The Impact of Squamous Cell Carcinoma (SCC) Antigen in Patients with Advanced Cancer of Uterine Cervix Treated with (Chemo-)Radiotherapy

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Abstract. The impact of squamous cell carcinoma antigen (SCC) in the follow-up of patients with advanced cervical cancer treated with (chemo-) radiotherapy in primary and postoperative settings was evaluated. One hundred and forty-one patients with histologically proven squamous cell carcinoma of the uterine cervix were treated at the department of radiotherapy and radiation oncology. The serum level of SCC before treatment was elevated in 72% of the patients (cut-off level: 2.0 ng/ml). The course of SCC levels during (chemo-)radiotherapy reflects the tumor response: those patients, who had no significant decline of tumor marker values, had a lower response rate and worse outcome (p<0.001). Patients with a SCC level below the median of 7.2 U/ml had a significantly better prognosis and a better treatment response than those above the median (p=0.001). After treatment, 98% of patients with complete remission and 87% of patients with partial remission had a serum level below the cut-off. In the case of recurrent disease, 82% of patients had a significant increase of SCC serum levels (p<0.001) before clinical manifestation of relapse. The lead-time ranged between one and 16 months (median: 4.5 months). We concluded that SCC is an essential tumor marker for monitoring treatment response and detecting recurrences in patients with squamous cell carcinoma of the uterine cervix undergoing (chemo-)radiotherapy. In this retrospective analysis, the value of SCC correlated with prognosis in patients with carcinoma of the cervix treated with (chemo-)radiotherapy.

Squamous cell carcinoma antigen (SCC) is a subfraction of the tumor-associated antigen TA-4 and shows a high specificity in a variety of squamous cell cancers in humans. A specificity of more than 95% was found in squamous cell carcinomas of the uterine cervix, of the lung and of the head and neck region. The highest sensitivity of up to 83% was determined in squamous cell carcinomas of the uterine cervix (1). Early clinical experiences from Kato et al. showed a good correlation of the serum SCC with the extent of disease, the prognosis and the detection of recurrence in squamous cell carcinomas of the uterine cervix (2, 3). Since then, serum SCC has been established as a valuable tumor marker in this tumor entity. Nevertheless, there are a large number of benign diseases, such as inflammatory conditions, exhibiting an elevation of serum SCC, which may limit the value of this marker (4). Radiotherapy is the standard treatment for locally advanced cervical cancer. Besides improved radiotherapy techniques in the last few years, intensified treatment in a multimodal context could markedly improve prognosis in locally advanced cervical carcinoma. In particular, cisplatin-based chemotherapy given concomitantly with radiation therapy improved the overall survival and local control in cervical cancer (5, 6). However, the impact of serum SCC level changes on the prognosis of patients treated with (chemo-)radiotherapy in primary or postoperative settings is so far obscure (7, 8).

We evaluated the serum SCC levels of all patients with cervical squamous cell cancer treated with (chemo-)radiotherapy in primary or postoperative settings in our department to assess the impact of serum SCC level changes on prognosis, follow-up and after-care.

Patients and Methods

One hundred and forty-one consecutive patients with histologically proven squamous cell carcinoma of the uterine cervix were treated at the Department of Radiotherapy and Radiation Oncology in the Münster University Hospital, Germany, between 1982 and 2003. The median age was 58 years (range: 33-78). The stages according to the International Federation of Gynecology and Obstetrics
(FIGO) classification were I in 5 patients, II in 72 patients, III in 54 patients and IV in 10 patients. The median follow-up was 33 months, ranging from 4 to 92 months.

Eighty-eight patients received postoperative external beam radiotherapy (EBRT) of the pelvis with a total dose of 45 to 50 Gy under megavoltage conditions. Additional chemotherapy was given in 7 cases (Group A). Fifty-three patients received definitive EBRT of the pelvis with total doses between 45 and 55 Gy and intracervical HDR brachytherapy with 28 to 42 Gy, 7 Gy once a week. Additional chemotherapy was given in 13 cases (Group B). The chemotherapy schedule comprised 4-6 cycles of cisplatinum, 40 mg/m², once a week.

Patients were followed-up regularly at three-month intervals. Diagnostic procedures included physical examination, cervical cytology, complete laboratory tests and serial measurement of serum SCC. Chest X-ray and abdominal CT-scan were routinely performed every 6-12 months, and in case of suspected relapse. Serum SCC levels were measured before surgery (Group A) or radiotherapy (Group B), respectively, and regularly during the follow-up. In Group B, additional measurement of the serum SCC level was performed during radiotherapy once a week. Serum SCC was measured using a microparticle enzyme immunoassay system (Imx, Abbott Diagnostics). The lower level of sensitivity of this system was 0.3 ng/ml. The cut-off level of serum SCC in the Münster laboratory was 2.0 ng/ml.

