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Virulence of Papillary Endometrial Carcinoma

KATHERINE A. O'HANLAN, M.D.,* PHYLLIS A. LEVINE, M.D.,† DAWN HARBATKIN,† CHERYL FEINER, MPH,‡ GARY L. GOLDBERG, M.D.,* JOAN G. JONES, M.D.,§ AND LORNA RODRIGUEZ-RODRIGUEZ, M.D.*

*Division of Gynecologic Oncology, †Department of Obstetrics and Gynecology, ‡Department of Biostatistics, Montefiore Medical Center, and §Department of Pathology, Albert Einstein College of Medicine, New York, New York 10461

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While uterine papillary serous carcinoma (UPSC) has been well described as a virulent subtype of endometrial adenocarcinoma (AC), with behavior similar to that of papillary serous ovarian carcinoma, the papillary endometrial (PE) variant has not been well characterized. We studied 117 patients with endometrial carcinoma identified by our tumor registry, pathology files, and practice records from March 1981 to February 1989: 76 with AC, 26 with PE, and 15 with UPSC. Age and demographic data were similar for all three groups. All of the AC patients, 84% of PE patients, and 87% of UPSC patients had early-stage disease by clinical exam; however, 10% of AC patients, 23% of PE patients, and 87% of UPSC patients had extrauterine disease at surgery ($P < 0.05$). Deep myometrial invasion occurred in 29% of AC patients, 36% of PE patients, and 60% of UPSC patients ($P < 0.05$). Comparative analysis of the PE and UPSC groups revealed more marked nuclear anaplasia ($P < 0.05$) and more frequent vascular space involvement (nonsignificant) in the UPSC group. At 3 years, 75% of the AC group was alive without disease. In contrast, the median progression-free interval for the PE group was 33 months, and for the UPSC group, 9 months ($P < 0.05$). These data suggest a transition of increasing virulence corresponding with increasing papillary features, from AC to PE to UPSC. The papillary feature may be a new, significant risk factor in endometrial carcinoma. © 1990 Academic Press, Inc.

INTRODUCTION

The endometrial cavity may demonstrate tissue histologically similar to any other mullerian tissue including ovarian, tubal, cervical, and upper vaginal epithelium [1]. It is not surprising that the morphologically corresponding carcinomas may also be found originating within the uterine cavity. Uterine papillary serous carcinoma (UPSC) is one such variant which is associated with a virulent course, much like its more common histologic counterpart, ovarian papillary serous carcinoma. The virulence of the papillary endometrial (PE) variant of the more classic endometrioid adenocarcinoma (AC) has not been well characterized. The possibility exists that these two papillary entities may reflect a spectrum of morphologic transition from the "endometrioid" endometrial tumor to the "ovarian" serous endometrial tumors. Their respective patterns of spread and virulence would be expected to correspond to that of the individual tumor histotype with increasing virulence from classical AC to PE to UPSC. To address this question, a retrospective study of the three tumor types was undertaken at the Weiler Hospital of the Albert Einstein College of Medicine and the Bronx Municipal Hospital Center.

MATERIALS AND METHODS

One hundred seventeen patients with uterine carcinoma were identified from the tumor registries and pathology records of the Hospital of the Albert Einstein College of Medicine and Bronx Municipal Hospital Center receiving treatment from March 1980 to February 1989, and from the office practice files of the members of the Division of Gynecologic Oncology receiving treatment between January 1982 and February 1989. There were 76 patients with AC, 26 patients with PE, and 15 patients with UPSC.

All patients' charts were reviewed for demographic, therapeutic, and survival data. All available Pap smear results were reviewed in cases of patients with papillary histologies. This information was only infrequently available in cases of patients with classical adenocarcinoma. Patients with all stages, grades, pathologic findings, and outcomes were included. All of the patients were available for follow-up from 2 months to 9 years after initial therapy (median 18.5 months).

