Clinical Value of Squamous Cell Carcinoma Antigen (SCCAg) in Anal Cancer – A Single-Center Retrospective Analysis

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Abstract. *Aim: To assess the clinical value of squamous cell carcinoma antigen (SCCAg) in anal cancer for chemoradiotherapy (CRT) patients. Patients and Methods: In 24 patients with SCC of the anus, SCCAg was determined before CRT and at every follow-up visit. Results: 16/24 (66.7%) had normal SCCAg and 11/16 (68.8%) achieved complete remission (CR), while 7/8 (87.5%) with elevated SCCAg achieved CR. In two patients, elevated SCCAg was observed after radiotherapy. One was false-positive and one was true-positive leading to diagnosis of metachronous recurrent and metastatic disease after interim CR. Conclusion: SCCAg was inappropriate to predict the clinical outcome but can provide additional information on the regular follow-up examinations to detect a relapse.*

There is a variety of tumor markers for diagnosis, treatment and monitoring of malignancies. Squamous cell carcinoma antigen (SCCAg) is a tumor marker expressed by many different tumor entities, such as head and neck cancer (1), cervical cancer (2), non-small cell cancer (3), esophageal cancer (4) and hepatocellular carcinoma (5).

Squamous cell cancer (SCC) of the anal canal and margin (SCCACM) are rare malignancies that are primarily treated with curative concurrent chemoradiation (CRT) with mitomycin C (MMC) and 5-fluororuracil (5-FU) (6, 7).

Prognostic factors in SCCACM are tumor classification (T), lymph node involvement (N+), grading, skin ulceration, tumor site (canal or perianal skin) and male sex (8, 9).

SCCAg is a tumor-associated antigen, first obtained from SCC of the uterine cervix (10), but also expressed in anal cancer (11). Median pre-treatment levels of SCCAg in patients with SCCACM who received CRT with MMC and 5-FU showed positive correlation with tumor classification and lymph node involvement (12). Compared to a normal pre-treatment SCCAg level, elevated pre-treatment SCCAg levels are associated with a lower complete response rate. In addition, overall survival (OS) and disease-free survival (DFS) are lower in patients with elevated pre-treatment SCCAg (12, 13). The clinical value of periodically measured post-treatment SCCAg levels compared to pre-treatment SCCAg levels in patients with SCCACM, regarding outcome and recurrence, remains uncertain.

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Patients and Methods

From 2010 to 2014, pretreatment serum SCCAg measurement was performed in 24 patients with suspected squamous cell carcinoma of the anal canal and/or margin before local excision was performed to confirm the diagnosis histologically. Blood samples for pretreatment measurement of SCCAg were taken at the first consultation at the proctologist. The upper limit of normal SCCAg was 1.5 μg/l. Patients with metastatic and/or recurrent disease were also excluded as patients who had received prior pelvic radiation. Then, all patients received a primary curative CRT with MMC and 5-FU. The pelvic dose was 45.0 Gray (Gy) in nodal-positive carcinomas and 39.6 Gy in nodal-negative carcinomas. In the resonance imaging, pathologically enlarged lymph nodes received a boost to 50.0 Gy. The applied dose in the anal tumor areas was stage-dependent. T1 and T2 tumors received 50.0 Gy and 56.0 Gy was applied to T3 tumors. Sequential serum SCCAg measurement after chemoradiation was performed in 21 patients, additionally to the regular follow-up examinations (imaging of the pelvis and rectoscopy) at first at a three-month interval for two years and then twice a year. SCCAg pretreatment values were compared with post treatment values at the last follow-up examination regarding outcome and disease recurrence.

