Comparative Genomic Hybridization Analysis for Esophageal Squamous Cell Carcinoma

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Introduction

Esophageal cancer, which is very frequent worldwide, is a solid tumor that continues to have a high mortality rate, although diagnostic and therapeutic modalities have improved considerably. There is a need for accurate prognostic indicators to distinguish high-risk patients from other patients so that optimal treatment protocols can be designed on a case-by-case basis. Esophageal squamous cell carcinoma (ESCC), in particular, requires such indicators because it is highly malignant. Although histopathological examination allows us to diagnose the tumor, it provides little biological information such as metastatic potential and sensitivity and resistance to radiation and anticancer drugs. Pathologists are expected to report pathological diagnosis together with the biological characteristics for each, but it is difficult to do so, and patient prognosis remains undefined.

It is also important to determine whether lymph node metastasis is present, because the therapeutic strategies differ for cases with and without metastasis. If the presence of lymph node metastasis could be assessed with a reliable diagnostic method before treatment, less invasive treatments could be used to treat patients with ESCC, in particular with superficial ESCC (SESCC).

Comparative genomic hybridization (CGH), a molecular cytogenetic technology, provides for global overview of chromosomal gains and losses within the tumor. The number of DNA sequence copy number aberrations (DSCNAs) detected by CGH is correlated with the disease stage and biological behavior of a tumor; thus, comprehensive analysis of genetic alterations in biopsy specimens may permit us to determine the biological characteristics of each tumor and to predict the prognosis of each patient at the time of diagnosis.

Prediction of Prognosis in ESCC Patients Undergoing Curative Resection by CGH

There are a few reports of the relationship between postoperative prognosis and CGH analysis in patients with ESCC. Kwong et al. reported that multivariate analysis confirmed a gain in 12p as an independent prognosticator for relapse-free survival after esophagectomy in addition to pathological stage. Yen et al. reported that pathologic staging and CGH data (gains of 5p and 7q; and deletions of 4p, 9p, and 11q) were significant prognostic factors in a univariate analysis, but pathologic staging became the only significant factor in a multivariate analysis.

We applied CGH to 51 ESCCs to clarify the relation between DSCNAs and the clinicopathology of the disease. Gains of 8q24-qter and 20q12-qter and loss of 11q22-23 were linked to nodal metastasis. Gains of 5p15 and 14q21 were associated with distant organ metastasis. These observations suggest that nodal and distant organ metastases involve different genes. Gains of 5p15, 8q24-qter, and 14q21 were significantly associated with an unfavorable outcome. Multivariate analysis revealed the 5p15 gain to be an independent prognostic marker with a higher significance than that of nodal status. The present findings indicate that CGH analysis may be used to predict the likelihood of a poor or favorable outcome in cases of ESCC. If a patient has these chromosomal abnormalities, postoperative adjuvant chemoradiotherapy may be recommended.

Prediction of Lymph Node Metastasis in Patients with SESCC by CGH

Flexible endoscopic procedures allow easy detection of SESCC, and therapeutic modalities for SESCC have been improved. However, patients with SESCC still have poor prognosis in comparison with early cancers of other parts of the digestive tract. This is because of anatomical and biological characteristics, such as early spreading to the surrounding tissue and early metastasis to the lymph
nodes, inherent to ESCC.

It is important to provide treatment that is optimized to the individual patient to improve prognosis. Selection of treatment protocols for SESCC depends greatly on lymph node status. Unfortunately, there are no reliable markers available to distinguish cases without lymph node metastasis from those with it before treatment.

Previously, we reported that this and the loss of 11q22-qter allow the prediction of lymph node metastasis in ESCC. Our recent report indicates the predictability of lymph node metastasis by CGH analysis in SESCC patients before surgery. We studied 34 cases of SESCC comprising 26 training samples obtained from resected specimens and 8 blinded samples obtained by preoperative biopsy. In a study of 26 training samples, 14 samples with neither 8q24 nor 20q12-qter gain showed lymph node metastasis and nodal metastasis was detected in 9 of 12 patients with 8q24 and/or 20q12-qter gains. In a study of 8 blinded samples, two of the 8 samples showed no gain of 8q24 or 20q12-qter, and histopathological examinations revealed no nodal metastasis for these two tumors. These results indicate that detection of specific DSCNs in biopsy specimens facilitates prediction of presence or absence of nodal metastasis at the time of histological diagnosis of SESCC. Information concerning nodal status permits selection of the best treatment protocol for each patient with SESCC. Less invasive methods such as mediastinoscope-assisted transhiatal esophagectomy can be used to treat patients without 8q24 or 20q12-qter gains. Because lymph node metastasis was always accompanied by gains of 8q24 and/or 20q12-qter, transthoracic esophagectomy with lymphadenectomy would be recommended for treatment of patients with SESCC who have these abnormalities.

References