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Clinical Implications of Elevated Pretreatment Carcinoembryonic Antigen in Patients with Advanced Squamous Cell Carcinoma of the Uterine Cervix

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Key Words
Carcinoembryonic antigen · Cervical cancer · Prognostic factors · Squamous cell carcinoma · Tumor markers

Abstract
Object: The aim of this study was to investigate the prognostic significance of pretreatment levels of carcinoembryonic antigen (CEA) for treatment outcome in comparison with squamous cell carcinoma antigen (SCC) in cervical cancer patients following concurrent chemoradiotherapy (CCRT). ***Methods:*** A total of 148 patients with stage IB2–IVA squamous cell carcinoma of the uterine cervix who were treated with a full course of CCRT were included for analysis. The pretreatment blood samples of tumor markers were obtained before initiation of CCRT. Values for SCC <2 and CEA <5 ng/ml, respectively, were regarded as normal. Cox's proportional hazards model was performed for risk stratification for disease-free survival (DFS) and cause-specific survival (CSS). ***Results:*** Pretreatment CEA and SCC levels were elevated in 37.2 and 64.2% of the patients, respectively. Positive pelvic lymph node, stage and pretreatment CEA levels >10 ng/ml were three independent prognostic factors for DFS and CSS. The 5-year DFS for the low- and high-CEA groups was 80 and 56%, respectively (p = 0.02, hazard ratio 2.6), whereas the 5-year CSS for the low- and high-CEA groups was 84 and 63%, respectively (p = 0.01, hazard ratio 3.2). ***Conclusion:*** Despite lower sensitivity, pretreatment CEA levels >10 ng/ml predict a poor outcome in advanced squamous cell carcinoma of the cervix.

Introduction

Cervical cancer is one of the most common malignancies in women worldwide [1]. The role of tumor markers and human papillomavirus in cervical neoplasms has been extensively studied in the past decade. Squamous cell carcinoma antigen (SCC) is the most sensitive marker in squamous cell carcinomas and carcinoembryonic antigen (CEA) in adenocarcinomas [2, 3]. The pretreatment SCC levels were reported to correlate with clinical stage, lymph node metastasis and survival in squamous cell carcinoma of the uterine cervix [2, 4–8]. By contrast, CEA is one of the oncofetal antigens and can be detected

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Table 1. Patient characteristics and pretreatment tumor marker distribution (total n = 148)

Characteristics	SCC				CEA				Total number
	<2	2–10	>10	mean/median ng/ml	<5	5–10	>10	mean/median ng/ml	
Age									31–76 (median 54)
<45 years	7	6	4	7.5/3.4	12	3	2	4.3/2.9	17 (30.4%)
45–65 years	30	37	28	10.7/3.7	37	13	25	8.1/3.6	95 (64.2%)
>65 years	16	10	10	8.2/2.6	24	7	5	5.0/3.3	36 (25.0%)
Stage									
IB2–IIA (bulky)	13	10	5	6.3/3.1	15	5	8	12.0/3.8	28 (18.9%)
IIB	29	30	24	9.5/3.6	56	14	13	10.1/3.6	83 (56.1%)
III–IVA	11	13	13	12.8/4.3	22	4	11	9.4/3.2	37 (25.0%)
Tumor size									
≤4 cm	4	5	4	8.2/1.1	5	3	5	8.9/2.3	13 (8.8%)
>4 cm	49	48	38	10.3/3.8	88	20	27	9.5/3.5	135 (91.2%)
Pelvic lymph node									
Negative	48	42	36	9.4/3.4	82	17	27	9.9/3.6	126 (85.1%)
Positive	5	11	6	9.8/4.3	11	6	5	8.8/5.4	22 (14.9%)

The number of patients according to the tumor marker level (<2, 2–10 and >10 ng/ml, respectively) and the mean and median tumor marker levels (in ng/ml) are shown. Bulky tumors are defined as cervical tumors with a lateral dimension >4 cm.

