

Value of Squamous Cell Carcinoma Associated Antigen (TA-4) in Patients with Invasive Carcinoma of the Uterine Cervix

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We investigated the usefulness of tumor-associated antigen (TA-4) by a radioimmunoassay method in estimating the extent of disease and tracking the clinical course of disease in 58 patients with cervical cancer. According to our results and those of other authors, the normal range of serum TA-4 was arbitrarily taken to be less than 2 ng/ml. The proportion of the pretreatment positive serum TA-4 level of 48 squamous cell carcinoma patients was 60%. And 40% in 5 adenocarcinoma patients. Advanced disease group showed higher incidence of positive serum TA-4 level; 40%, 72%, 63%, and 100% in stage I to IV, respectively. And the absolute values of TA-4 were higher in advanced disease. In patients treated with radiation, elevated serum TA-4 level usually declined after 3000 cGy and further dropped to normal range in 44% after 5000 cGy. The positive rate in primary cervical cancer was 59% (32/54) and 100% (4/4) in recurrent cervical cancer. And 15 patients with recurrent or persistent disease during follow-up revealed 80% positive serum TA-4 level. In conclusion, it would be suggested that serial serum TA-4 measurements may be helpful in tracking the clinical course during and after treatment.

Key Words: TA-4, Cervix Cancer, Radiotherapy

INTRODUCTION

Recurrence of uterine cervical cancer is usually locoregional and it is not easily detected by conventional diagnostic methods. Therefore, some sensitive and reliable method is required for monitoring the disease to determine the effectiveness of treatment, to predict the prognosis, and to detect the recurrence. Although several investigators reported of the isolation of tumor-antigens of cervical carcinoma, they had difficulty in developing conventional method for measuring those antigens^{1,2)}. Tumor-associated antigen TA-4 was found and named by Kato and Torigae. It is a protein with a molecular weight of approximately 48,000 daltons which was originally purified from squamous cell carcinoma of the uterine cervix³⁾. Using radioimmunoassay (RIA) method, they reported that TA-4 was detected in the circulation of patients with cervical squamous cell carcinoma and the serum TA-4 levels reflected some tumor behaviors⁴⁻⁶⁾. Due to recent development of TA-4 RIA KIT, the practical application of this antigen has

become easily available. The current study was undertaken to investigate serial serum TA-4 level of cervical carcinoma patients undergoing radiation therapy and compare the TA-4 level with clinical course.

MATERIALS AND METHODS

For this study 58 patients with invasive carcinoma of the uterine cervix, treated at the Chungnam National University Hospital, were evaluated. We followed the International Federation of Gynecology and Obstetrics (FIGO) Staging System. Tumor was classified histopathologically as large cell nonkeratinizing, keratinizing, small cell, and adenocarcinoma according to the criteria of Reagan⁹⁾. Table 1 shows the clinical features of patients. Radiotherapy was done with 6 MV photon beam from a linear accelerator. Radiation was given through AP and PA parallel opposed portals and both lateral portals. 50 Gy was applied to this field over 5 to 6 weeks, 5 times a week. Low dose rate intracavitary radiotherapy was done 2 or 3 weeks after teletherapy. Point A dose was about 30 Gy. Some patients received chemotherapy before radiotherapy. Blood sample was collected before radiotherapy, after 30 Gy, after 50 Gy, and after ICR.

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Serum TA-4 level was measured by using a double antibody radioimmunoassay kit (Dainabot Ltd., Japan). A level of 2.0 ng/ml was taken as the upper limit for normal, representing 95% in a population of healthy woman¹⁰⁻¹²⁾. Analysis of variance, chi-

square, and student t-test were used for comparison of groups.

RESULTS

1. Pretreatment Serum TA-4 Level in Patients with Cervical Carcinoma According to Clinical Stage

Serum TA-4 levels according to clinical stage are shown in Fig. 1. Serum TA-4 level was elevated more frequently with advanced disease. Absolute value was also higher with advanced disease. Serum TA-4 level over 2.0 ng/ml was observed from 40% in stage I, 72% in stage II, 63% in stage III, and 100% in stage IV, respectively. Mean value of serum TA-4 level was 3.1 ng/ml in stage I, 6.6 ng/ml in stage II, 10.2 ng/ml in stage III, and 17.7 ng/ml in stage IV.

