cancer was present. The second was described as more difficult and more important than the first one: to demonstrate that a negative smear meant cancer was not present. The third step was to organize medical practice to employ this test routinely. A negative Pap smear does not guarantee that a patient is free of cervical or uterine cancer. A patient with a visible cervical lesion or symptoms of pain, discharge, or bleeding requires evaluation beyond a Pap smear. A negative Pap smear under these circumstances does not ensure the absence of malignancy, and evaluation including colposcopy and biopsies of the cervix and the endocervix should be promptly performed.
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We are in the process of reviewing the cytology and pathology of all available Pap smears and cervical tissues from patients in our study. It is imperative, however, to keep in mind that a negative Pap smear report has an effect that will subsequently determine the course of events. A negative Pap smear, whether shown later on to be truly or falsely negative, will at the time of the negative report influence attitudes and decisions of both the physician and the patient and therefore have a definite effect on the woman’s survival. Those patients who were successfully treated to date are limited to those who have had stage IB cancer and underwent a radical hysterectomy and bilateral pelvic lymphadenectomy. Prompt diagnosis and surgery are essential for the management of patients with rapidly progressive cervical cancer.

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