Results

All patients received concurrent CRT as primary treatment. Concurrent CRT comprised of MMC (12 mg/m^2 body surface area) on day 1 and 29; and 5-FU (1,000 mg/m^2 body

Table I. *Baseline characteristics for all 24 patients.*

Variable	N
Gender	
Men	12
Women	12
Age: Median age (range)	55.5 (41-91)
Follow-up: Median in months (range)	14.2 (2.7-40.9)
Location	
Anal canal	16
Anal margin	7
Anal canal and margin	1
Treatment	
CRT with MMC and 5-FU	21
RT alone	3

Table II. *Clinical tumor classification according to UICC V. 7.0.*

Stage	N
I (T1 N0)	3
II (T2-3 N0)	11
III (T4; N+)	10

surface area) on day 1 to day 4 and day 29 to day 32 of radiotherapy. The median age was 55.5 years (range=41-91). The median follow-up was 14.2 months (range=2.7-40.9). In 3 patients, chemotherapy was waived due to advanced age and/or severe comorbidities. These patients underwent a sole radiation with the mentioned doses. All patients had at least 1 follow-up visit. Baseline patients' characteristics and treatments are summarized in Table I, while data on tumor classification, according to Union Internationale Contre le Cancer (UICC), are provided in Table II.

The pre-treatment levels of SCCAg in 24 patients according to UICC tumor stages V. 7.0 were 1.6 μg/l in stage I tumors (T1N0M0; n=3), 1.1 μg/l in stage II tumors (T2-3N0M0; n=11), 1.1 μg/l in stage III tumors (N+ status; n=10). In 3 patients, no post treatment SCCAg levels were available; n=1 in stage II and n=2 in stage III. The patient with stage II SCCAM had an elevated pre-treatment SCCAg but follow-up examinations (imaging of the pelvis and rectoscopy) were unremarkable. Two patients with stage II tumor had normal SCCAg values before chemoradiation was carried out. One of them presented with recurrent lymph node metastases.

The median post-treatment levels of SCCAg decreased in UICC stage I (SCCAg=1.0 μg/l; n=3) and II (SCCAg=0.8 μg/l; n=10) tumors, while a slight increase in patients with stage III tumors was observed (SCCAg=1.2 μg/l; n=8) (Figure 1) due to one false-positive result and one simultaneously recurrent and metastatic disease. Of the 16 patients who had normal SCCAg levels, 11 (68.8%) achieved a complete remission after initial treatment. One patient developed local recurrent disease. He received a salvage abdominoperineal resection and is still disease-free. Two patients presented with distinct metastases of the liver and the lung, respectively. Two patients with initial lymph node metastases developed recurrent lymph node metastases and distinct metastases of the skin and lung, respectively. Two patients were presented with increased post treatment serum SCCAg; the first case was a false positive value where further examination excluded recurrent or distant disease, while the second case was diagnosed as metastatic and recurrent disease.

Table III. *Clinical outcome of patients with normal and elevated SCCAg.*

Variable	Normal SCCAg; n=16	Elevated SCCAg; n=8
Complete response	11/16	7/8
No complete response		
Isolated metastases	2	0
Metastases and local recurrence	2	1
Local recurrence	1	0
Alive	16	7
Deceased	0	1

Seven out of 8 patients (87.5%) with elevated pretreatment SCCAg (>1.5 μg/l) achieved complete response. One patient had recurrent ulcerative lymph node metastases and died to lethal arterial bleeding. His SCCAg level was still normal. The clinical outcome of patients with and without elevated pretreatment SCCAg is shown Table III.

The clinical outcome in patients without lymph node (stage I and II) and lymph node involvement (stage III) is as follows: Ten out of 24 patients had initial lymph node involvement, of which six had normal and four increased baseline SCCAg values. One of these developed local recurrent disease, although his SCCAg value was still normal. Four out of 6 patients with normal pre-treatment SCCAg developed recurrent and/or metastatic disease. One of these presented with an increased value greater than 1.5 μg/l (upper limit of normal SCCAg) and was diagnosed with simultaneous recurrent and metastatic disease. In two patients, no follow-up SCCAg values were available. One patient without any SCCAg values after CRT, who belonged to the group of patients with normal SCCAg prior to CRT, presented with recurrent lymph node metastasis and metastatic disease.

