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P53 Overexpression and Outcome of Radiation Therapy in Head & Neck Cancers

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Purpose : Experimental studies have implicated the wild type p53 in cellular response to radiation. Whether altered p53 function can lead to changes in clinical radiocurability remains an area of ongoing study. This study was performed to investigate whether any correlation between change of p53 and outcome of curative radiation therapy in patients with head and neck cancers.

Methods : Immunohistochemical analysis with a mouse monoclonal antibody (D0-7) specific for human p53 was used to detect to overexpression of protein in formalin fixed, paraffin-embedded tumor sample from 55 head and neck cancer patients treated with curative radiation therapy (median dose of 7020 cGy) from February 1988 to March 1996 at St. Mary's Hospital. Overexpression of p53 was correlated with locoregional control and survival using Kaplan-Meier method. A Cox regression multivariate analysis was performed that included all clinical variables and status of p53 expression.

Results : Thirty-seven (67.2%) patients showed overexpression of p53 by immunohistochemical staining in their tumor. One hundred percent of oral cavity, 76% of laryngeal, 66.7% of oropharyngeal, 66.7% of hypopharyngeal cancer showed p53 overexpression (P=0.05). The status of p53 had significant relationship with stage of disease (P=0.03) and history of smoking (P=0.001). The overexpression of p53 was not predictive of response rate to radiation therapy. The locoregional control was not significantly affected by p53 status. Overexpression of p53 didn't have any prognostic implication for disease free survival and overall survival. Primary site and stage of disease were significant prognostic factors for survival.

Conclusions : The p53 overexpression as detected by immunohistochemical staining had significant correaltion with stage, primary site of disease and smoking habit of patients. The p53 overexpression didn't have any predictive value for outcome of curative radiation therapy in a group of head and neck cancers.

Key Words : p53, Radiation therapy, Head & neck cancer

INTRODUCTION

The p53 gene has been extensively studied and represents the most common mutated gene in human malignancies, including squamous cell carcinoma of head and neck. Normally functioning wild type p53 protein (WTp53) has cell regulatory functions, including apoptosis, which has been shown to be an important pathway for tumor cell death following exposure to therapeutic radiation.[1,2] The protein product derived from mutated p53 (MTp53) gene is nonfunctional and blocks cells from undergoing apoptosis following irradiation. These cells continue to proliferate, despite injury due to ionizing radiation. Consequently, tumor cells that have MTp53 are belived to be more radioresistant than those with WTp53.

Experimental studies have implicated the p53 in cellular response to radiation. Whether altered p53 function can lead to changes in clinical radiocurability remains an area of ongoing study. This study was performed to investigate

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whether any correlation between change of p53 and outcome of curative radiation therapy in patients with head and neck cancers.

MATERIALS AND METHODS

The clinical data for 55 patients with head and neck cancer who were treated in at St. Mary's Hospital from February 1988 to March 1991. All patients received primary curative radiation therapy. Doses ranged from 6480 to 7660 cGy with median of 7020 cGy. Follow-up ranged from 12~75 months with median of 25 months.

Immunohistochemical analysis with a mouse monoclonal antibody (D0-7) specific for human p53 was used to detect to overexpression of protein in formalin fixed, paraffin-embedded tumor sample processed at that time of diagnosis. Achival tissue material were cut and mounted on prove-on slide. Then the sections were dewaxed and were stained using mouse monoclonal antibodies to human p53 protein (Clone D0-7, NeoMarkers, Fremont, CA, USA). Specimens for normal laryngeal epithelium were used as negative controls. Immunohistochemically processed sections were examined microscopically at ×400 magnification.

The labeling was quantified using a square graticule for counting labelded and unlabelded tumor cell nuclei. The tumor cell nuclei were counted in random fields, moving across the tumor from one end to the other, taking care not to overlap fields. In each field, the nuclei were counted in every other small square of graticule. The total number of nuclei counted in each section were >500 nuclei, and the labeling index (LI) was calculated as the percentage of the labeled nuclei. Each specimen was arbitrarily grouped into the following categoty: negative (0%) vs. weakly positive (1~10%) vs. moderately positive (11~79%) vs. strongly positive. (80~100%) The negative and weakly positive cases regarded as p53 (−) group. The moderately and strongly positive group regarded as p53 (+) group. Fig. 1 showed various labeling index of each specimen. The labeling index was assessed by two independent pathologists.

