Molecular Diagnosis of Head and Neck Cancer

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Abstract

Patients with advanced stages of head and neck cancer frequently develop loco-regional recurrence as well as distant metastases. These data indicate that traditional diagnostic methods such as histopathology and radiology are not sensitive enough to detect the small numbers of tumor cells which are left behind, defined as minimal residual disease (MRD). Sensitive diagnostic assays based on molecular markers appear to be powerful tools to improve the staging of these patients. At the DNA level, tumor-specific p53 mutations seem to have great potential for the detection of “occult” tumor cells at surgical margins and lymph nodes. At the RNA level HNSCC associated antigens like the E48 antigen, allow the detection of rare HNSCC cells in blood and bone marrow and, it is hoped, also in lymph nodes and lymph node aspirates. However, the molecular assays which are used to detect MRD are subject to certain (technical) problems which affect their sensitivity and specificity. In this paper we will present examples of molecular assays such as the plaque assay using p53 mutations and the E48 RT-PCR, and show their use for MRD detection in cervical lymph nodes. In addition, we will discuss the problems and pitfalls associated with these sensitive techniques.

Introduction

Head and Neck Cancer

Head and neck squamous cell carcinoma (HNSCC) are the main histologic type of tumors of the upper aerodigestive tract. It accounts for approximately 5% of all newly diagnosed malignant tumors in Western Europe and the United States. Annually there are approximately 500,000 new cases of HNSCC worldwide, and in 1995 over 1,800 cases in the Netherlands alone (Parkin 1988; Vokes 1993; Boring 1994; Netherlands Cancer Registry 1998). HNSCC
patients can be divided into four different clinical stages I-IV, according to the TNM classification of the International Union Against Cancer (UICC). In this classification system patients are grouped according to their tumor size and presence of lymph node or distant metastases. In general patients with stages I or II have a relatively good prognosis as they can often be cured with single modality treatment, i.e., surgery or radiotherapy. Patients with the more advanced stages III and IV are treated with combined surgery and radiotherapy. Despite advances in these treatments, these patients have a rather poor prognosis with a high incidence of locoregional recurrence and distant metastases.

Inaccurate Diagnosis of HNSCC

Local Relapse

Clinical studies provide statistical evidence that 40%-50% of the patients with resectable advanced tumors develop local recurrence, despite improvements in therapy. This failure in treatment results in part from a failure in diagnosis. This is illustrated by the fact that in approximately 15%-30% of the stage III and IV patients with histopathologically tumor-free resection margins a local recurrence develops (Leemans et al. 1994). These clinical data indicate that routine histopathology is not sensitive enough to detect the small tumor deposits that eventually develop into a recurrence (Brennan et al. 1995). These undetectable tumor cells have been defined as minimal residual disease (MRD) (Hermanek 1993; Pantel et al. 1996).

Distant Metastases

In addition to local relapse, about 15%-25% of the HNSCC patients with advanced tumor stages develop distant metastases after treatment (most commonly in the lungs, liver and skeletal system) (Hong et al. 1985; Zbaren and Lehmann 1987; Cerezo et al. 1992; Leemans et al. 1993). Like local relapses, distant relapses occur in patients who had no evidence of distant metastases at the time of locoregional therapy, again indicating that the current methods of staging have a limited sensitivity in detecting small disseminated tumor deposits. For example, spiral computed tomography (CT) of the thorax and liver or bone scintigraphy can nowadays detect distant lesions of approximately 1 cm in diameter. Currently, no curative treatment options are available for these patients.

Regional Recurrence – the NO Neck

A particular staging problem with regard to treatment planning is the assessment of the clinically N0 neck. Routinely, the neck is staged by palpation and, if necessary, by various imaging modalities such as CT or magnetic res-