Prognostic Value of Tumor-Infiltrating CD4+ T-Cell Subpopulations in Head and Neck Cancers

Cécile Badoual,1,3 Stéphane Hans,4 José Rodriguez,6 Severine Peyrand,5 Christophe Klein,2 Nour El Houda Agueznay,1 Véronique Mosseri,7 Ollivier Lacourreye,4 Patrick Bruneval,3 Cécile Badoual,1,3 Stéphane Hans,4 José Rodriguez,6 Severine Peyrand,5 Christophe Klein,2 Nour El Houda Agueznay,1 Véronique Mosseri,7 Ollivier Lacourreye,4 Patrick Bruneval,3 Cécile Badoual,1,3 Stéphane Hans,4 José Rodriguez,6 Severine Peyrand,5 Christophe Klein,2 Nour El Houda Agueznay,1 Véronique Mosseri,7 Ollivier Lacourreye,4 Patrick Bruneval,3

Abstract

Purpose: CD4+ T cells play a central role in initiating and maintaining anticancer immune responses. However, regulatory CD4+CD25+ T cells which express Foxp3 have also been shown to inhibit antitumor effectector T cells. In view of these heterogeneous CD4+ T-cell populations, this study was designed to determine the prognostic value of various tumor-infiltrating CD4+ T-cell populations in head and neck squamous cell carcinoma.

Experimental Design: Eighty-four newly diagnosed untreated patients with histologically proven primary head and neck squamous cell carcinoma were included in this study. Double or triple immunofluorescence staining was done to assess and quantify the activated CD4+CD69+ T cells, regulatory CD4+Foxp3+ T cells, and mixed CD4+CD25+ T cells comprising both activated and regulatory T cells.

Results: On univariate analysis, high levels of tumor-infiltrating CD4+CD69+ T cells were correlated with both better locoregional control (P = 0.01) and longer survival (P = 0.01). Infiltration by regulatory Foxp3+CD4+ T cells was positively associated with a better locoregional control of the tumor. Multivariate analysis showed that the only significant prognostic factors related to locoregional control were T stage (P = 0.02) and CD4+Foxp3+ T-cell infiltration of the tumor (P = 0.02). In the Cox multivariate analysis, only two variables influenced overall survival probability: T stage (P = 0.036) and CD4+CD69+ T-cell infiltration (P = 0.017).

Conclusion: This study shows that tumor-infiltrating activated CD4+CD69+ T cells are associated with a good prognosis in head and neck squamous cell carcinoma. In addition, regulatory Foxp3+CD4+ T cells are positively correlated with locoregional control may be through downregulation of harmful inflammatory reaction, which could favor tumor progression.

Patients with head and neck squamous cell carcinoma have benefited from recent advances in radiation therapy, chemotherapy, and surgical techniques. However, despite new treatment modalities and their success in terms of organ preservation and overall quality of life, survival rates for this disease have not improved over recent years (1).

Extensive analysis of the phenotype of tumor cells by genetic and molecular approaches, designed to provide a better understanding of the biology of this aggressive tumor, has led to the identification of abnormalities that are often present during progression of head and neck cancer (loss of chromosomal region 9p21 associated with the P16 tumor suppressor gene, high levels of P53 mutations, overexpression of epidermal growth factor receptor, vascular endothelial growth factor, and cyclin D1, etc.; ref. 2). Antibodies or inhibitors directed against some of these amplified molecules are currently under clinical investigation (3, 4).

Head and neck tissues with a normal or benign appearance (i.e., minimal dysplasia) already contain clonal genetic changes such as mutations, potential targets of a possible early immune response limiting the extent of the disease, as reported in other preneoplastic lesions (5).

Few studies have examined the role of host immune responses in the course of head and neck cancers, although various arguments suggest that T lymphocytes may play a role in the control of the development of this cancer. Head and neck cancer–associated tumor antigens have been identified and are recognized by specific CD4+ and CD8+ T lymphocytes (6–8). In patients with head and neck cancers, antitumor functions of
T lymphocytes are often compromised (9) but the presence of functional T cells, as measured by expression of the CD3-ζ-chain or a good proliferative response of lymphocytes to CD3 antibodies, has been found to be associated with better survival and prognosis (10, 11).

