ANTICANCER RESEARCH *25*: 1539-1542 (2005)

Tumor Markers and Lymphatic Metastasis in Head and Neck Cancer Patients

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Abstract. *Objective: This study was conducted to evaluate the relationship between the lymph node status and tumor marker status in patients with histologically confirmed head and neck cancer. Materials and Methods: 134 patients were included in this retrospective analysis. 33/134 were classified as N0 and 101/134 as N+. The wall of the lymph node was ruptured by the metastasis in 70/134 patients (poor prognosis). We analyzed the sensitivity of squamous cell carcinoma antigen (SCC), carcinoembryotic antigen (CEA) and CYFRA 21-1 in the total population and in the subgroups. Results: We observed elevated SCC levels in 21.6%, CEA levels in 23.9% and CYFRA 21-1 levels in 50.0% of all patients. If there was no lymphatic metastasis, the SCC sensitivity was 15.1%, the CEA sensitivity was 21.2% and the CYFRA 21-1 sensitivity was 36.4%. Lymph node-positive disease had increased SCC levels in 23.8% of the patients, increased CEA levels in 24.8% and increased CYFRA 21-1 levels in 54.5%. The subgroup of patients with ruptured lymph nodes had the following sensitivities: SCC 18.6% CEA 8.6%, and CYFRA 21-1 50.0%. Conclusion: No significant relationship between the lymph node metastasis and the elevation of tumor markers in patients with advanced head and neck cancer was found.*

It is well known that the status of cervical lymph nodes is the most important prognostic factor in squamous cell carcinoma of the upper aerodigestive tract. The presence, number, volume and extranodal spread of cevical lymph nodes reduces local control and overall survival in patients with advanced cancer of the head and neck region (1). Various tumor markers have been used in this patient group in the past. Despite the high cost of each laboratory investigation, the sensitivity of the studied markers was low, and, thus, they were not established in daily practice (2).

The present study analyzed the relationship between the elevation of selected tumor markers and the status of lymphatic metastasis.

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Key Words: Head and neck cancer, lymphatic metastasis, SCC, CYFRA 21-1, CEA.

Materials and Methods

Methodological remarks. Three methodological questions had to be clarified before starting the retrospective analysis of our data pool:

1. Is the N-status an equivalent parameter to define the lymphatic metastasis? The hypothetical answer is "no". Table I summarizes the actual N-classification according to the TNM-criteria (1997 version) (19). Two reasons should be noted. At first, the prognostic difference between N0– and N+ patients is already the most important one. Secondly, the quality of clinical classification has improved during recent years because of the indroduction of ultrasound, CT and MRI in clinical practice.

2. Which parameter is the most important regarding the lymphatic metastasis? The continued growth of the tumor through the wall of the lymph node seems to be very important. This extranodal spread is the most negative point in the mode of lymphatic metastasis of the individual patient.

3. Which are the most usual tumor markers for head and neck (HNC) patients? While squamous cell carcinoma antigen (SCC) and carcinoembryonic antigen (CEA) have low sensitivities, the published data of Niemann *et al.* (2) suggest that CYFRA 21-1 may be a marker with higher sensitivity and specificity. Because of the confusing data in the literature, we measured all the tumor markers, describing the sensitivity in the group of histological confirmed squamous cell carcinoma of the head and neck.

Patients. We analyzed the data of 134 patients (121 men, 13 women) who were treated at the Department of Otolaryngology, Plastic Surgery (Head: Klaus Küttner, MD) of the Municipal Hospital Suhl, Germany, between 1981 and 1998. The mean age

Table I. *N-classification according the TNM system 1997 (19).*

Localization	N-Stage	Description
Epipharynx	Nx	Regional lymph nodes can not be assessed
	N0	No regional lymph node metastasis
	N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above supraclavicular fossa
	N2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above supraclavicular fossa
	N3	Metastasis in lymph node(s), more than 6 cm in dimension, in the supraclavicular fossa
Head & Neck (Others)	Nx	Regional lymph nodes can not be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
	N2	(a) Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension (b) Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension (c) Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
	N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Table II. *Tumor localization and UICC stadium.*

	UICC I	UICC II	UICC III	UICC IV
Larynx	2	2	6	8
Oropharynx	0	3	9	38
Hypopharynx	0	3	6	44
Epipharynx	0	1	0	1
Cavum oris	0	2	1	3
CUP	0	0	0	5
Total	2	11	22	99

Table III. *TNM classification.*

T	1	2	3	4	X
N0	2	11	10	10	0
N1	1	2	9	13	0
N2	2	8	8	31	3
N3	2	3	1	16	2

Table IV. *Reference values of the used tumor markers.*

Marker	Normal values	Pathological values
SCC antigen	<1.8 ng/ml	>2.2 ng/ml
CEA	<3.5 ng/ml	>4.5 ng/ml
CYFRA 21-1	<2.0 ng/ml	>2.2 ng/ml

was 57.5 years (±11.2 years) at the time of diagnosis. The patients were coincidentally selected out of 865 patients treated at this department during this period.