during embryonic development. It is also re-expressed when adult tissues undergo neoplastic changes [6]. However, CEA can only reflect tumor burden in patients with CEA-releasing tumors [6, 7, 9]. Pretreatment CEA levels were raised in 22–58% of the patients with cervical cancer [2, 3, 6–10]. However, pretreatment SCC levels were increased in 60–80% of patients with advanced-stage cervical cancer [4, 7–9]. Despite major criticism of its lower sensitivity and specificity as a tumor marker, it is questionable whether the prognostic value of elevated pretreatment CEA levels should be ignored. Most reports presenting the clinical utility or prognosis of CEA include different histological types. Furthermore, the majority of studies reporting the prognostic value of tumor markers enrolled patients with different tumor sizes. If the pretreatment serum level of a biomarker is correlated with tumor burden, its biological implications will be obscured because inferior outcomes are always observed in bulky tumors. Thus, it would be interesting to conduct a tumor marker study in a patient cohort with controlled tumor burden or stratified by stage. On the other hand, a reliable biomarker may still be of clinical utility despite its lower sensitivity. To our knowledge, the clinical implications of elevated pretreatment CEA levels have not yet been resolved in advanced cervical cancer.

The purpose of this study was to investigate the prognostic value of CEA in patients with advanced squamous cell carcinoma of the cervix treated in the concurrent chemoradiotherapy (CCRT) era, and to compare the results with that of SCC. Combined use of CEA and SCC may help to identify patients at increased risk of treatment failure.

Patients and Methods

Patient Characteristics

Between January 2001 and June 2006, a total of 148 patients with untreated stage IB2–IVA squamous cell cancer of the uterine cervix without evidence of enlarged para-aortic lymph nodes were enrolled in this study. The study patients had comprehensive pretreatment examinations and completed curative-intent CCRT at the China Medical University Hospital. A positive node was defined as the presence of at least one enlarged lymph node with a maximal dimension of >1 cm on CT of the abdomen. Most of our study patients (91.2%) had bulky tumors with a lateral dimension >4 cm on CT or pelvic examination. Patient characteristics are summarized in table 1.

Tumor Marker Levels

In all patients, tumor markers were assessed prospectively. Blood was sampled before initiation of CCRT and then every 2–3 months. Serum levels of SCC and CEA were measured with a commercial ELISA kit (Imx; Abbott Laboratories, Tokyo, Japan) and an autoanalyzer (ES-300; Roche Diagnostics, Mannheim, Germany), respectively. In our study, values <2 and <5 ng/ml for SCC and CEA, respectively, were regarded as normal.

Table 2. Pretreatment tumor marker levels and correlation with different clinical parameters

Clinical parameters	CEA >5 ng/ml	CEA >10 ng/ml	SCC >2 ng/ml	SCC >10 ng/ml
Stage				
IB2–IIB	40 (36.0)	21 (18.9)	69 (62.1)	29 (26.2)
III–IVA	15 (40.5)	11 (29.7)	26 (70.3)	13 (35.1)
Parametrium				
Negative	13 (46.4)	8 (28.6)	15 (53.6)	5 (17.9)
Positive	42 (35.0)	24 (20.0)	80 (66.7)	37 (30.8)
Pelvic LN				
Negative	44 (34.9)	27 (21.4)	78 (61.9)	36 (28.6)
Positive	11 (50.0)	5 (22.7)	17 (77.3)	6 (27.2)
Age				
≤65 years	43 (38.4)	27 (24.1)	75 (70.0)	32 (28.6)
>65 years	12 (33.3)	5 (13.8)	20 (55.6)	10 (27.8)

No significant difference was found. Numbers in parentheses represent percentages.

Treatment

Irradiation consisted of external beam radiotherapy (EBRT) followed by high-dose intracavitary brachytherapy (HDRICB). Initially, the whole pelvis was treated with 10 MV X-ray via anterior and posterior parallel fields or box variants where the anteroposterior diameter was >18 cm. The standard dose prescribed was 45 Gy, consisting of 25 fractions given over 5 weeks. The radiation dose for patients in FIGO stage IIB–IVA bilateral parametrial disease was boosted to 54–57.6 Gy, with 4-cm-wide midline shielding. For patients with positive pelvic nodes, the radiation doses to involved nodes were escalated to 61.2–64.8 Gy with small field boost.