Among lymphocytes, most studies have focused on analysis of CD8+ T cells which have been shown to be potent mediators of antitumor immunity (12). The role of CD4+ T cells is more controversial and is often considered to be a double-edged immunologic sword as CD4+ T cells play a central role in initiating and maintaining anticancer immune responses (13–15). In the absence of CD4+ T-cell help, specific CD8+ T cells can become lethargic (16) or be deleted (17). CD4+ T-cell help is needed during the primary antigen-specific response to imprint CD8+ T cells with the ability to develop into long-lived functional memory cells (18). In antitumor immunity, CD4+ T cells have also been shown to be important in sustaining the functions of adoptively transferred CD8+ T cells (19). Lastly, CD4+ T cells could inhibit tumor growth in the absence of CD8+ T cells by directly lysing MHC class II–positive tumor cells (20) or by promoting the recruitment of other effector cells, such as macrophages and eosinophils (21). On the other hand, a naturally occurring CD4+ T-cell subset, regulatory CD4+CD25+ T cells, has emerged as the dominant T-cell population governing peripheral self-tolerance by inhibiting effector T cells (22, 23). Because the CD3+CD4+CD25+ phenotype also identifies activated T cells, new markers such as Foxp3 have been described which seem to discriminate activated and regulatory CD4+CD25+ T cells (24, 25). In animal models, removal of CD4+CD25+ T cells improved immune-mediated tumor clearance and enhanced the response to immunotherapy (26–28). As observed in other cancers (29, 30), an enrichment of CD4+CD25+ T cells among tumor-infiltrating lymphocytes derived from head and neck cancer has already been reported (31).

In view of these heterogeneous CD4+ T-cell populations, this study was designed to determine the significance and prognostic value of various populations of tumor-infiltrating CD4+ T cells in head and neck cancers.

Materials and Methods

Patients. Eighty-four newly diagnosed untreated patients with histologically proven primary head and neck squamous cell carcinoma were included in this prospective study. Patient characteristics are presented in Table 1.

Each patient’s disease was staged according to the fifth edition of the Union Internationale Contre Cancrum/American Joint Committee on Cancer system for head and neck cancer (32). Treatment modalities consisted of surgery, alone or combined with radiotherapy and chemotherapy. Fifty-eight patients received induction chemotherapy before surgery and were staged clinically. This study was conducted in accordance with French laws and after approval by local ethics committees.

Immunofluorescence staining. Tissue samples obtained before any treatment at initial endoscopy or surgery were immediately frozen and stored at −80°C. Frozen specimens were sectioned at 4 to 6 μm with a cryostat, placed on slides, air dried, and fixed for 10 minutes with 100% acetone.

Before incubation with primary antibodies, the slides were treated with avidin/biotin blocker (Vector Laboratories, Burlingame, CA) and Fc receptor was blocked with human serum (5%). The antibodies used for the various double or triple immunofluorescence stainings are described in Supplementary Table S1. The various antibodies were diluted in PBS. Isotype-matched antibodies were used as negative controls. In each case, we checked that the secondary antibodies did not cross-react with the isotype or species of the other primary antibody immunoglobulin in the double or triple immunofluorescence technique.

Fluorescent images of mounted sections were analyzed with an epifluorescent microscope (DMR, Leica Microsystems, Wetzlar, Germany).

A quantitative grading system was used to quantify the tumor-infiltrating CD4+ T-cell subpopulations. The mean of positive stained cells in at least five fields using a 40× objective was selected for each analysis. High and low levels of CD4+ T-cell subpopulations were defined using the median of tumor infiltration for these cells as cutoff value. Two authors (C.B. and E.T.), blinded for clinical data, independently scored the slides.

Confocal analysis. Triple immunofluorescence staining was analyzed with a confocal laser scanning microscope Zeiss LSM 510 (Carl Zeiss, Oberkochen, Germany). All images were acquired with a Zeiss Plan-Neofluar 40× objective with a ×8 electronic zoom.

Optical slice thickness was adjusted to 2 μm for all channels. Multichannel images were recorded by sequential excitation to avoid crosstalk. For triple labeling, excitation was 488 nm and emission was 505 to 530 nm for FITC; excitation was 543 nm and emission was 560 to 615 nm for Cy3; and excitation was 633 nm and emission was >650 nm for Cy5.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
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<tr>
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<td>M1</td>
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Abbreviation: ND, not determined because of diffuse carcinomatosis.
Statistical analysis. The relationship between the different CD4+ T-cell subpopulations was analyzed by the χ² test or the Fisher's exact test as necessary.