Overexpression of p53 was correlated with locoregional control and survival using Kaplan-Meier method. A Cox regression multivariate analysis was performed that included all clinical variables and status of p53 expression.

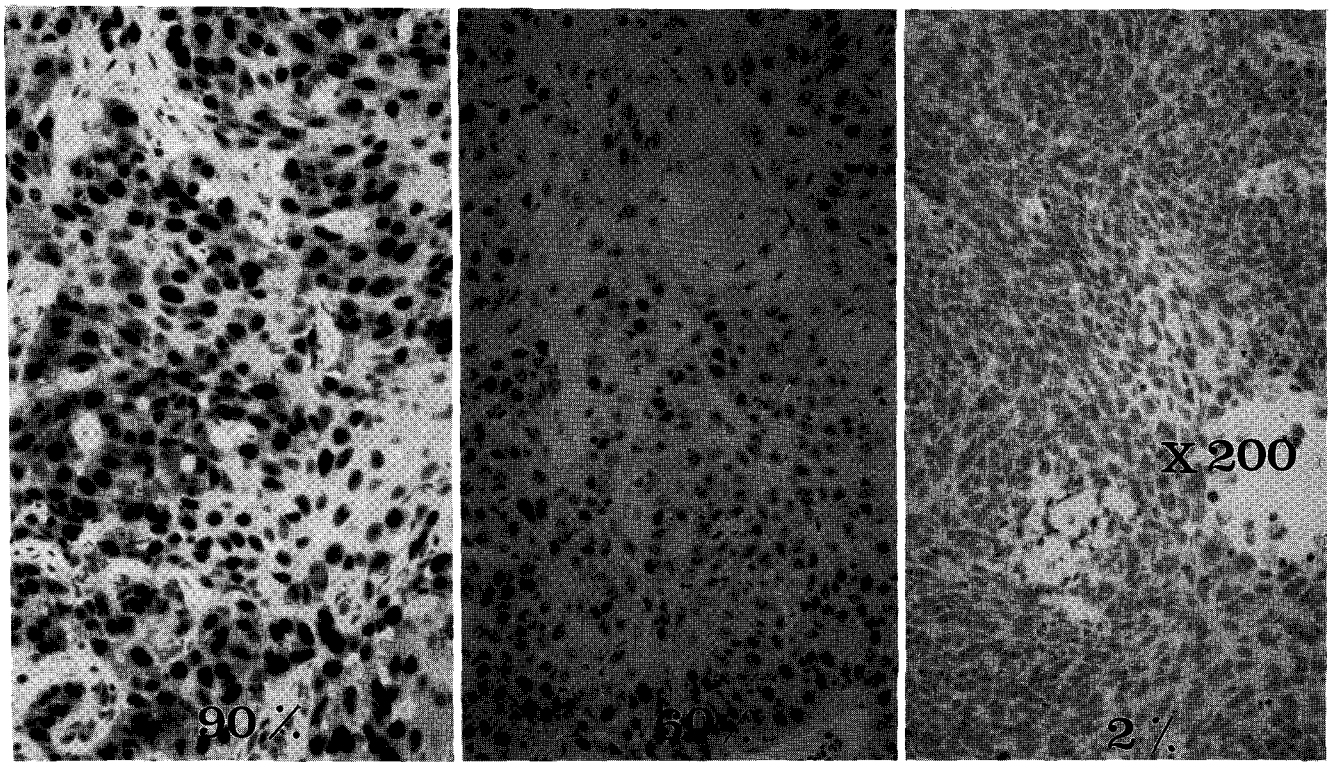

Fig. 1. Labeling index.