After adequate tumor regression, HDRICB was performed using an ^{192}Ir remote afterloading technique at 1-week intervals. The standard dose prescribed for each HDRICB was 6.0 Gy to point A. Details on the treatment method have been described in our previous study [12].

Chemotherapy consisted of cisplatin delivered weekly at a dose of 40 mg/m^2 i.v., with a total dose of up to 60 mg. The first cycle of cisplatin was initiated at the first radiotherapy (RT) treatment. In accordance with the duration of RT, the treatment plan included a total of five to six cycles of cisplatin (for further details on drug administration, see Chen et al. [13]).

Tumor Response at First Brachytherapy

HDRICB was usually initiated after EBRT of 40 Gy was administered. The tumor response to EBRT was recorded in an examination under anesthesia on a subjective basis as follows:

(1) NRT (no gross residual tumor): complete or nearly complete regression of the pelvic tumor, non-specific fibrosis or granulation over the cervix, and

(2) GRT (gross residual tumor): gross tumor or palpable nodularity on the cervix, and/or palpable induration of the parametrium.

Follow-Up and Analysis of Outcome

Treatment response was assessed 4 weeks after completion of treatment. Biopsy was performed in case of suspected residual disease. Serial tumor markers were checked for abnormal levels. Patients were followed up every 1–2 months during the first year and thereafter every 3 months. A pelvic examination was performed during each follow-up visit. Tumor marker levels were determined every 3 months and radiographic examinations (chest radiography and abdominopelvic CT scan) were conducted yearly. Pelvic recurrence was diagnosed in case of disease recurrence within the irradiated field either by pathological confirmation of cancer or imaging findings showing regrowth of the tumor or enlargement of a pelvic lymph node. Distant metastases were diagnosed in case of tumor growth in the para-aortic lymph nodes or outside the pelvis on imaging.

Statistical Analysis

Patient survival was assessed from the date of initiation of therapy to the date of the last follow-up examination. Statistical analysis of the data was carried out by χ^2 test. Disease-free survival (DFS) and cause-specific survival (CSS) were calculated using the Kaplan-Meier method. Significance levels between the curves were calculated using the log-rank test. Multivariate analysis was performed using Cox's proportional hazards model to assess both DFS and CSS. All patients were stratified by pelvic node involvement, stage, tumor size, age, results of examination under anesthesia, pretreatment tumor marker levels and initial hemoglobin level. $p < 0.05$ was considered statistically significant.

Results

Treatment Outcome

The median duration of follow-up was 49 months (range, 24–89 months). One hundred and twenty-two patients were alive (112 without evidence of recurrent disease, 4 with pelvic failure and 6 with distant metastasis); 26 patients died of the disease (2 with pelvic recurrence, 17 with distant metastasis and 7 with both). The 5-year CSS was 93% for stage IB2–IIA, 82% for stage IIB and 67% for stage III–IVA. The 5-year DFS was 85% for stage IB2–IIA, 79% for stage IIB and 59% for stage III–IVA.

Association between Pretreatment Tumor Markers and Clinical Parameters

Abnormal pretreatment CEA and SCC serum levels were found in 37.2% (55/148) and in 64.2% (95/148) of the study patients, respectively. Table 1 shows the initial tumor marker levels according to different clinical parameters of the patients. There was a trend to increased mean or median SCC levels with advanced stage, but this was not observed for CEA levels. Using different cutoff val-