**Results**

The median SCC serum value before treatment was 3.4 U/ml for all patients, 2.8 U/ml for Group A, and 7.2 U/ml for Group B. The overall pretreatment sensitivity was 72%. Elevated serum SCC level prior to therapy correlated with tumor stage and histopathological grading as follows: in the advanced stages III and IV, 83% of patients had an elevated serum SCC above the cut-off level; 82% of G3-tumors were associated with an elevated serum SCC level in contrast to 60% in G2-tumors. These differences reached statistical significance ($p=0.03$).

Thirty-nine patients achieved a complete and 14 patients a partial remission 3 months after the end of radiation therapy. One patient out of 39 patients with complete remission after therapy had an elevated serum SCC value without evidence of disease, whereas 87% of patients with partial remission had decreased serum SCC below the cut-off level. It is noteworthy, that all of the remaining 13% of patients with persistent elevation of serum SCC level after therapy relapsed within the first year after the end of (chemo-)radiotherapy. The course of SCC levels during

![Figure 1. Influence of pretreatment SCC on overall survival - Group B (<median: 79.2 % (2 years); >median: 48.8 % (2 years)).](image)
(chemo-)radiotherapy also reflected the clinical course of
disease: those patients, who had no significant decline of
tumor marker values, had a lower response rate and worse
outcome \((p<0.001)\). Patients with a SCC level below the
median of 7.2 U/ml had a significantly better prognosis and
a better treatment response than those above the median
\((p=0.001)\) (Figure 1). Uni- and multivariate analyses of the
most important prognostic factors are given in Table I.

Thirty-seven out of 144 (25.7\%) patients had a relapse
during the observation period. In 30 of these 37 patients, the
increase of serum SCC level preceded the clinical diagnosis
of relapse. This resulted in a sensitivity of 82\%. The median
lead-time was 4.5 months (range: 1 to 16 months).

**Discussion**

Our results indicate that SCC is a valuable tumor marker in
diagnosis, treatment monitoring and follow-up of patients with
squamous cell carcinoma of the uterine cervix. We could show
that 72\% of all patients had initially increased serum SCC
levels. Similar results were reported by Duk et al. (55.7\%),
Lozza et al. (57\%) and Abe et al. (87.7\%) (9-11). Duk and
Lozza also demonstrated a relationship between increased
serum SCC level and FIGO stage; Duk et al. additionally
observed a correlation between elevated serum SCC level and
pathological grading (9, 10), as we also showed in our patients.

We found a high sensitivity of 71\% and a very high
specificity of 98\% for serum SCC, as high as reported by
Gaarenstroom et al. (12) in their ROC analysis showing a
sensitivity of 70\% and a specificity of over 90\%. Duk et al.
(9) observed a substantially higher sensitivity at 85.5\%, but
a specificity of less than 90\%, resulting in a positive
predictive value of 49\% only.

The median lead-time between rising serum SCC levels
after therapy and clinical discovery of a relapse was 4.5
months in this analysis. This value ranged in the literature
between 2 and 13 months (13). However, it is unproven that
earlier detection of recurrent disease will lead to a better
survival. In general, recurrent cervical carcinoma often has
a poor prognosis, despite more extensive surgical
procedures such as pelvic exenteration (13-15).

Our analysis of the Münster patients with cervical
cancer showed a good correlation between serum SCC
level, therapy response and outcome. Patients with a SCC
value below the median of 7.2 U/ml had significantly
better prognosis and a better treatment response than
those above the median. Additionally, we found that
persistent increase of serum SCC levels during and after
(chemo-) radiotherapy was a strong predictor of
treatment failure. Similar results were also reported by
other authors (16). Our prognostic findings support
several reports in the international literature for patients
with squamous cell carcinoma of the uterine cervix
treated with radiotherapy (16-18) as well as with chemo-
radiotherapy (7, 8, 19, 20).

**Conclusion**

Serum SCC is a valuable tumor marker in patients with
squamous cell carcinoma of the uterine cervix. It is a
valuable tool for follow-up and after-care of these patients,
not only reflecting tumor response, but also providing
important diagnostic information for early detection of
relapse. In this retrospective analysis, the value of the SCC
correlated with prognosis in patients with carcinoma of the
cervix treated with (chemo-)radiotherapy.

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**Table I. Uni- and multivariate analysis of prognostic factors (Group A + Group B).**

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<th>Factor</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tr>
<td>Stage I/II</td>
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<tr>
<td>Stage III/IV</td>
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<tr>
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(p-value)
References


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