Histologic slides were reviewed by members of the Department of Pathology, with the pathologic material of 26 PE and 15 UPSC tumors undergoing further analysis and classification by three of the authors (J.G.J.,

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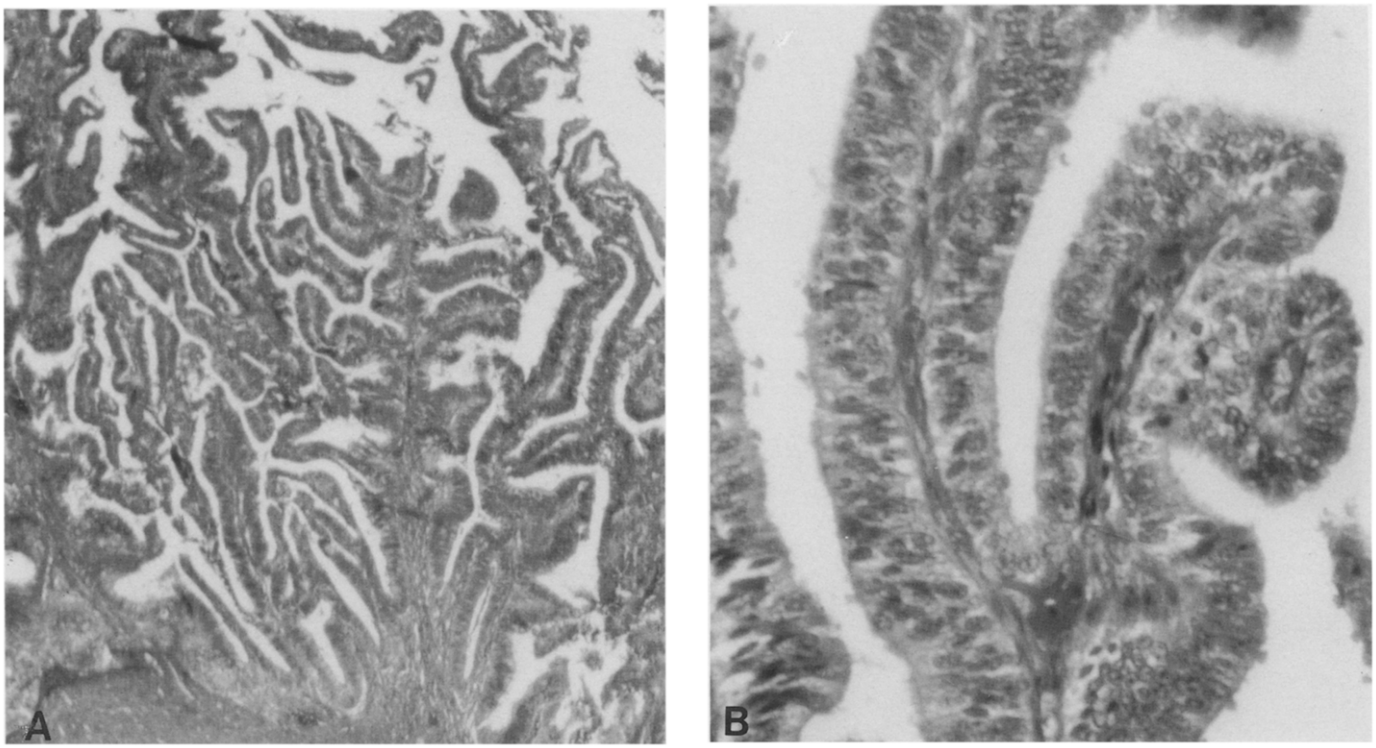

FIG. 1. In the well-differentiated papillary endometrioid (PE) carcinoma, (A) the tumor forms slender stalks (H&E, ×50), (B) lined by relatively bland, minimally stratified columnar cells (H&E, ×320).