Table 3. Failure pattern for the patients with different parameters

Variables	Total, n (n = 148)	NED, % (n = 112)	Local, % (n = 13)	Distant, % (n = 30)	PALN, % (n = 25)
Stage					
IB2–IIA	28	85.7	0	14.3	10.7
IIB	83	80.7	7.2	16.8	13.3
III–IVA	37	56.7	18.9	32.4	29.7
Age					
≤65 years	112	76.8	9.8	21.4	17.8
>65 years	36	72.2	5.6	16.6	13.9
Pelvic LN					
Negative	126	82.5	7.1	14.3	7.9
Positive	22	36.3	18.2	54.5	68.2
EUA					
NGT	37	75.7	5.4	21.6	13.5
GRT	111	75.7	9.9	19.8	18.0
Initial hemoglobin					
<10 mg/dl	26	61.5	15.4	30.8	34.6
>10 mg/dl	122	78.6	7.4	18.0	13.1
Pretreatment SCC					
<10 ng/dl	106	76.4	11.1	19.8	15.3
>10 ng/dl	42	73.8	9.5	23.8	21.4
Pretreatment CEA					
<10 ng/dl	118	79.6	6.8	16.9	15.1
>10 ng/dl	30	60.0	16.7	33.3	23.3

NED = No evidence of disease; LN = lymph node; EUA = examination under anesthesia before the first brachytherapy; NGT = no gross residual tumor; GRT = gross residual tumor.

Table 4. Multivariate analysis of prognostic factors for DFS and CSS

Prognostic factors	DFS			CSS		
	HR	95% CI	p value	HR	95% CI	p value
Pelvic LN status						
Negative	1			1		
Positive	7.4	2.5–25.8	0.0001	8.2	2.2–27.6	0.0001
Stage						
IB2–IIB	1			1		
IIIA–IVA	3.5	1.2–12.7	0.01	2.7	1.1–11.6	0.03
Age						
>65 years	1			1		
≤65 years	1.2		0.72	1.1		0.71
EUA						
NGT	1			1		
GRT	1.0		0.90	0.88		0.52
Initial hemoglobin						
>10 mg/dl	1			1		
<10 mg/dl	1.2		0.39	1.1		0.62
Pretreatment SCC						
<10 ng/dl	1					
>10 ng/dl	1.1		0.66	1.4		0.48
Pretreatment CEA						
<10 ng/dl	1			1		
>10 ng/dl	2.6	1.1–7.9	0.02	3.2	1.2–9.4	0.02

HR = Hazard ratio; CI = confidence interval; other abbreviations as in table 3.

ues, there was no clear association of stage, parametrial invasion or lymph node status with initial SCC or CEA levels (table 2).

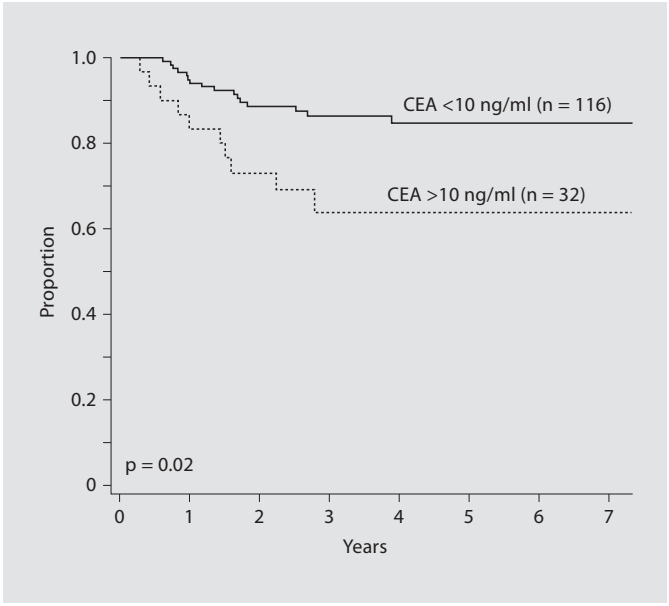
Posttreatment Outcome and Tumor Marker Levels

All patients underwent pelvic examination, tumor marker assessment and imaging after CCRT. One hundred forty-seven (99.3%) patients had at least one SCC/CEA value recorded during the first 3 months after CCRT. Serial checkups of tumor markers were done if the level was above normal. In 89.1 (49/55) and 92.6% (88/95) of the patients, CEA and SCC levels returned to normal within 3 months.

