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Orosomucoid:Prealbumin Ratio—a Marker of the Host–Tumor Relationship in Head and Neck Cancer

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Abstract—*The OPR was studied in* 203 *patients with squamous cell carcinoma of the head and neck at the time of diagnosis, before any specific treatment. The mean initial OPR value was significantly higher in cancer patients than in* 63 *healthy controls*: 5.29 ± 3.09 *vs.* 2.63 ± 1.07; $P < 0.001$. *There was no significant difference by anatomic site, but the OPR was significantly lower in stage I–II disease than in stage III–IV*: 5.10 ± 3.85 *vs.* 3.23 ± 1.99, $P < 0.001$. *An initial OPR under or over* 6 *seems to be an important prognostic factor: at* 2 *years,* 51% *of patients with an OPR* < 6 *were alive vs. only* 24.5% *of those with an* OPR > 6, $P < 0.001$. *The difference was also noted in patients with stage III–IV disease (mean survival:* 16 *months vs.* 7 *months,* $P < 0.001$) *and in* 89 *of the patient who received chemotherapy (mean survival* 16 *months vs.* 6 *months,* $P < 0.001$) *whatever the response to chemotherapy. The OPR index, which explores nutritional and acute phase reactant proteins, seems to reflect the host–tumor relationship. Its initial value is strongly related to prognosis at* 2 *years.*

1. INTRODUCTION

Orosomucoid, α1-acid glycoprotein, is an acute phase reactant protein. Its serum level is frequently elevated in cancer patients [1–5]. Prealbumin, a nutritional protein, is often decreased in these same patients [6–11]. Following the results published by Hollinshead *et al.* [10] emphasizing the usefulness of the orosomucoid:prealbumin ratio (OPR) as a marker of the host–tumor relationship, we conducted a preliminary study which demonstrated the existence of a significant relationship between the OPR, the evolution and the extension of cancerous pathologies. In addition, this ratio was found to have an unquestionable prognostic value at the time of diagnosis [12, 13].

The present study concerns 203 head and neck cancer patients; such pathologies are generally characterized by their local–regional spread, and are accompanied by inflammatory phenomena in often malnourished patients [14].

2. PATIENTS AND METHODS

2.1. *Patients*

The OPR was evaluated in 203 patients between 1978 and 1982. There were 180 men and 23 women, mean age 64 years (range 29–92). All patients had an epidermoid carcinoma of the upper aerodigestive tract. The various anatomic disease sites and classifications (TNM, CIM) are listed in Table 1. The OPR was also analyzed in 63 healthy individuals whose ages were similar to those of the cancer patients.

Initial treatment consisted in a multidrug chemotherapy regimen (91 patients), irradiation (75 patients) or surgery (37 patients). Average patient survival was 24 months (range 1–83). A total of 185 patients were followed up for over 1 year or died during this period. The OPR was evaluated prior to any therapy, then during the entire disease course for 158 patients.

The OPR was also analyzed as a function of disease evolution: patients were classified either as being in complete remission, with no apparent clinical, radiological, endoscopic or biological signs of lesions, or as having perceptible disease; this last category was subdivided into progressive disease, regression or stable disease.

2.2. *Assay techniques*

Orosomucoid and prealbumin were measured in serum using the modified Mancini method of radial immunodiffusion [15]. Normal values ranged from

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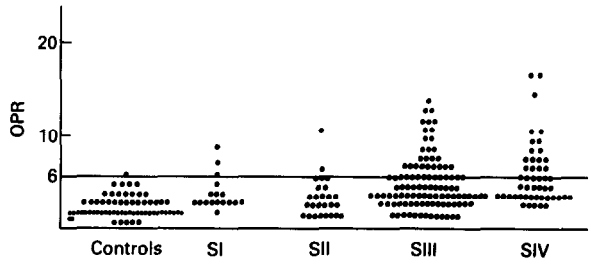
Table 1. Head and neck cancers. OPR distribution as a function of the disease site and stage

Site (CIM code)	No. of cases	Distribution by stage I	II	III	IV	X	Initial OPR (mean ± S.D.)
Lip and oral cavity (140–145)	77	10	10	42	13	2	5.08 ± 3.23
Oropharynx (146)	53	3	2	34	14	0	5.98 ± 3.29
Rhinopharynx–nasal fossa (147, 160)	8	1	0	1	3	3	4.53 ± 2.22
Hypopharynx (148)	29	1	4	16	8	0	5.29 ± 2.65
Larynx (161)	28	2	9	10	5	2	4.91 ± 2.99
Upper aerodigestive tract (poorly defined) (149)	8	0	1	1	5	1	—
Total	203	17	26	104	48	8	5.29 ± 3.09
Controls	63						2.63 ± 1.07 ($P < 0.001$)

