Tumor-infiltrating lymphocytes favor the response to chemoradiotherapy of head and neck cancer

Keywords: head and neck cancer, HPV, prognostic value, radiotherapy, tumor infiltrating lymphocytes
discrepancy can be attributed to the high percentage of old patients included in our cohort and to the fact that our study enrolled patients affected by HNSCC in various anatomical locations, rather than the oropharynx only (the most common location of HPV-associated HNSCC). Furthermore, robust tumor infiltration by CD3+ and CD8+ T cells correlated with improved clinical outcome in HPV− HNSCC patients only, whereas a modest benefit was observed in HPV+ individuals. Importantly, we failed to observe a significant difference in the lymphocytic infiltration between the HPV+ and HPV− patients included in our study. Mixed findings have been reported on the prognostic value of TILs according to HPV status in HNSCC patients. Thus, additional studies, preferably in patients affected by oropharyngeal tumors, are required to better elucidate the prognostic significance of TILs in HPV+ and HPV− patients (Fig. 1).

How can we explain our findings? Accumulating evidence suggests that the immune microenvironment can alter the response of various cancers to CRT. Indeed, several preclinical and clinical studies have demonstrated limited responses to radiotherapy in tumor-bearing hosts (be them laboratory animals or patients) lacking a normal CD8+ T-cell repertoire, suggesting that the immune system can boost the efficacy of anticancer treatment. Our findings lend further support to this hypothesis. In addition, the significantly reduced incidence of metastases observed in HNSCC patients manifesting a robust tumor infiltration by CD3+ and CD8+ T cells possibly reflects the existence of a systemic immunosurveillance mechanism that prevents metastatic dissemination.

Taken together, our results indicate that CD3+ and CD8+ T cells can be used as markers to predict disease progression and highlight the importance of TILs in determining the response to chemoradiation in HNSCC patients. Hence, the combination of CRT with novel immunotherapies that activate T cells with might be useful in HNSCC patients that are characterized by low levels of CD8+ TILs at baseline, perhaps enhancing treatment responses and improving disease outcome. An in-depth understanding of the role of CD8+ T cells in correlation to HPV status is urgently required to better elucidate the contribution of TILs to tumor-targeting immune responses against HNSCC.

Disclosure of Potential Conflict of Interest
No potential conflicts of interest were disclosed.

References
1. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet 2008; 371:1695-709; PMID:18486742; http://dx.doi.org/10.1016/S0140-6736(08)60728-X
2. Lesterhuis WJ, Haanen JB, Punt CJ. Cancer immunotherapy—revisited. Nat Rev Drug Discov 2011; 10:591-600; PMID:21804596; http://dx.doi.org/10.1038/nrd3500
3. Bhardwaj N. Harnessing the immune system to treat cancer. J Clin Invest 2007; 117:1130-6; PMID:17476342; http://dx.doi.org/10.1172/JCI32136
4. Balmymas P, Michel Y, Wangenblast J, Seitz O, Weiss C, Rodel F, Rodel C, Fokas E. Tumour-infiltrating lymphocytes predict response to definitive chemoradiotherapy in head and neck cancer. Br J Cancer 2013; Forthcoming; PMID:24129245; http://dx.doi.org/10.1038/bjc.2013.640
5. Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br J Cancer 2011; 105:93-103; PMID:21629244; http://dx.doi.org/10.1038/bjc.2011.189

6. Denkert C, Loibl S, Noske A, Roller M, Müller BM, Komor M, Budczies J, Darb-Esfahani S, Kronenwett R, Hanusch C, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 2010; 28:105-13; PMID:19917869; http://dx.doi.org/10.1200/JCO.2009.23.7370

7. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010; 363:24-35; PMID:20530316; http://dx.doi.org/10.1056/NEJMoa0912217

8. Nordfors C, Grün N, Tertipis N, Ahrlund-Richter A, Haeggblom L, Sivars L, Du J, Nyberg T, Marklund L, Munck-Wikland E, et al. CD8(+) and CD4(+) tumour infiltrating lymphocytes in relation to human papillomavirus status and clinical outcome in tonsillar and base of tongue squamous cell carcinoma. Eur J Cancer 2013; Forthcoming; PMID:23571147; http://dx.doi.org/10.1016/j.ejca.2013.03.019

9. Kong CS, Narasimhan B, Cao H, Kwok S, Erickson JP, Koong A, Pourmand N, Le QT. The relationship between human papillomavirus status and other molecular prognostic markers in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys 2009; 74:553-61; PMID:19427557; http://dx.doi.org/10.1016/j.ijrobp.2009.02.015

10. Burnette B, Weichselbaum RR. Radiation as an immune modulator. Semin Radiat Oncol 2013; 23:273-80; PMID:24012341; http://dx.doi.org/10.1016/j.semradonc.2013.05.009