For 36 patients with disease relapse, elevated pretreatment CEA and SCC levels were found in 52.8 (19/36) and 58.3% (21/36) of patients, respectively, whereas increases in posttreatment CEA and SCC levels were noted in all patients with recurrent disease with higher pretreatment serum levels.

Risk Factors Associated with Survival Rate and Failure

The failure patterns in patients with different clinical parameters are listed in table 3. The risk factors associated with CSS and DFS were examined by multivariate analyses (table 4). Independent risk factors for CSS were positive pelvic lymph node (p = 0.0001, hazard ratio 8.2, 95% confidence interval 2.2–27.6), stage III–IVA disease (p = 0.01, hazard ratio 3.5, 95% confidence interval 1.2–12.7) and CEA levels >10 ng/ml (p = 0.02, hazard ratio 3.2, 95% confidence interval 1.2–9.4). The independent risk factors for DFS were positive pelvic lymph node (p = 0.0001, hazard ratio 7.4, 95% confidence interval 2.5–25.8), stage III–IVA disease (p = 0.01, hazard ratio 3.5, 95% confidence interval 1.2–12.7) and CEA levels >10 ng/ml (p = 0.02, hazard ratio 2.6, 95% confidence interval 1.1–7.9). As depicted in figures 1 and 2, the 5-year CSS for the low- and high-CEA group was 84 and 63%, respectively, whereas the 5-year DFS for the low- and high-CEA group was 80 and 56%, respectively. In subgroup analysis



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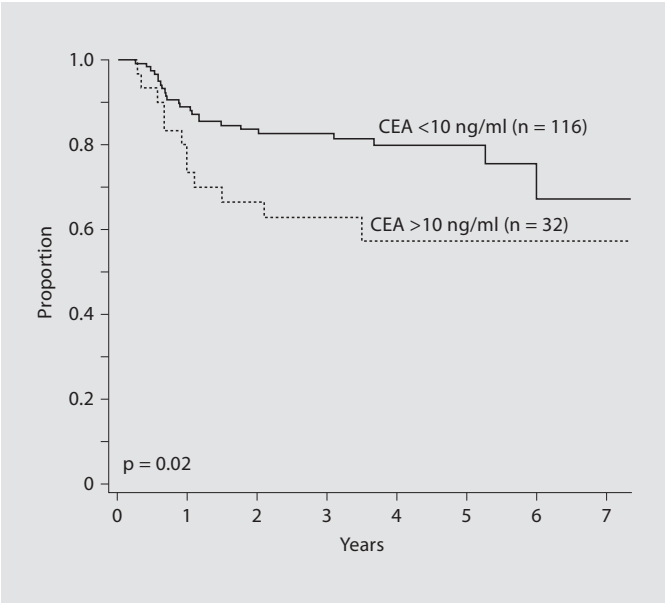

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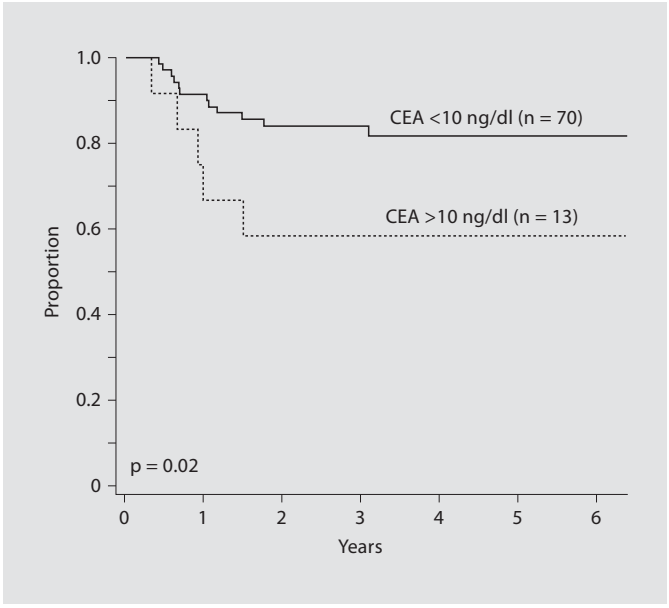
Fig. 1, 2. CSS (**1**) and DFS curves (**2**) according to CEA levels.