Survival variables were estimated using the Kaplan-Meier method and compared by the log-rank test. Multivariate analysis using the Cox proportional hazard model determined the influence of each variable, when adjusted to others, on locoregional control (relapse-free survival) and overall survival. The level of significance was set at \( P \leq 0.05 \).

Overall survival was defined as the time from initial diagnosis until death or until last follow-up (right censored data).

Overall survival took all deaths into account. At the time of data analysis, 32 patients had died and 93.7% of deaths seemed to be directly related to the original primary cancer (locoregional failure or metastatic disease).

Locoregional control was calculated from the end of treatment and was defined as the absence of disease or either persistent or recurrent disease at the primary site or in the cervical lymph nodes. Patients with persistent disease at the end of treatment were considered to have experienced failure at time zero. Patients with no signs of relapse were censored at the time of last follow-up or death. The median follow-up for the whole population was 18 months.

Results

Head and neck tumors are infiltrated by activated and regulatory CD4+ T cells. In the first analysis, we showed that head and neck cancers were infiltrated by CD4+ T cells (Fig. 1). Large numbers of CD4+ T cells (>10 CD4+ T cells per field) were observed in 51 of 84 tumors. CD4+ T cells were predominantly found in the stroma of tumors (Fig. 1).

To more accurately define the phenotype of these tumor-infiltrating CD4+ T cells, we then characterized various CD4+ T-cell subpopulations focusing on activated and regulatory CD4+ T cells.

CD4+CD25+ T cells, including both activated and regulatory CD4+ T cells, were present in variable numbers mainly in peritumoral area (Fig. 1). Double immunofluorescence staining revealed that most CD25+ cells corresponded to cells that were also recognized by anti-CD4 monoclonal antibody (Fig. 1 and data not shown).

The median level of CD4+CD25+ T-cell infiltration was 3.7 (range, 0-16) in the whole population (Table 2).
Because CD25 antigen expression in T cells cannot allow precise discrimination between activated and regulatory T cells, we specifically measured the infiltration of regulatory and activated CD4+ T cells using the Foxp3 and CD69 markers, respectively.

The number of CD4+Foxp3+ and CD4+CD69+ T cells was lower than that observed for CD4+CD25+ T cells. The distribution of CD4+Foxp3+ and CD4+CD69+ T cells ranged from 0 to 15 cells per field (median, 1.5) and from 0 to 11 cells per field (median, 2.6) in the whole population, respectively (Table 2).

As expected, Foxp3 immunostaining was mainly located in the nucleus (Fig. 1). Infiltrating CD4+CD69+ T cells and CD4+Foxp3+ T cells were detected in the peritumoral area (Fig. 1). Most CD69+ T cells colocalized with CD4+ and CD3+ T cells (Fig. 2).

As CD4 antigen can be expressed by cells of the myeloid lineage, such as monocytes and dendritic cells (33), we excluded a possible bias in the interpretation of the above results by doing triple immunofluorescence staining with confocal analysis. We selected the tissue samples in which CD25+ or CD69+CD3− T cells were observed; those samples

<table>
<thead>
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<th>CD4+CD25+</th>
<th>CD4+CD69+</th>
<th>CD4+Foxp3+</th>
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<tr>
<td>3.7 (0-16)</td>
<td>2.6 (0-11)</td>
<td>1.5 (0-15)</td>
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**Table 2.** Univariate analysis of the relationships between the levels of the various CD4+ T-cell subpopulations infiltrating tumors and locoregional control and survival for patients with head and neck squamous cell carcinoma

**Locoregional control, P (log-rank) | Overall survival, P (log-rank)**
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<td>0.054</td>
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<td>0.01</td>
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<td>0.02</td>
<td>0.07</td>
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Fig. 2. CD4+CD25+ and CD4+CD69+ cells correspond to CD3+ T cells. Top, tissues were stained with antibodies to human CD3, CD25, and CD69 as depicted in Fig. 1. Some CD3+CD25+ and CD3+CD69+ cells were observed in some cases. Bottom, triple immunofluorescence staining with confocal examination illustrates the fact that all CD4+CD25+ and CD4+CD69+ cells were also stained by anti-CD3 antibodies. Bar, 6 μm (original magnification, top, ×400; bottom, 6-μM bar).
corresponded to 10% of all the tumors analyzed (Fig. 2 and data not shown). All CD4+CD25+ or CD4+CD69+ cells were also positive for CD3 (Fig. 2 and data not shown). In all of these cases, CD4+CD3+ cells never expressed CD25 or CD69 (Fig. 2). Triple immunofluorescence labeling with anti-Foxp3 was not done because it had already been shown that non-T cells do not express this molecule (22). These experiments support the assertion that in this study, CD4+Foxp3+, CD4+CD25+, and CD4+CD69+ cells really correspond to T cells.