Of the 14 patients without lymph node involvement (stage I and II), increased baseline SCCAg values were measured in 4 patients prior to CRT with MMC and 5-FU; all in clinical complete remission at their last follow-up

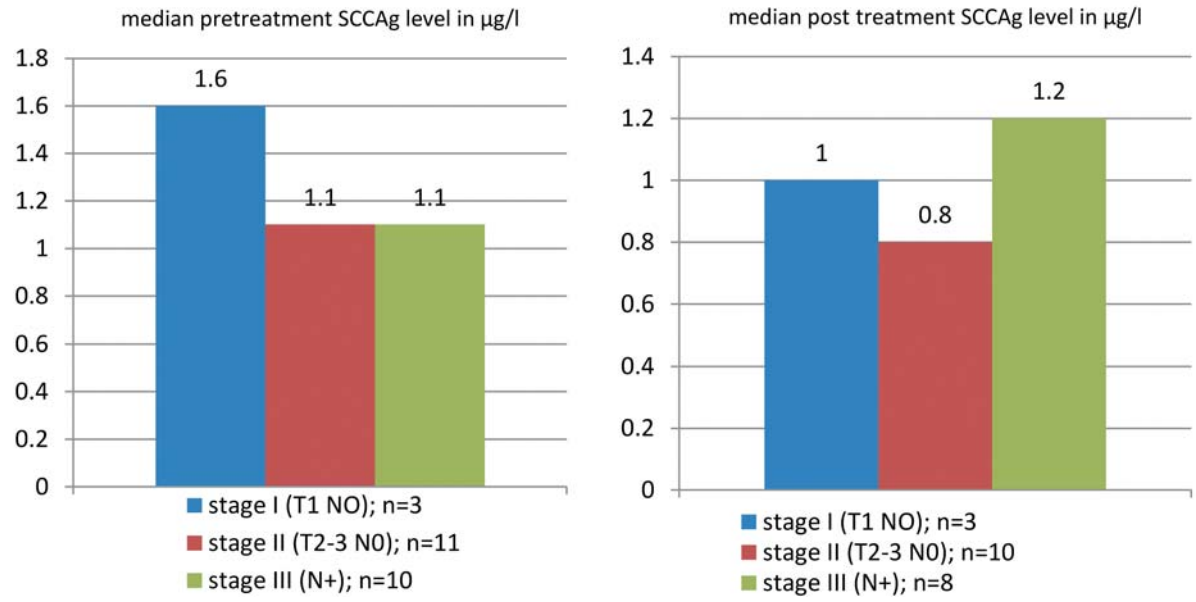

Figure 1. *Pre- and post-therapeutic levels of SCCAg according UICC stages V. 7.0 of SCCAM.*

examination. In one patient with increased pre-therapeutic SCCAg, no follow-up measurement was performed. An increase in SCCAg above the upper limit of 1.5 µg/l until the last follow-up examination was also not observed in the other patients. One out of ten patients with normal pretreatment SCCAg developed metastatic disease, while the SCCAg was still normal. In another patient, a false-positive rise of SCCAg was observed; however, an extended tumor search did not reveal any local recurrence and/or distinct metastases or other malignancy. The clinical outcome is summarized in Table IV.

Sensitivity at diagnosis was 33.3%. In the follow-up, SCCAg showed a 16.6% sensitivity and 93.3% specifity. The post treatment positive predictive value (ppv) for relapse was 50.0% and the post treatment negative predictive value (npv) was 73.7%.

Discussion

We investigated the clinical value of periodically measured post treatment SCCAg levels at the last follow-up examination compared to pretreatment SCCAg as a further component of the follow-up examinations (rectoscopy and imaging of the pelvis) after a curative chemoradiation with MMC and 5-FU in patients with SCCACM regarding outcome and recurrence. Other histological types than SCC were excluded from this study. Regardless of the retrospective character of this study, its strength is the consistent treatment with curative standardized chemoradiation with MMC and 5-FU. Only three patients did not receive concomitant chemotherapy. Furthermore, patient with recurrent and/or metastatic disease were also excluded from this analysis, as patients who had prior pelvic irradiation or in which a different concept of chemoradiation, such as neoadjuvant therapy, was performed.

Approximately 30-40% of patients with SCCAM have initial lymph node involvement (14). In our study, 10 out of 24 (41.6%) patients had lymph node metastases in diagnostic imaging prior to CRT.