P.A.L., K.A.O'H.). Discrimination between PE and UPSC was based on the recommendations by Hendrickson *et al.* [2]. Papillary endometrial carcinoma was characterized by minimally stratified, elongate, regular cells with nuclei usually of low grade, arranged on delicate fibrovascular stalks constituting at least 20% of the tumor volume (Fig. 1). UPSC includes a spectrum of anaplastic nuclear morphology within cells irregularly arranged on complex, branching and fusing, thick, fibrous stalks, with frequent tufting and budding of the cells, which appear as free-standing cells around an irregular surface of stratified serous cells (Fig. 2).

Categorical data for independent samples were analyzed using the χ^2 test and, when appropriate, the Fisher's exact test.

The Mantel–Haenszel χ^2 statistic [3] was used to analyze variables measured on an ordinal scale, such as surgical stage, nuclear grade, and depth of invasion. Analyses by nonparametric rank sum techniques in every case yielded the same findings.

Continuous data for independent samples were analyzed using the Kruskal–Wallis test [4] when three groups were compared and the Wilcoxon rank sum test [4] when two groups were analyzed.

A multiple logistic regression analysis was performed to determine which factors were associated with tumor subtype, after adjustment for the presence of other variables. Independent variables included surgical stage, nuclear grade, upstaging, and clinical stage.

The endpoint in this analysis was recurrence, progression as defined by clinical findings, or death. Progression-free interval distributions were estimated using the Kaplan–Meier product limit method [5]. The Gehan–Wilcoxon test [5] was used to compare these distributions.

To allow any potentially important difference to be recognized, no adjustments to the significance level were made to control for the multiple number of independent univariate analyses performed. For multiple comparisons of survival and ordinal data, specifically, to assess differences between AC and PE groups, and PE and UPSC groups, a Bonferroni multiple comparison procedure was employed [6]. The significance level for multiple comparisons for categorical data was adjusted using the technique of Brunden [7]. All data analyses were performed using the statistical package SAS.

RESULTS

PE and UPSC showed similar distributions with respect to age, ethnicity, hypertension, diabetes, nulliparity, obesity, and oral estrogen ingestion, and were not