**Relationship between tumor infiltration by CD4+ T-cell subpopulations and clinical variables.** A statistically significant correlation was observed between the levels of CD4+CD25+ T-cell infiltration and the number of CD4+CD69+ T cells present in the tumors (see Supplementary Table S2; *P* < 0.001). When the median value was used as a cutoff to define low and high levels CD4+CD25+ or CD4+CD69+ T infiltration, a matching between these two variables was observed in 72.5% of cases (see Supplementary Table S2). This concordance drops to 60% and 58% for the relationship between CD4+CD25+ and CD4+Foxp3+ T-cell infiltration or CD4+CD69+ and CD4+Foxp3+ T-cell infiltration, respectively (see Supplementary Table S2 and data not shown).

For some patients, double immunostaining for CD69 and Foxp3 was done. We did not find colocalization between these two markers (data not shown).

We did not find any correlation between the levels of CD4+ T cells detected in the tumors and various clinical variables including primary tumor site, T stage, lymph node involvement, presence of metastases, and response to chemotherapy (data not shown).

**Value of tumor-infiltrating CD4+ T-cell subpopulations in head and neck cancer to predict locoregional control and survival.** On univariate analysis, tumor-infiltrating CD4+CD69+ T cells were the only CD4+ T-cell subpopulation positively correlated with both better locoregional control (*P* = 0.01) and longer survival (*P* = 0.01) when considered as a continuous variable (Table 2; Fig. 3).

Survival at 24 months of patients with no CD4+CD69+ T-cell infiltrate at the time of diagnosis was 42% [95% confidence interval (95% CI), 25-68] versus 89% (95% CI, 77-100) in patients with the highest levels of tumor-infiltrating CD4+CD69+ T cells (*P* = 0.01; Fig. 3).

When the number of CD4+CD69+ corresponding to the median (2.6) was used as the cutoff to define low-level and high-level CD4+CD69+ T-cell infiltration, overall survival at 24 months was 54% in the low-level group versus 70% in the high-level group (*P* = 0.04; see Supplementary Fig. S1).

The estimated 2-year locoregional control rate was 39% in the group with low-level CD4+CD69+ T-cell infiltration compared with 70% in the group with high-level CD4+CD69+ T-cell infiltration (*P* = 0.002).

When considered as a continuous variable, CD4+Foxp3+ T-cell infiltration was positively correlated with better locoregional control (*P* = 0.026) but did not influence overall survival (*P* = 0.07; Table 2).

Locoregional control in patients with the lowest or highest CD4+Foxp3+ T-cell infiltration was 31% (95% CI, 17-57) and 99% (95% CI, 98-100), respectively (Fig. 3).

When the number of CD4+Foxp3+ T cells corresponding to the median (1.5) was used as the cutoff to define low-level and high-level CD4+Foxp3+ T-cell infiltration, a better locoregional control was also observed in the high-level group compared with the low-level group (*P* = 0.02; see Supplementary Fig. S1).

Although not statistically significant, a trend towards longer survival (*P* = 0.059) and better locoregional control (*P* = 0.054)
was observed in the group of patients with a high level of tumor-infiltrating CD4+CD25+ T cells at diagnosis (Table 2).

Because of the high number of cells, it was difficult to accurately quantify the CD3+CD4+ T-cell infiltration as a continuous variable. However, when we arbitrarily used a cutoff value of 10 cells per field to discriminate low-level and high-level CD3+CD4+ cell infiltration, low levels of CD3+CD4+ T cells were associated with absence of locoregional control (P = 0.02) but did not influence overall survival (P = 0.2).