(fig. 3, 4), the 5-year DFS for low and high CEA was 81 and 58% in stage IIB disease (p = 0.02), and 69 and 25% in stage III–IVA tumors (p = 0.06), respectively. For the 126 patients without enlarged pelvic lymph node (fig. 5), the 5-year DFS for low- and high-CEA levels was 86 and 65%, respectively (p = 0.03).

Discussion

A clinically useful biomarker for assessing outcome should be always reliable, easily obtainable and not costly. In the era of high-throughput predictive assays in radiation oncology, the use of traditional tumor markers might be reasonable if these markers were significantly correlated with clinical outcome. Despite previous reports that CEA results do not support its routine use for screening or diagnosis of early cervical cancer [2, 3, 6–10], it would be interesting to point out the clinical implications of elevated pretreatment CEA levels, because sampling of this marker is neither costly nor time-consuming. However, most reports dealing with the clinical utility or prognosis using CEA include histological types of adenocarcinoma or adenosquamous carcinoma. In a study conducted by Borras et al. [3], CEA levels were found to be increased in 38.5% of adenocarcinomas compared to 32% of squamous cell carcinomas. Because some studies reported that in patients with adenocarcinoma treatment outcome was poor [14, 15], it is questionable to conclude the prognostic value of CEA from a patient cohort with a combination of two histopathological types. In one available study on squamous cell carcinomas of the cervix alone, the upper limit of normal for CEA was 2.5 ng/ml [6]. The incidence of a high serum level was 30.2% in stage IB2–IIA disease and 29.2% in stage IIB tumors. The authors suggested pretreatment SCC in conjunction with CEA is a valuable tumor marker to predict outcome and to foresee a clinical response to neoadjuvant chemotherapy. In addition, Molina et al. [2] reported on 159 patients treated by radical hysterectomy or irradiation. In univariate analysis, a cutoff value of 5 μg/ml for CEA was a prognostic factor for both the 115 patients with squamous tumors and the 26 patients with adenocarcinoma in disease-free survival. However, CEA lost its clinical significance when SCC (cutoff value was 2 ng/ml) was entered into multivariate analyses. Thus, the authors suggested further studies including a larger patient cohort are necessary to demonstrate the prognostic value of pretreatment CEA levels.

The current study is the largest series investigating the association between pretreatment CEA levels and outcome in squamous tumors of the cervix. In comparison to other CEA studies, our data are unique regarding two points. Firstly, all the study patients received standard radiation treatment plus weekly cisplatin. Thus, the efficacy of CCRT could be simply correlated with the evolu-



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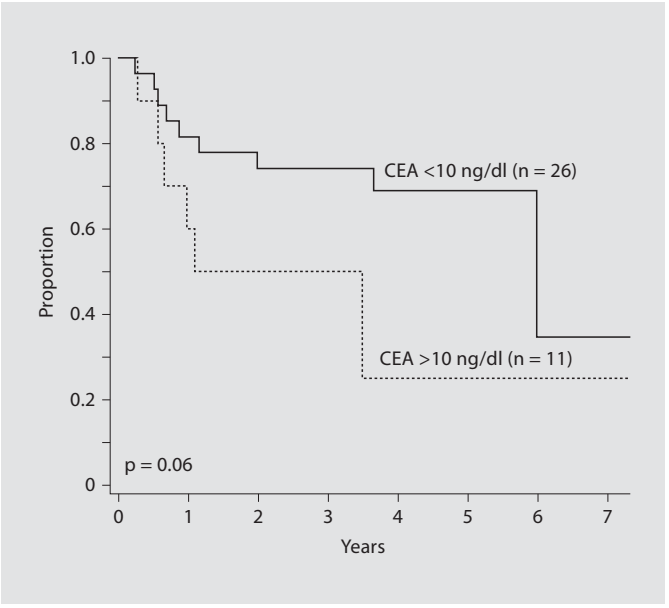