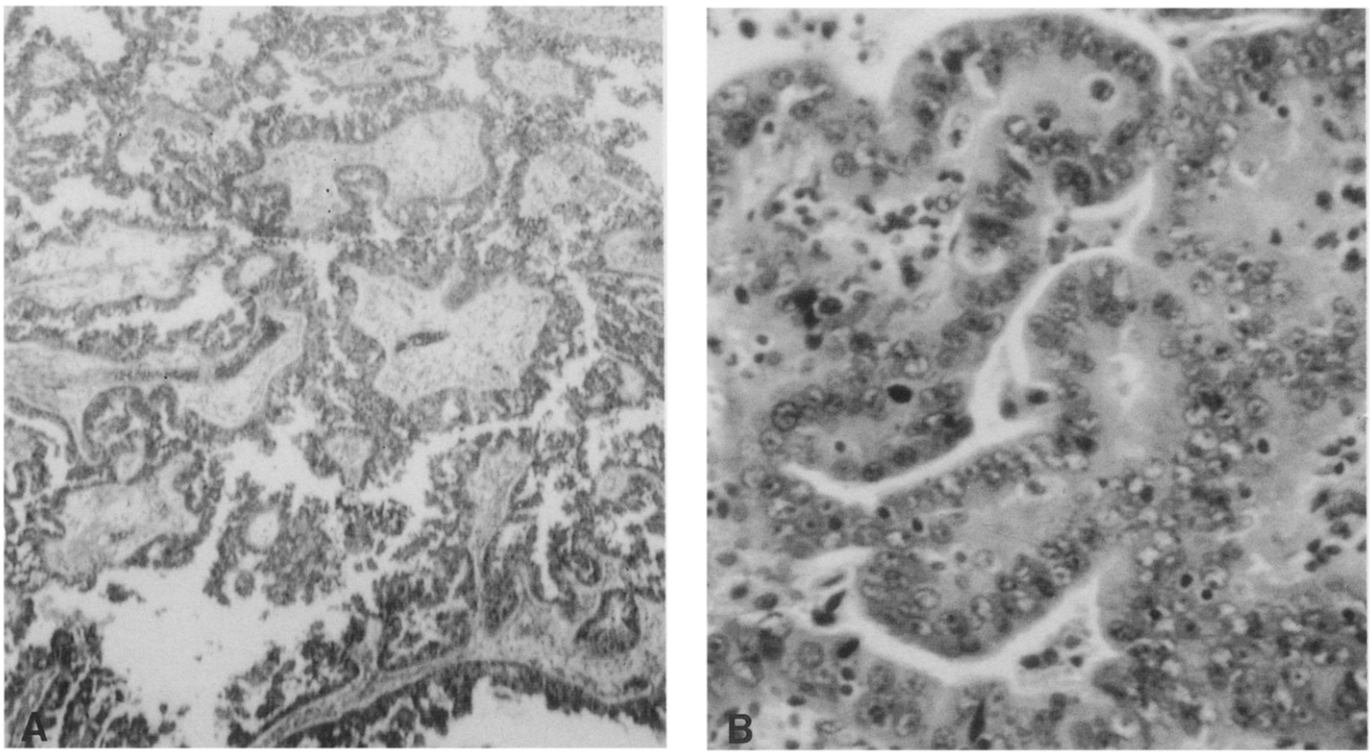

FIG. 2. In the uterine papillary serous carcinoma (UPSC), (A) the tumor forms a complex arrangement of broad fibrous stalks, (H&E, ×50), (B) lined by tufted, pleomorphic cells with frequent mitoses and macronucleoli (H&E, ×320).

different from the data commonly accepted for patients with AC [8] (Table 1). Vaginal bleeding was the most frequent presenting symptom in all three groups of patients. Abdominal symptoms of either fullness or pain did not occur in any of the AC patients, but were noted in 5% of the PE patients and 27% of the UPSC patients.

Papanicolaou smear (Pap) results were available from 31 patients with papillary histotypes. The Pap revealed adenocarcinoma cells in 4 of 17 PE patients and 8 of 14 UPSC patients.

All of the AC patients and 84% of the PE patients had stage I or II disease at diagnosis. Similarly, 87% of patients with UPSC were early clinical stage. Extrauterine disease was found at surgery in 10% of patients with AC, 23% of patients with PE, and 87% of patients with UPSC ($P < 0.05$ Mantel–Haenszel χ^2) (Table 2). Although an increased rate of upstaging is demonstrated with increasing concentration of papillary features ($P < 0.05$, Mantel–Haenszel χ^2), when multiple comparisons were performed, surgical stage and rate of upstaging, in fact, showed no significant difference between AC and PE groups, and revealed a significant difference only between the PE and UPSC groups ($P < 0.05$ Mantel–Haenszel χ^2) (Table 3).

In the AC group, 29% of patients demonstrated deeper than one-third myometrial invasion, while 36% of the PE

TABLE 1
Demographic Data

Variable	AC (n = 76)	PE (n = 26)	UPSC (n = 15)
Median age (range)	67(38–91)	65(32–80)	67(50–76)
Race[a]			
Afro-American	11(15)[b]	6(24)	4(27)
Hispanic	7(10)	4(16)	2(13)
Caucasian	53(75)	15(60)	9(60)

[a] One patient was Oriental.
[b] Number (%).

TABLE 2
Disease Status by Tumor Type

Surgical stage	AC (n = 69)[a]	PE (n = 26)	UPSC (n = 15)
Early: stages I + II	62(90)[b]	20(77)	2(13)
Advanced: stages III + IV	7(10)	6(23)	13(87)

$P < 0.05$, Mantel–Haenszel χ^2.
[a] Seven patients were treated with primary radiation.
[b] Number (%).