As expected, T stage and presence of metastases were predictive factors of both locoregional control and overall survival (data not shown). Lymph node infiltration was not associated with clinical prognosis probably because most patients were initially treated by chemotherapy, excluding accurate histologic staging of lymph node involvement at diagnosis.

Because most immunocytochemistry studies assessing tumor-infiltrating immune cells pointed to CD8 antigen detection as a predictor of clinical outcome (34, 35), we also included this variable in this analysis. The levels of CD8+ T-cell infiltration in the stroma were not predictive of locoregional control (P = 0.89) or overall survival (P = 0.59).

Similar results were obtained when intratumoral instead of peritumoral CD8+ T-cell infiltrates were considered (data not shown).

Multivariate analysis showed that the only significant prognostic factors related to locoregional control were T stage (P = 0.02; relative risk, 2.79) and CD4+Foxp3+ T-cell infiltration of the tumor (P = 0.02; relative risk, 0.69; Table 3). In the Cox multivariate analysis, only two variables influenced overall survival probability: T stage (P = 0.036; relative risk, 2.53) and levels of CD4+CD69+ T-cell infiltration (P = 0.031; relative risk, 0.79; Table 3).

Differences in treatment modalities were included in this model and did not change the significance of these variables.

**Discussion**

In this study, we show that high levels of tumor-infiltrating CD4+CD25+ T cells are significantly associated with better survival and locoregional control in head and neck cancer patients. The prognostic value of CD4+CD69+ T cells on survival remained significant when multivariate analysis adjusted on clinical variables was done.

To our knowledge, this is the first report showing a prognostic value of tumor-infiltrating activated CD4+ T cells in human tumors. In some other studies, expression of activated markers by peritumoral lymphocytes was also correlated with longer survival (36). CD69 is expressed on recently activated T cells and may represent a surrogate marker of an ongoing immune response (37).

Activated CD4+ T cells could inhibit tumor growth by lysing tumors cells or by secreting cytokines (IFNγ, tumor necrosis factor α, etc.) with antitumor activity (21, 38). They also play a major cooperative role for CD8+ T cells in in vivo tumor eradication and promote recruitment of other antitumor effector cells, such as macrophages and eosinophils (21).

The clinical significance of CD4+ T cells inside tumors is controversial in the literature. A large number of tumor-infiltrating CD4+ T cells were found to be an independent favorable prognostic factor in pancreatic adenocarcinomas and esophageal squamous cell carcinomas (39, 40). Head and neck squamous cell carcinoma patients with active disease had significantly lower CD4+ T-cell counts than those with no evidence of disease (41). Intratumoral T cells composed of CD4+ and CD8+ T cells, of which infiltration was highly correlated, were associated with improved clinical outcome in advanced ovarian carcinoma (42). On the contrary, other groups have reported that an increased level of tumor-infiltrating CD4+ T cells is associated with poor outcome in renal cell carcinoma (35, 43).

The heterogeneity of the phenotype of CD4+ T cells may explain these contradictory results. For example, CD4+ T-cell subpopulations included T-helper 2 cells producing type 2 cytokines (interleukin 4, interleukin 5, interleukin 13, etc.), which inhibit the T-helper 1 cell–mediated immune response and could also influence tumor-host behavior (44).

CD4+ T cells are also divided into helper effector T cells and regulatory T cells. A population of regulatory CD4+ T cells, such as activated T cells, express CD25 but also the transcription factor Foxp3, which has been shown to be specific for regulatory CD25+CD4+ T cells in mice and humans (22, 45). Experimental depletion of regulatory CD25+CD4+ T cells in mice improved immune-mediated tumor clearance and enhanced the response to immune-based therapy (26–28).

In humans, regulatory CD4+CD25+ T cells have been reported to be increased in tumor-infiltrating lymphocytes and in the peripheral circulation of patients with various malignancies (29–31).