Table 2. Head and neck cancers. OPR as a function of the disease stage



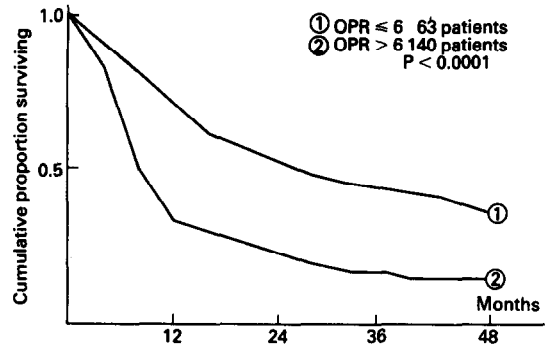


Fig. 1. Global survival as a function of OPR.

0.20 to 0.40 g/l for prealbumin and from 0.60 to 1.20 g/l for orosomucoid. In the healthy control population, the OPR value was lower than 6. Statistical tests (Student's *t* test, variance analysis, Mann and Whitney test, Krussal–Wallis test) were performed with a BMDP program [16] operating on a VAX 11/730 computer (Digital Equipment Corp.). Actuarial survival figures were compared by the log-rank test, and Cox's model was used to analyze survival with covariates.

3. RESULTS

3.1. *Study of initial OPR values prior to treatment*

The average initial OPR value was significantly higher in the 203 patients than in the controls: 5.29 ± 3.09 vs. 2.63 ± 1.07 ($P < 0.001$). As shown in Table 1, there was no significant difference as a function of the anatomic tumor site. By contrast, tumor size had an important role: the OPR of patients with a T4 tumor was higher than that of T3 patients (8.23 ± 4.97 vs. 5.78 ± 3.09; $P < 0.002$), and the average OPR of WHO stage III and IV patients was higher than that of stage I and II patients (5.70 ± 3.23 vs. 3.85 ± 1.99; $P < 0.0001$) (Table 2). No significant difference was noted as a function of the initial treatment (chemotherapy, radiotherapy or surgery).

3.2. *Study of OPR value during disease course*

3.2.1. *OPR and overall survival.* As illustrated by Fig. 1, patients with an initial OPR < 6 survived longer than other patients (median survival 26 months vs. 8 months, $P < 0.0001$). At two years, 51% of patients whose initial OPR was < 6 were still alive vs. only 24.5% of those who had a higher value.

3.2.2. *OPR and disease evolution.* The OPR was determined more than twice for 145 patients; in 87.6% of cases, variations in this ratio concurred with disease evolution. During disease remission or regression, the OPR remained stable if it was initially < 6, and tended to decrease if it was initially > 6. By contrast, OPR rose in all cases of progressive disease.

3.2.3. *OPR and disease stage.* Comparison of stage I and II patients with stage III and IV patients

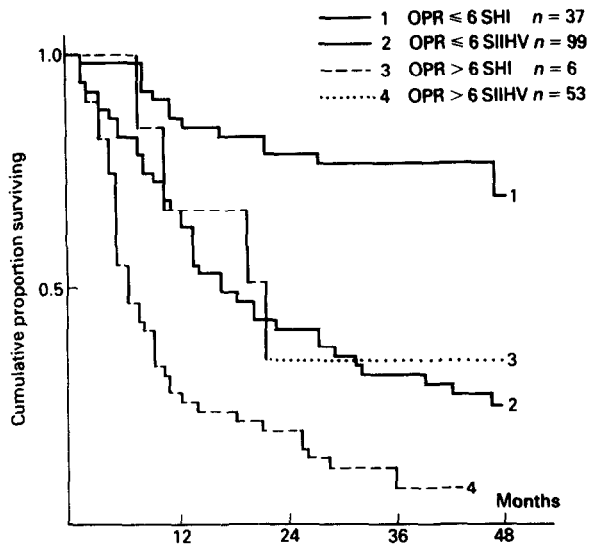


Fig. 2. Survival according to disease stage and OPR.