The N-status was re-categorized according to the TNM-system of 1997 (19). A neck dissection was performed in 80/134 patients. Table II describes the localization and UICC stage of the disease, Table III shows the TNM data of the patients.

Methods. All blood samples were taken after histological confirmation of cancer of the head and neck region and before starting surgery and/or radiochemotherapy. SCC, CEA and CYFRA 21-1 were measured at the clinical laboratory of the Hospital Suhl (Head: Klaus Zimmermann, PhD), that is controlled by external quality assurances. The used reference intervals are shown in Table IV. The survival data were calculated according to the patients files at the out-door archive of the Department of Radiotherapy at Suhl (Head: Dietmar Fröhlich, MD). The histological diagnosis was performed at the Department of Pathology Suhl (Head: Ulrich Schütze, MD). MRI and CT scans were produced at the Institute of Radiodiagnostics, Suhl (Head: Norbert Albrecht, MD) and the ultrasound was performed by the colleagues of the ORL department Suhl (including JB and AH).

Results

N-status. We analyzed the ratio N0:N1:N2:N3 in different time-intervals. Before 1990, the nodal status was classified by palpation alone. In 1994, CT scan was established in the routine diagnostic staging procedures and, since 1997, MRI scans have been used routinely. Figure 1 shows the increasing proportion of patients with N1-classification over the years. Because of this shift, all following analyses were done with 33 N0 patients and 101 lymph node-positive (N+) patients. 70/101 N+ patients showed a ruptured lymph node capsula, *e.g.* extranodal spread, with a poor prognosis for the patient.

Table V supports our methodology with the most important step in the prognosis of patients being made with the shift from N0 to N1.

Tumor markers. The SCC antigen was elevated in 25% of all patients (sensitivity). Patients without lymph node metastasis showed increased SCC levels in only 15%,