TABLE 3
Upstaging by Tumor Type

Surgical–FIGO stage	AC (n = 69)[a]	PE (n = 26)	UPSC (n = 15)
−1–0	50(72)[b]	20(77)	4(27)
1	13(19)	4(15)	3(20)
2	4(6)	2(8)	4(27)
3	2(3)	0(0)	4(27)

$P < 0.05$, Mantel–Haenszel χ^2.
[a] Seven patients were treated with primary radiation.
[b] Number (%).

TABLE 5
Architectural Grade by Tumor Type

Architectural grade	AC (n = 76)	PE (n = 26)	UPSC (n = 15)
1	50(66)[a]	11(42)	9(60)
2	7(9)	7(27)	0(0)
3	19(25)	8(31)	6(40)

[a] Number (%).

group and 60% of the UPSC group demonstrated deep invasion ($P < 0.05$ Mantel–Haenszel χ^2) (Table 4).

Architectural grading revealed no association with tumor histotype (Table 5). Further analysis of the PE and UPSC groups with respect to nuclear grade, however, revealed significantly more nuclear anaplasia in the UPSC group ($P < 0.05$ Mantel–Haenszel χ^2) (Table 6) and higher rate of vascular space invasion, 87% versus 55% (N.S.).

With one exception, the CA-125 was elevated in all patients with advanced or recurrent papillary tumors, and was useful in following disease status (Fig. 3).

Analysis of progression-free intervals by tumor histotype revealed a statistically significant difference between AC and PE groups, as well as between PE and UPSC groups ($p < 0.05$, Gehan-Wilcoxon test) (Fig. 4). At three years, more than 75% of patients with AC were disease free. In contrast, the median progression-free intervals for the PE group was 33 months and for the UPSC group, 9 months.

Multivariate analysis, specifically stepwise logistic regression, showed a high surgical stage to be independently associated with UPSC tumor histotype in comparison with PE ($p < 0.05$), and that advanced clinical staging was independently associated with PE in comparison to AC.

DISCUSSION

In 1963, Karpas and Bridge originally described a postmenopausal woman who underwent surgery for endometrial carcinoma and died of disseminated cancer [9]. Pathologic study of all the material revealed psammoma bodies within a papillary carcinoma. Spjut *et al.* described a patient whose uterine carcinoma was diagnosed by the presence of psammoma bodies and malignant papillary cells in the Pap smear [10]. Lauchlan, in 1968, advanced a theory of a conceptual unity of all mullerian tumors, explaining the presence of both normal mullerian cells and the morphologically similar tumors occurring in "inappropriate and unexpected locations" within the mullerian tract [1]. Factor reported three cases of UPSC in 1974, noting that surgical staging was required to determine the primary site because of the metastatic pattern and histologic similarity to ovarian carcinoma [11]. Hendrickson *et al.* compiled the first large series of 26 early-stage and 34 advanced-stage UPSC patients, noting a very virulent histologic picture correlating with a high abdominal recurrence rate [2].

The papillary feature was subsequently identified as a poor prognostic feature [12–14]. However, in these studies, UPSC was included in the papillary group. The known virulence of UPSC tumors may have skewed the data for the entire group, and therefore conclusions from those data cannot be drawn regarding each papillary feature. In our study, we have subdivided the patients with

TABLE 4
Depth of Invasion by Tumor Type

Depth of invasion	AC (n = 66)[a]	PE (n = 25)[b]	UPSC (n = 15)
Superficial: inner third or less	47(71)[c]	16(64)	6(40)
Deep: outer two thirds	19(29)	9(36)	9(60)

$P < 0.05$, Mantel–Haenszel χ^2.
[a] Data not available for 10 patients.
[b] Data not available for 1 patient.
[c] Number (%).

TABLE 6
Nuclear Grade by Tumor Type[a]

Nuclear grade	PE (n = 20)[b]	UPSC (n = 15)
1	4(20)[c]	0(0)
2	8(40)	3(20)
3	8(40)	12(80)

$P < 0.05$, Mantel–Haenszel χ^2.
[a] Data not obtained for AC patients.
[b] Data not available for 6 patients.
[c] Number (%).