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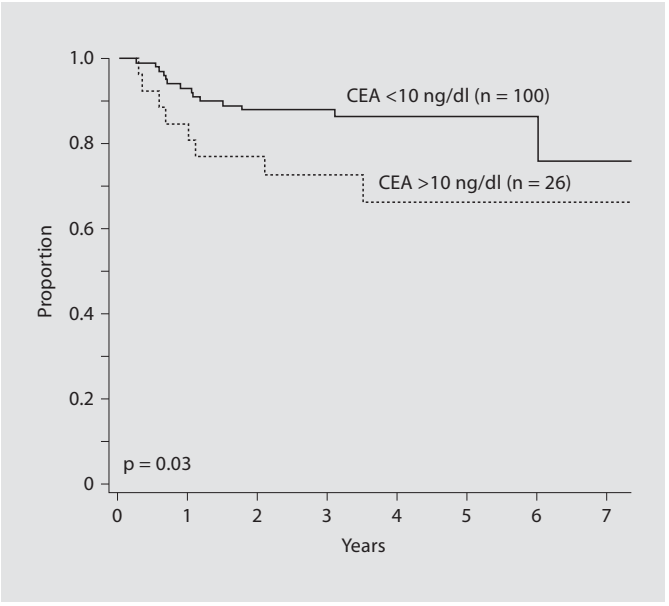

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Fig. 3–5. DFS curves of stage IIB (**3**) and III–IVA patients (**4**) and patients with negative pelvic lymph nodes (**5**) according to CEA levels.

tion of tumor markers. In addition, the biological implication of a marker could also be tested since there was no clear association between pretreatment CEA levels and other clinical parameters. In the study by Molina et al. [2], only 48.7% (57/117) of tumors were categorized as bulky mass, compared with 91.2% in our study. Thus, the discrepancy between the two investigations might be attributed to patient selection bias. The influence of other clinical parameters, such as tumor size or lymph node status, would be substantial when analyzing the prognostic value of a tumor marker.

Based on our results, a series of tumor markers checks is recommended to assess disease evolution once pretreatment serum levels are elevated. Furthermore, patients might be anticipated to have a poor CCRT outcome when pretreatment CEA levels are >10 ng/ml. The findings were also consistent when stratified by other well-known prognostic factors such as positive pelvic lymph node or clinical stage. It could be hypothesized that the behavior of biochemical marker-producing malignant cells might be different from that of nonproducing malignant cells in terms of responsiveness to CCRT in the

irradiated area, or to weekly cisplatin in the non-irradiated area.

Hong et al. [4] reported that a pretreatment SCC level >10 ng/ml was an independent prognostic factor in 401 patients with squamous cell carcinoma of the cervix treated with RT alone. It is questionable why their results cannot be confirmed in our study. In their investigation, 22.4% (90/401) of the patients had non-bulky stage I–IIA tumors. In addition, in their study and other reports tumor burden in squamous cell carcinomas of the cervix always correlated with the initial SCC level [2, 5–8]. Thus, clinical stage probably obscured the prognostic significance of SCC in our data. By contrast, two findings helped us confirm the prognostic value of pretreatment CEA levels. Firstly, there was no obvious correlation between pretreatment CEA levels and tumor burden. In addition, CEA-secreting tumors also had a worse outcome in our subgroup analysis. Nonetheless, it is essential to conduct further prospective studies to clarify the current findings, and it is also imperative to find the optimal cutoff value in terms of clinical significance.

In summary, our results showed a pretreatment CEA level >10 ng/ml is a prognostic marker for advanced squamous cell carcinoma of the cervix. The risk of treatment failure in the CCRT era can be precisely predicted from pelvic lymph node status, staging and pretreatment CEA level. Despite unsatisfactory sensitivity, incorporation of the pretreatment CEA level could be feasible when developing a prognostic model based on easily obtainable clinical information in most institutions performing CCRT.