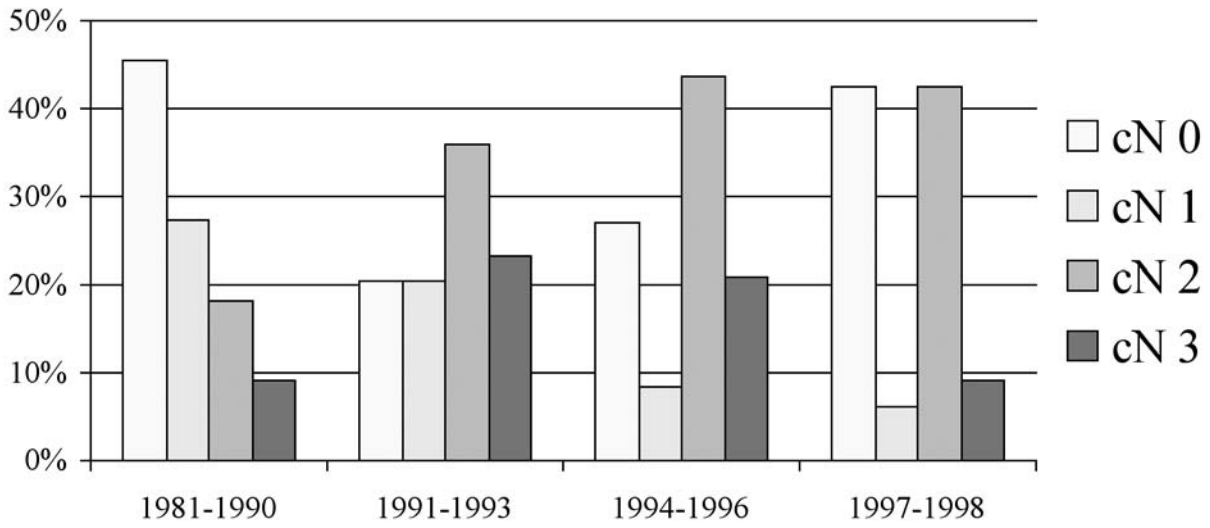

Figure 1. *TNM distribution at different diagnostic levels (time-periods).*

Table V. *p values (log rank) regarding the N status and overall survival*

N	0	1	2	3
0	-	0,03	0,02	0,01
1	0,03	-	0,71	0,90
2	0,02	0,71	-	0,35
3	0,01	0,90	0,35	-

compared to a sensitivtiy of 24% in patients with lymph node-positive disease. The histological diagnosis of extranodal spread had no influence on the sensitivity of the SCC antigen. Log rank showed no significant difference between N0 and N+ groups ($p=0.404$).

CEA showed a sensitivity of 24% in total. Twenty-one % of N0 patients and 26% of N+ patients had increased CEA values, $p=0.704$. Only 9% of the patients with ruptured lymph nodes capsules showed elevated CEA.

Pathological elevated CYFRA 21-1 values were observed in 50% of all patients. If the patient was classfied as N0, the sensitivity was 37.5% compared to 56% in N+ patients. The subgroup with extranodal spread had a sensitivity of 50% only.

Figure 2 summarizes the percentages according to N-status and the different tumor markers.

Discussion

The diagnostic and therapeutic methods for the management of lymph node metastasis of advanced head and neck cancer are still being discussed (3, 4). The main reason is the importance of this locoregional control for the prognosis of the patients. Since expensive modern methods (PET scan, sentinel lymph node scintigraphy *etc*.) have been investigated by different groups with contrary results (5-8), the usage of tumor markers has been established in few study groups as a daily practice (9, 10).

In a former study we described the possibility of recognizing recurrent disease by the warning system of serum markers earlier and we had hoped to apply this timely advantage in a better and more successful treatment of the recurrent disease (11). To date, we have no real answer regarding this hope.

The squamous cell carcinoma antigen, as well as the carcinoembryogenis antigen, showed a low sensitivity (less than 50%) in our patients. Their measurement was only indicated for cases of primary (baseline) increased data. This observation supports the opinion of other authors regarding these markers (12, 13). A high sensitivity of CYFRA 21-1 was seen in several studies: Niemann *et al.* (2) reported about 60% of increased CYFRA 21-1. Luo *et al.* (14) also reported similar results in their subgroup of patients with advanced laryngeal cancer. In contrast, Pradier *et al.* (15) have reported a low sensitivity of this marker. Only 30% of all patients had elevated serum markers and the authors did not recommend the usage of CYFRA 21-1 in the monitoring of radiotherapy patients with tumors in the head and neck region.

Our basic hypothesis has already been discussed in the paper of Adamiak *et al.* (16). They demonstrated a characteristic correlation in 146 patients between the concentration of SCC antigen and the presence of metastases to regional lymphatic glands, using the R-Spearman correlation. Similarly, we found increasing

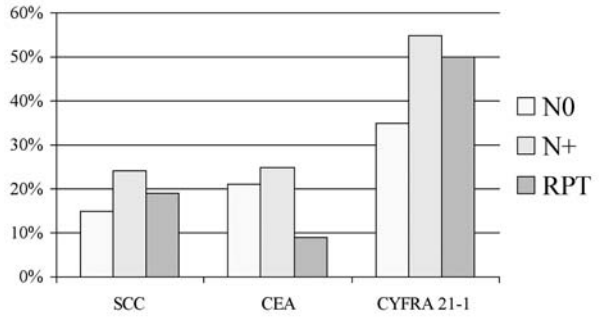

Figure 2. *Sensitivity of different markers related to stage of lymphatic disease (RPT – extranodal spread).*

incidences of elevated SCC antigens, CEA and CYFRA 21-1 with lymphatic metastasis. No correlation was seen in our group between the extranodal spread of lymphatic metastasis and the changing incidences of tumor markers. This result is difficult to explain, because the continuing growth of the tumor through the wall of the nodal capsule is the most important step for the patients' prognosis. Patients with distant metastasis have shown higher incidences of elevated CYFRA 21-1 levels again (17).

In summary, our results have not shown a strong correlation between the histological picture of lymphatic metastasis and the behavior of the tested tumor markers CYFRA 21-1, SCC antigen and CEA. In our opinion, the measurement of such serum markers has a low clinical value in the primary diagnosis, as well as the monitoring of the therapeutic response (18).

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Received August 2, 2004
Accepted February 8, 2005