2. Pretreatment Serum TA-4 Level in Patients with Cervical Carcinoma According to the Histologic Type

Serum TA-4 levels according to the histologic type are shown in Fig. 2. The proportion of positive serum TA-4 levels in squamous cell carcinoma

Table 1. Patient Profiles

	Primary	Recurrent
Total	54	4
Age	54 (31~73)	59 (54~61)
Stage		
I	20(37%)	
II	25(46%)	
III	8(15%)	
IV	1(2%)	
Pathology		
Squamous	48	4
Keratinizing	27	3
Non-keratinizing	15	1
Small	2	
Not Specified	4	
Adenocarcinoma	5	
Other	1	

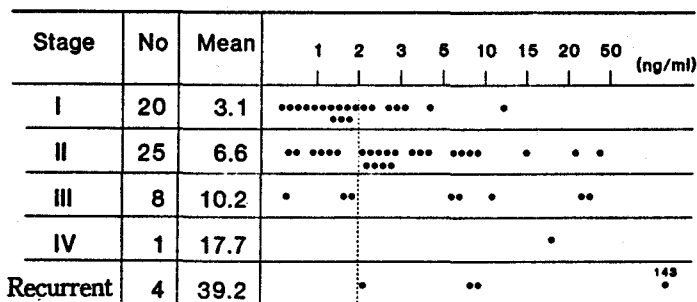


Fig. 1. TA-4 level according to Stage.

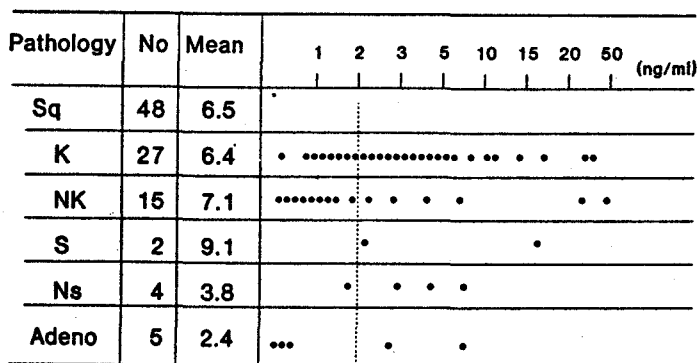


Fig. 2. TA-4 level according to Pathology.

patients was 60% (29/48), which was significantly higher than 40% (2/5) in adenocarcinoma patients ($p=0.026$). Mean value of serum TA-4 level in squamous cell carcinoma patients was 6.5, which was much higher than 2.4 in adenocarcinoma patients. The proportion of positive serum TA-4 value in large cell keratinizing type patients was 67% (18/27), which was higher than 40% (6/15) in nonkeratinizing type. But the mean value was 6.4 ng/ml in large cell keratinizing type which was lower than 7.1 ng/ml in nonkeratinizing type.

3. Sequential Serum TA-4 Level During and After Radiation Therapy

22 patients initially showed positive TA-4 level before radiotherapy. Fig. 3 shows the pattern of decline in serum TA-4 level during radiotherapy. During the application of the initial 3000 cGy, the TA-4 level decreased rapidly, when radiation reached a total 5000 cGy, the TA-4 level decreased gradually in response to radiotherapy. Two patients showed nearly no improvement after 5000 cGy and they gave up further treatment. Their serum TA-4 value continued above normal range. Only 3 patients continued to show a persistent positive serum TA-4 level after ICR. Two patients among them showed persistent disease and one patient seemed to show complete response and his serum TA-4 value returned to normal after several months but later she got recurrence at the primary site.

4. Serum TA-4 Level in Failure Cases

32 out of 54 patients (59%) with primary cervical carcinoma showed positive serum TA-4 level. But 4 initially recurrent patients showed 100% of positive level. During treatment, 4 patients showed persistent disease, and they all showed positive TA-4 level, and during follow-up seven patients recurred, and 4 of them showed positive level. A proportion of positive level among all failure patients was 80% (12/15), which was much higher than 59% of primary cervical carcinoma patients (Table 2).