In our study, the level of tumor-infiltrating CD4+Foxp3+ T cells was positively correlated with a better locoregional control in both univariate and multivariate analysis. This finding contrasts with recent results reported by Curiel’s group indicating a significant correlation between tumor CD4+ T regulatory cell content defined by the expression of CD25 and Foxp3 and survival in patients with ovarian carcinomas but

**Table 3. Factors influencing locoregional control and survival as determined by the Cox proportional hazards models in head and neck squamous cell carcinoma patients**

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<th></th>
<th>Locoregional control</th>
<th>Overall survival</th>
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<tr>
<td></td>
<td>P</td>
<td>Relative risk (95% CI)</td>
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<tr>
<td>T stage (T1-T2 vs T3-T4)</td>
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<td>2.79 (1.16-6.69)</td>
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<td>CD4+CD69+</td>
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<tr>
<td>CD4+Foxp3+</td>
<td>0.02</td>
<td>0.69 (0.5-0.95)</td>
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Abbreviation: NS, not significant.
the influence of CD4+Foxp3+ on disease-free survival was not determined (46). In line with our results, a large number of Foxp3 positive cells were also considered to be a significant predictor of longer event-free survival and disease-free survival in patients with Hodgkin lymphoma (47). Various factors can explain the different effect of the presence of CD4+ T regulatory cells in the clinical course of the disease. The role of regulatory T cells may differ according to the clinical stage of the tumor. Various authors have reported that the frequency of regulatory CD4+ T cells increased during tumor progression (46, 48) and their in vivo depletion is efficient to eradicate established tumor only when it is not done during the priming phase of the antitumor immune response (48).

In contrast, it has recently been shown that adoptive transfer of CD4+CD25+ regulatory T lymphocytes in mice suppressed colitis-associated colon cancer and development of spontaneous intestinal adenomas (49, 50). Treatment with regulatory T cells also induced down-regulation of Cox-2 and proinflammatory cytokines known to promote malignancy (50–52).

The functionality of regulatory T cells was not monitored because most patients in this study received induction chemotherapy before surgery and we had to use tissue samples from initial endoscopy and not surgery to avoid bias in interpreting the results. This biopsy material was too limited to isolate and do functional assays on the different subpopulations of CD4+ T cells combined with routine analysis and immunofluorescence studies.

One possible interpretation bias in the present study could be that CD4+CD25+ and CD4+CD69+ cells did not only represent T cells but also included cells from the monocytic-dendritic lineage as these cells could also express CD4. Triple immunofluorescence staining and confocal analysis confirmed that all CD4+CD25+ or CD4+CD69+ cells detected actually corresponded to T cells. Only low levels of CD4 are observed in tissue macrophages and are difficult to detect and lower than the levels observed in peripheral monocytes or helper CD4+ T cells (53). It has also been shown that activation of monocyte-macrophages by proinflammatory cytokines such as tumor necrosis factor α and IL-1, cytokines highly expressed on head and neck tumors (54), which could up-regulate CD25 or CD69 on these cells, also down-regulated total CD4 expression on monocyte-macrophages at the level of transcription (55). As regards a possible interference with CD4+ dendritic cells, it is known that some immature dendritic cells express CD4 and induction of CD25 and CD69 has been reported when they differentiate into a mature state (56). However, one of the many changes observed during the dendritic cell maturation process is a decrease in CD4 expression (56, 57).

All these data support the assumption in this study that tumor-infiltrating CD4+CD25+ or CD4+CD69+ can be considered to be T cells.

We did not use confocal analysis to count tumor-infiltrating CD4+ T cells as the rapid fading and the time required for image acquisition with this microscope were not compatible with the analysis of multiple variables in a large series of patients.

CD4+CD25+ T cells are the prominent subpopulation of CD4+ T cells infiltrating head and neck tumors. The relationships between tumor infiltration by these cells and the plasma concentration of the soluble chains of interleukin-2 receptors, previously reported as a prognostic marker in head and neck cancer (58), are currently being analyzed.

Most immunocytochemical analyses assessing immune cell infiltration in cancer patients have emphasized the value of CD8+ T cells to predict clinical recurrence and probability of survival (59, 60). In this study, we did not find any prognostic value associated with the presence of CD8+ T cells measured either in the tumor stroma or within tumor cells. This result could be related to the fact that CD8+ T lymphocytes, and not CD4+ T cells, seem to be particularly sensitive to apoptosis in patients with head and neck squamous cell carcinoma (61).

In light of these results, depletion of CD25+ T cells, sometimes incorrectly considered to be mainly composed of regulatory T cells, may be harmful in head and neck cancer as these cells also include activated CD4+ T cells, the presence of which is associated with a good prognosis. In addition, even regulatory Foxp3+CD4+ T cells may be beneficial in some cancers by down-regulating an inflammatory reaction which could favor tumor progression (51, 52).

Acknowledgments

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