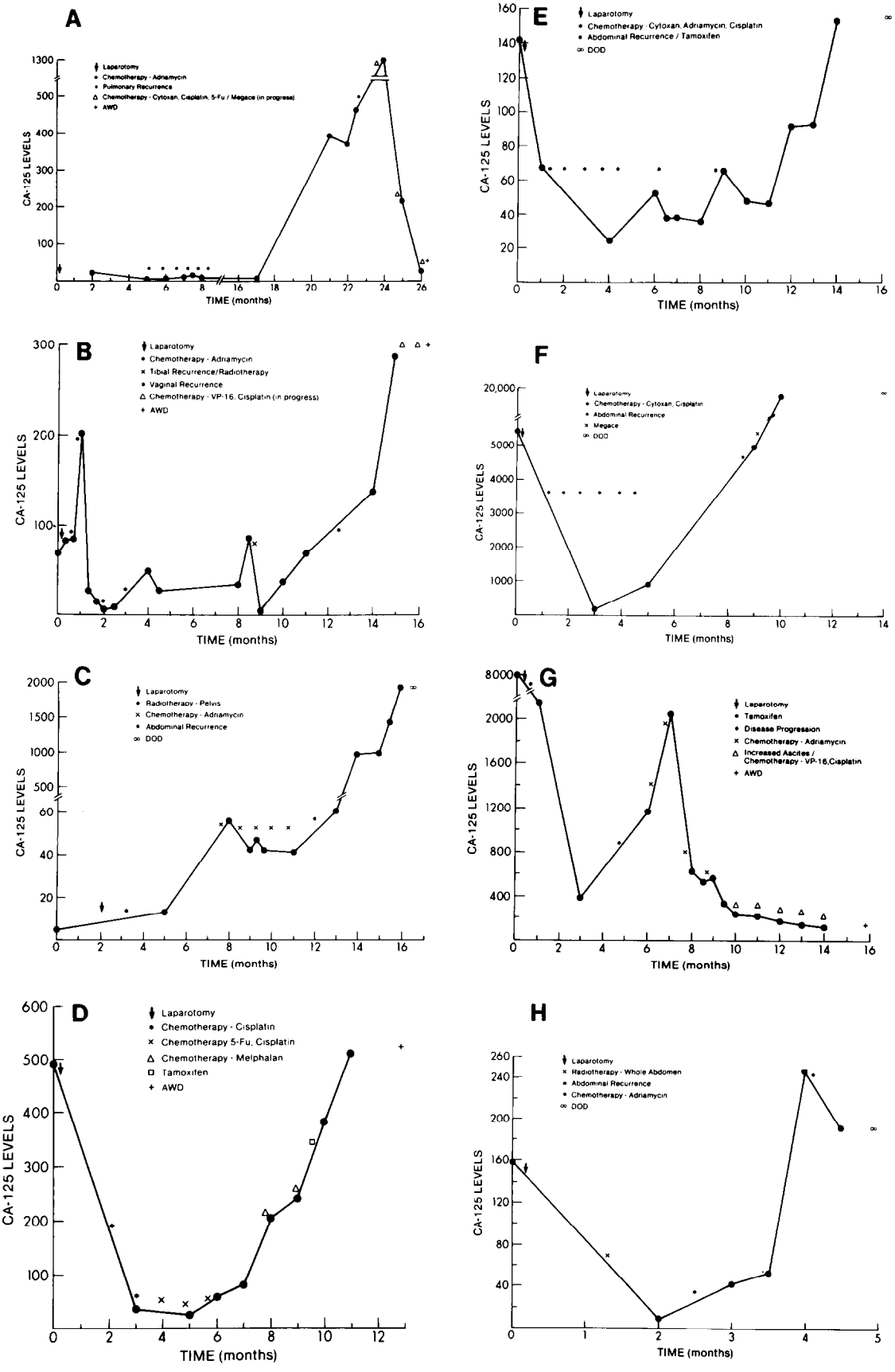

FIG. 3. Graph of CA-125 serum assay (U/ml) versus time: (A–D) patients with PE, (E–H) patients with UPSC.