References

1 Boring CC, Squires TS, Tong T, Montgomery S: Cancer statistics 1994, CA Cancer J Clin 1994;4:7–26.
2 Molina R, Filella X, Lejarcegui JA, Pahisa J, Torne A, Rovirosa A, Mellado B, Ordi J, Puig-Tintore LM, Alicarte J, Biete A, Iglesas J: Prospective evaluation of squamous cell carcinoma and carcinoembryonic antigen as prognostic factors in patients with cervical cancer. Tumor Biol 2003;24:156–164.
3 Borras G, Molina R, Xercavins J, Ballestra A, Iglesas J: Tumor antigens CA 19.9, CA 125, and CEA in carcinoma of the uterine cervix. Gynecol Oncol 1995,57:205–211.
4 Hong JH, Tsai CS, Chang JT, Wang CC, Lai CH, Lee SP, Tseng CJ, Chang TG, Tang SG: The prognostic significance of pre- and post-treatment SCC levels in patients with squamous cell carcinoma of the cervix treated by radiotherapy. Int J Radiat Oncol Biol Phys 1998;41:823–830.
5 Duk JM, Groenier KH, de Bruijn HW, Hollema H, ten Hoor KA, van der Zee AG, Aalders JG: Pretreatment serum squamous cell antigen: a newly identified prognostic factor in early-stage cervical cancer. J Clin Oncol 1996;14:111–118.
6 Bae SN, Namkoong SE, Jung JK, Kim CJ, Park JS, Kim JW, Lee JM, Kim SJ: Prognostic significance of pretreatment squamous cell antigen and carcinoembryonic antigen in squamous cell carcinoma of the uterine cervix. Gynecol Oncol 1997;64:418–424.
7 Yoon SM, Shin KH, Kim JY, Seo SS, Park SY, Kang S, Cho KH: The clinical values of squamous cell carcinoma antigen and carcinoembryonic antigen in patients with cervical cancer treated with concurrent chemoradiotherapy. Int J Gynecol Cancer 2007;17:872–878.
8 Volgger B, Aspisirengil C, Genser-Krimbacher E, Ciresa-Koenig A, Daxenbichler G, Fuchs D, Windbichler G, Marth C: Prognostic significance of TPA versus SCC-Ag, CEA and neopterin in carcinoma of the uterine cervix. Cancer Lett 2008;262:183–189.
9 te Velde ER, Persijn JP, Ballieux RE, Faber J: Carcinoembryonic antigen serum levels in patients with squamous cell carcinoma of the uterine cervix: clinical experience. Cancer 1982;49:1866–1873.
10 Kjorstad KE, Orjasaester H: The prognostic value of CEA determinations in the plasma of patients with squamous cell carcinoma of cervix. Cancer 1982;50:283–287.
11 Ngan HY, Cheng GT, Yeung WS, Wong LC, Ma HK: The prognostic value of TPA and SCC in squamous cell carcinoma of the cervix. Gynecol Oncol 1994;52:63–68.
12 Chen SW, Liang JA, Yeh LS, Yang SN, Shiau AC, Lin FJ: Comparative study of reference points by dosimetric analyses for late complications following uniform external radiotherapy and high-dose-rate brachytherapy for cervical cancer. Int J Radiat Oncol Biol Phys 2004;60:663–671.
13 Chen SW, Liang JA, Hung YC, Yeh LS, Chang WC, Lin WC, Yang SN, Lin FJ: Concurrent weekly cisplatin plus external beam radiotherapy and high-dose rate brachytherapy for advanced cervical cancer: a control cohort comparison with radiation alone on treatment outcome and complications. Int J Radiat Oncol Biol Phys 2006;66:1370–1377.
14 Hong JH, Tsai CS, Wang CC, Lai CH, Chen WC, Lee SP, Chang TC, Tseng CJ: Comparison of clinical behaviors and responses to radiation between squamous cell carcinomas and adenocarcinomas/adenosquamous carcinomas of the cervix. Changgeng Yi Xue Za Zhi 2000;23:396–404.
15 Eifel PJ, Burke TW, Morris M, Smith TL: Adenocarcinoma as an independent risk for disease recurrence in patients with stage IB cervical carcinoma. Gynecol Oncol 1995;59:38–44.