As described in the literature (7, 12, 15), we also observed that patients with initial lymph node metastases have a worse outcome than patients without initial lymph node involvement; however, if clinically enlarged lymph nodes in patients with SCCAM are biopsied, only in 50% the clinical diagnosis is histologically confirmed (16). Five of ten patients with N+ status developed during medical course recurrent and/or metastatic disease, which is a complete response rate of 50.0%, whereas only 1 of 14 patients without lymph node involvement developed distant metastasis, which is a complete response rate of 92.9%. These clinical results emphasize the importance of initial lymph node involvement in SCCAg for patients' outcome. The pre-treatment SCCAg level, in our study, does not reflect the correlation between nodal involvement and increased baseline SCCAg, as was shown by Williams *et al*. (12), when normal median pretherapeutic SCCAg was observed in stage III. Fontana *et al*. also showed that increased baseline SCCAg does not offer any prognostic value (17). Instead, the median baseline SCCAg was increased

Table IV. *Clinical outcome of patients with and without lymph node involvement and the corresponding results of SCCAg before and after chemoradiation (CRT).*

Outcome variable	Lymph node involvement (stage III)		No lymph node involvement (stage I+II)	
	Patients (n=4) with increased baseline SCCAg	Patients (n=6) with normal baseline SCCAg	Patients (n=4) with increased SCCAg after CRT	Patients (n=10) with normal SCCAg after CRT
Complete response	n=3	n=2	n=4	n=10
	n=5 (50.0%)		n=13 (92.9%)	
Recurrence	n=1	n=1	n=0	n=9
Metastases	n=0	n=2	n=0	n=1
Recurrence + metastases	n=0	n=1	n=0	n=0
	Increased SCCAg after CRT			
	0	1 false positive	0	1 true positive
	No SCCAg after CRT available			
	2 (one complete response and one recurrent+ metastatic disease)	0	1 (complete response)	0

in stage I (1.6 μg/l; upper limit: 1.5 μg/l). This might be related to the small number of patients and the sensitivity of approximately 50% (11, 15) at diagnosis. These circumstances may also explain why 87.5% of patients with increased pretreatment SCCAg achieved complete remission and that a complete remission was only observed in 68.8% of patients with initial normal SCCAg, although it has been shown, in two larger retrospective studies (12, 13), that patients with increased SCCAg prior to treatment have more often disease recurrence. Furthermore, three of ten patients with and none without lymph node involvement were immunocompromised.

To our best knowledge, there are no data on the reliability of SCCAg in immunocompromised patients. Six patients (stage-independent) developed recurrent and/or metastatic disease, which is a post treatment SCCAg sensitivity of 16.6% and a ppv of 50% due to one false positive value. An encouraging result is the high-follow-up specifity of 93.3% and npv of 73.3%. This confirms the results of Indinnimeo *et al.* (18) who observed post treatment SCCAg specifity of 93% and sensitivity of 0% in 18 patients with SCCACM. Even small, not pathologically enlarged lymph nodes, when monitored by imaging, may be tumor-affected (16); therefore, the high follow-up sensitivity of SCCAg might be important for patients with slightly enlarged lymph nodes (12).

We used the manufacturer's recommended cut-off <1.5 μg/l, although in cervical cancer a cut-off >4.4 μg/l was proposed to achieve better disease discrimination (19). The prognostic value remains uncertain, particularly when pretreatment SCCAg was in a multivariate analysis not statistically associated with tumor classification and nodal status at diagnosis, suggesting that SCCAg captures other tumor characteristics than clinical gathered data (12). Another limitation of this study is -apart from the small number of patients- the median follow-up of 14.2 months as, in larger studies, patients without lymph node involvement had an 5-year OS of approximately 85% and 58% in case of nodal involvement, respectively (20). However, most recurrences occur within 2 years, although in a few cases distant metastases occurred up to 11 years after diagnosis (21).

In summary, pre-treatment SCCAg levels, in our SCC collective of the anal canal treated with chemoradiation, were not appropriate to predict the clinical outcome and yielded only some additional information, particularly in patients without nodal involvement and in patients with an increased post treatment SCCAg. This emphasizes the importance of regular clinical follow-up examinations (including imaging) and confirms clinical practice. Yet, increased SCCAg levels after chemoradiation are suspicious for recurrent and/or metastatic disease and provide additional information to the clinician.

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