DISCUSSION

TA-4 is a protein with a molecular weight of approximately 48,000 daltons, which was originally purified from human squamous cell carcinoma of the uterine cervix⁹. As TA-4 has been found not only in cervical squamous cell carcinoma but also in a variety of malignant or benign disease and normal squamous cellular tissue, it would not be a

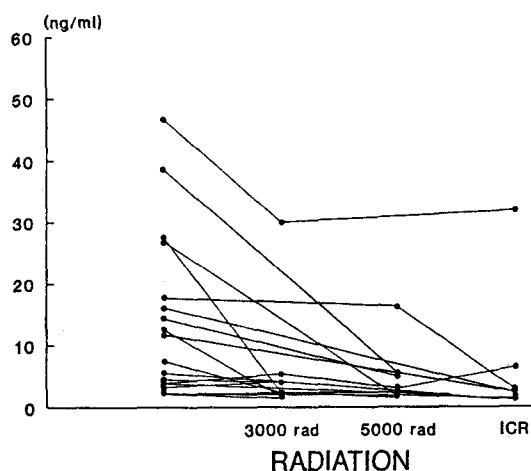


Fig. 3. TA-4 Changes after Radiation

Table 2. TA-4 Level in Failure Cases

Group	No	TA-4	Level (ng/ml)
I.	4	2.1 8 9.3 143	
II.	4	2.8 3 8.7 32	
III.	7	1 1 2.8 2.9 6 8.8	

I : Initially recurrent cases before radiotherapy

II : Persistent cases after radiotherapy

III : Recurrent cases after radiotherapy, although once considered as complete response

specific antigen to cervical squamous cell carcinoma¹³. But clinical trials have demonstrated good agreement between serum TA-4 level and the extent, prognosis, response to treatment, and progression of cervical squamous cell carcinoma^{5-8,10-12,14}. A large proportion of patients with advanced disease showed higher TA-4 level compared to patients with early disease. 16% to 40% of stage I versus 63% to 83% of stage III tumors showed high TA-4 level^{10,12}. Also, higher mean value of TA-4 was reported in advanced disease. The plasma half of TA-4 was about 20 minutes. Normalization of TA-4 level was observed to occur within 3 to 14 days after radical hysterectomy^{14,15}. During radiotherapy, serum TA-4 level decreased and dropped to normal range in 50% after 4000 cGy and 87.5% after 6000 cGy. The decline of serum TA-4 to normal level observed during radiotherapy was closely coincident with the histopathologic evidence of the disappearance of cervical cancer cells in biopsy specimens of the cervix¹⁴. The survival rate or disease free rate was significantly low in those with TA-4 value of ≥ 15 ng/

ml compared to that of those with lower level⁷). In general, good agreement was found between TA-4 antigen values and regression, progression, and recurrence of cervical carcinoma. Rising TA-4 level was associated with tumor progression or recurrence and preceded clinical evidence of recurrence by 3.6 months⁸). Declining TA-4 level was associated with objective tumor regression. However, declining level may also accompany disease progression or stabilization. Furthermore, fall of TA-4 level to ≤ 2.0 ng/ml may not always coincide with a tumor free state.

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국문초록 =

침윤성 자궁경부암 환자에서 SCC Antigen (TA-4) 측정의 유용성

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자궁경부암 환자의 병변의 범위 및 임상 경과를 추정하는데 TA-4의 유용성을 검토하고자 충남대학교병원에서 자궁경부암으로 진단 받은 58명의 환자를 대상으로 혈청 TA-4치를 RIA 방법으로 측정하여 ≤ 2 ng/ml을 정상 범위로 정하여 다음과 같은 결과를 얻었다.

- 1) 치료전 평평상피암 환자의 TA-4의 양성율은 60%, 선암은 40%였다.
- 2) 병기가 진행될수록 TA-4의 양성율및 평균치가 높아서, 양성율 병기 I는 40%, II는 72%, III는 63%, IV는 100%였으며 평균치는 병기 I에서 3.1, II는 6.6, III는 8, IV는 17.7 ng/ml였다.
- 3) 방사선 치료후 혈청내 TA-4치는 감소하여 5000 cGy 조사후 치료전 양성을 보였던 환자의 44%에서 TA-4치가 정상으로 돌아왔다.
- 4) 원발성 자궁경부암 환자의 양성율은 59%였으나 지속성 또는 재발성등 치료에 실패한 15명 환자의 양성율은 80%였다.

이상으로 연속적 혈청내 TA-4치의 측정은 자궁경부암 환자의 방사선치료에 따른 임상 경과를 관찰하는데 도움이 될 것으로 사료된다.