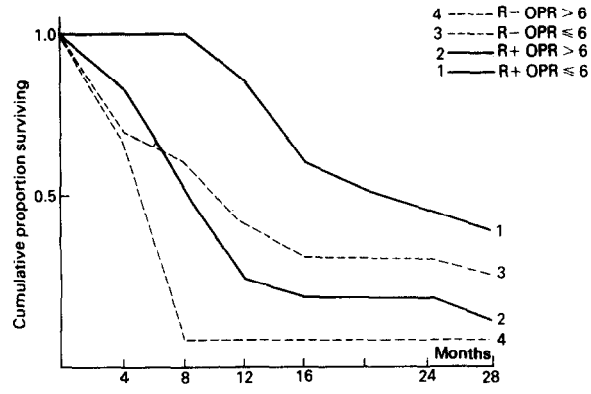


Fig. 3. Survival according to response (R+ or R−) to primary chemotherapy.

revealed a significant difference in the survival of these two groups: median survival was 69 months for stage I and II vs. 12 months for stage III and IV ($P < 0.0001$). Within each of these two groups, survival differed according to the initial OPR value. For stages I and II, the median survival was not reached at 6 years when the OPR was < 6 and it was 20 months when the OPR was > 6 ($P = 0.02$); in the stage III and IV patients, median survival was 16 months vs. 7 months ($P < 0.001$) (Fig. 2). There was no difference in WHO status among the different subsets of stage III and IV patients.

3.2.4. *OPR and induction chemotherapy.* The initial treatment for 91 patients consisted of an induction chemotherapy regimen including vincristine, bleomycin, methotrexate and *cis*-platinum. Fifty-five patients showed an objective response, with more than 50% reduction in the size of the tumor mass.

The OPR value was not significantly different for responders and non-responders (5.43 ± 2.82 vs. 6.23 ± 4.15). With this chemotherapy protocol, the survival of responders at 2 years was not significantly better than that of non-responders. However, if the initial OPR value is taken into account, the survival of patients who responded to chemotherapy and whose initial OPR was < 6 was significantly longer than that of responders whose initial OPR was > 6; survival for this last group was similar to that of the non-responders (Fig. 3). This observation shows the independence of the two factors (response to chemotherapy and OPR) as far as survival is concerned.

4. DISCUSSION

The findings of this study confirmed the results of our preliminary investigations covering 132 patients with various cancers [12].The present research was aimed at defining the value of the OPR in a homogeneous population of head and neck cancer patients; such patients are often malnourished owing to the mechanical complications caused by upper aerodigestive tract lesions, and many of these patients have a history of alcohol and tobacco abuse. In addition, these patients frequently present with major inflammatory reactions, even when they have focal lesions.

Prealbumin is a protein which accurately reflects the nutritional status of patients [11, 17–19], while orosomucoid assays are among the best screening tests for the detection of inflammatory syndromes of neoplastic origin and their consequences [20]. The relationship between nutrition and immune competence and the role of orosomucoid in cell growth are known [21–23]. A prognostic significance has been reported for acute phase reactant proteins [2, 4]. However, inhibition of hepatic synthesis of prealbumin seems to be related to malignancies more than to malnutrition [10, 25]. As in other cancers, the OPR at the time of diagnosis, prior to any treatment, was higher in head and neck cancer patients than in healthy controls. In prostatic cancer patients, this ratio has been described as a marker of the disease [26].

No significant difference was seen as a function of the anatomic disease site. By contrast, the OPR was linked to both tumor size and the extent of local–regional involvement: the OPR was higher for T4 tumors than for T3 lesions; it was also higher for stage III and IV disease than for stage I and II. The OPR thus appears to reflect both the tumor mass and the disease course.

The OPR was also studied on a longitudinal basis during the course of the disease. In 87.6% of cases, the OPR varied in the expected direction: it tended to rise when the disease progressed and dropped to normal values when regression occurred. By contrast, the OPR has no short-term predictive value because variations preceded modifications in

the nature of the disease in only 27 out of 145 cases. In the long term, however, the OPR appears more valuable. The survival of patients whose initial OPR was < 6 was significantly longer than that of patients whose OPR was > 6. The difference was also significant as a function of disease extension. Survival was linked both to the disease stage [27] and to OPR value, although these two factors are independent of each other. Thus, when the initial OPR was high, survival was just as short for patients with stage I and II disease as it was for patients with stage III and IV lesions. In patients initially treated by chemotherapy, neither the OPR nor the disease stage were predictive of response to treatment; this observation concurs with previous reports [28–30].

This multidrug regimen combining vincristine, bleomycin, methotrexate and *cis*-platinum did not produce any difference in survival at 2 years between responders and non-responders, whereas one of our more recent regimens using *cis*-platinum and 5-fluorouracil has produced differences [31, 32]. However, the survival of responders differed significantly depending on whether their initial OPR was greater than or equal to 6 or less than 6. The orosomucoid: prealbumin ratio thus appears to be a non-specific but highly useful marker of the host–tumor relationship in head and neck cancer patients. In parallel with OPR evaluations, we are currently investigating other clinical and biological tests of nutrition with the aim of increasing accuracy and specificity.

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