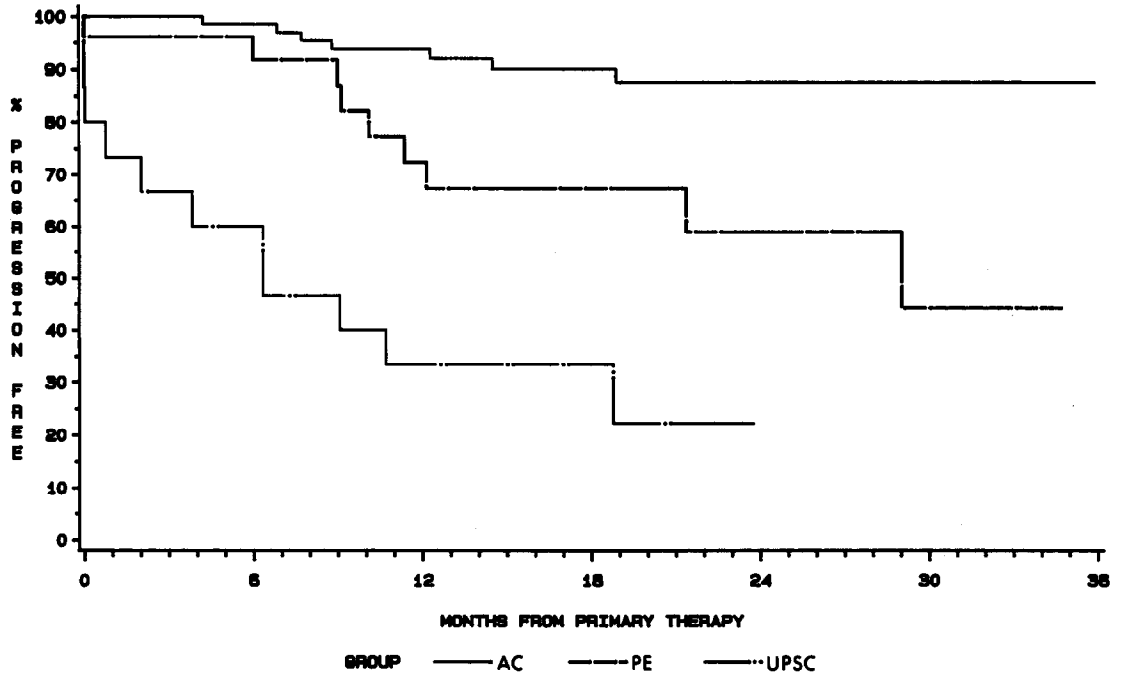

FIG. 4. Kaplan–Meier product limit estimates of progression-free survival analysis stratified by tumor type: AC versus PE versus UPSC.

papillary features in order to clarify the influence of each histotype on clinical presentation, surgical findings, and prognosis.

With regard to initial presentation, abdominal symptoms were found to occur with increasing frequency in patients with increasing papillary features, especially those with papillary serous features. We suggest that such symptoms should increase the suspicion of and, therefore, the search for extrauterine disease as these symptoms are likely due to serosal involvement of the abdominal viscera.

We observed a trend of Pap smears showing adenocarcinoma cells more often in the patients with UPSC than PE. Hendrickson *et al.* noted a similarly high rate of transcervical shedding in their patients with UPSC [2]. The common histologic observation of multiple, single cells suspended about the tufted, serous stalks may account for the high rate of positive cervical smears, as certain numbers of these isolated cells may actually become dislodged and free to be extruded through the cervix. The Pap smear remains an important screening tool in women with abdominal or pelvic symptomatology.

The median progression-free interval data reveal a significant gradient of virulence, with shorter progression-free intervals from AC to PE to UPSC. Hendrickson, Christopherson, and Chen and their co-workers have suggested that high nuclear grade may be associated with poor survival in patients with papillary tumors [2,14,15]. Our data support this theory, as 80% of PE tumors and 100% of UPSC tumors demonstrated marked nuclear anaplasia.

A gradient of increasing rate of upper abdominal tumor spread was observed from AC to PE to UPSC tumors. Lauchlan has theorized two modes of spread for UPSC. The first is a surface spread similar to ovarian carcinoma, with surface micrometastases being frequently found upon more careful pathologic inspection of apparently normal tissue [1]. Lymphovascular space invasion is the second route of spread, which accounts for the frequently reported finding of a small uterine primary with deep vascular space invasion and widely metastatic disease within the abdomen [16,17]. We noted a high rate of vascular space invasion in both our PE and UPSC tumor groups, 55 and 87%, respectively. This same rate is also seen in patients with only clinical stage I tumors, both of which are higher than the 7.2% rate of vascular space invasion reported in a recent G.O.G. study of 222 patients with clinical stage I AC [18]. Hendrickson *et al.* correlated deep invasion with poor prognosis, attributing the depth not to a confluent invasion through the myometrial wall, but to the growth of tumor emboli in deep vascular and lymphatic spaces [2].

We found an increasing gradient from AC to PE to UPSC tumor histotypes with respect to both depth of myometrial invasion and short progression-free intervals. Since patients with AC and PE tumors were not different with respect to architectural grade or surgical stage, our data suggest that deep myometrial invasion and possibly vascular space invasion account for the higher rate of upper abdominal spread and shorter progression-free interval found in each of the papillary groups over the AC group, and that within the papillary histotypes, nuclear

grade, deep invasion, and possibly vascular space invasion contribute to the further increase in the degree of virulence of UPSC over PE. These findings are in contrast to two recent studies which suggested that patients with PE have a prognosis similar to or better than that of patients with AC [15,19].

Most patients with AC recur distantly [12]. Most of our patients with PE who recurred did so in the abdomen, with one patient recurring in the lung and one in the tibia and vulva. The predominant sites of recurrence for UPSC patients were the abdomen and pelvis, similar to ovarian carcinoma. A transition of tumor behavior is suggested from AC to PE to UPSC, with the latter behaving more like an ovarian carcinoma and recurring more locally within the abdomen.

Many authors have discussed the need for surgical staging in cases of UPSC in a fashion similar to that currently performed for ovarian carcinoma. A meticulous search for extrauterine microscopic disease, including omentectomy and lymphadenectomy, should be performed in all cases of patients with any of the papillary variants. Aggressive cytoreduction and combination chemotherapy have been shown to improve survival in patients with ovarian carcinoma [20]. UPSC also appears to be a chemosensitive tumor [15,21–26]. Clinical studies are thus needed to confirm that the same aggressive approach to tumor debulking is warranted in patients with papillary variants. Given the short progression-free intervals in patients with PE, the benefit of adjuvant chemotherapy should be evaluated in a prospective fashion, once this high-risk factor has been confirmed.

It is not surprising that the CA-125 antigen, once elevated, follows the clinical course of disease in patients with both papillary subtypes. This tumor marker should be obtained in all patients with papillary histology, pre- and postoperatively, and at each follow-up visit.

In conclusion, we believe that the presence of papillary features in endometrial carcinoma is an important prognostic indicator. We suggest that all surgical specimens be sectioned extensively and scanned for papillary features, as well as the presence of other prognostic factors. Careful surgical staging as for ovarian carcinoma should be performed on all patients with the finding of papillary elements. We reconfirm previous reports that UPSC presents and behaves like an epithelial ovarian cancer, and that the prognosis is worse than that for endometrioid AC. We also observed that the PE variant has a presentation, behavior and prognosis worse than those of AC, with virulence intermediate between AC and UPSC for which therapy should be specifically tailored. Finally, we recommend a collaborative, randomized, controlled study to compare treatment modalities in patients with the different tumor histotypes, and to reconfirm the risk factors which may predict recurrence.

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