RESULTS

Thirty-seven (67.2%) patients showed overexpression of p53 by immunohistochemical staining in their tumor. Table 1 showed overexpression rates according to primary site, stage, pathologic grade of tumor and smoking status of patient. One hundred percent of oral cavity, 76% of laryngeal, 66.7 % of oropharyngeal, 66.7% of hypopharyngeal cancer showed p53 overexpression (P=0.05). The status of p53 had significant relationship with stage of disease (P=0.03) and history of smoking (P=0.001). Overexpression rate of p53 did not predict histological grade (P=0.707).

Table 2 showed the response rate according to primary site, stage, pathologic grade of tumor and performance status of patients, respectively. The overexpression of p53 was not predictive of response rate to radiation therapy. The response rate was significantly affected by primary site, stage and performance status of patients.

Table 1. P53 Overexpression Rate accoding to Patients and Tumor Parameter

Parameter	Case of p53 (+)/ all patients (% of expression rate)	*P*-value
Primary tumor site		0.047
Nasopharynx	5/13 (38.5)	
Larynx	19/25 (76.0)	
Hypopharynx	4/ 6 (66.7)	
Oropharynx	4/ 6 (66.7)	
Oral cavity	5/ 5 (100)	
Stage		0.034
Early (I / II)	17/20 (85.0)	
Advanced (III / IV)	22/35 (62.9)	
Grade		0.707
Well-differentiated	12/18 (66.7)	
Moderately-differentiated	18/25 (72.0)	
Poorly-differentiated	8/12 (66.7)	
Smoking status		0.001
Smoker	33/42 (78.6)	
Non-smoker	4/13 (30.8)	
Total	37/55 (67.3)	

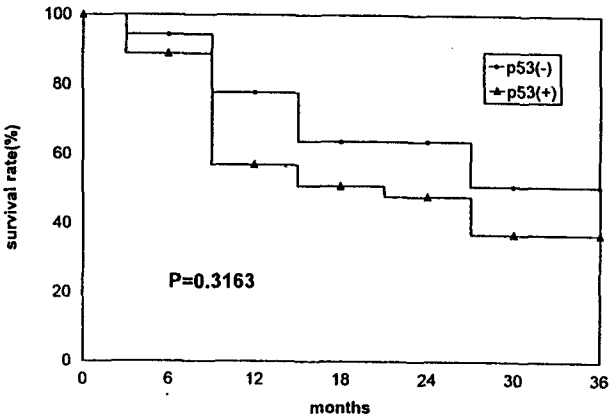

Fig. 2. Disease free survival by p53 status.

Table 2. Response Rate according to Clinicopathologic Parameter

Parameters	CR (%)	PR (%)	MR (%)	*P*-value
p53 status				0.671
Positive	0/ 33 (66.0)	11/15 (73.3)	6/7 (85.7)	
Negative	13/ 33 (39.4)	4/15 (26.7)	1/7 (14.3)	
Primary site				0.011
Nasopharynx	10/ 13 (76.9)	3/13 (23.1)	0/13 (0.0)	
Larynx	17/ 25 (68.0)	7/25 (28.0)	1/25 (4.0)	
Hypopharynx	1/ 6 (16.7)	2/ 6 (33.3)	3/ 6 (50.0)	
Oropharynx	3/ 6 (50.0)	0/ 6 (0.0)	3/ 6 (50.0)	
Oral cavity	2/ 5 (40.0)	3/ 5 (60.0)	0/ 5 (0.0)	
Stage				0.006
Early (I/II)	17/ 20 (85.0)	3/20 (15.0)	0/20 (0.0)	
Advanced (III/IV)	16/359 (45.7)	12/35 (34.3)	7/35 (20.0)	
Grade				0.701
Well-differentiated	12/ 18 (66.7)	4/18 (22.2)	2/18 (11.1)	
Mod.-differentiated	13/ 25 (52.0)	8/25 (32.0)	4/25 (16.0)	
Poorly-differentiated	8/ 12 (66.7)	3/12 (25.0)	1/12 (8.3)	
KPS				0.035
≥ 80	23/ 30 (76.7)	5/30 (16.6)	2/30 (6.7)	
< 80	10/ 25 (40.0)	10/25 (40.0)	5/25 (20.0)	

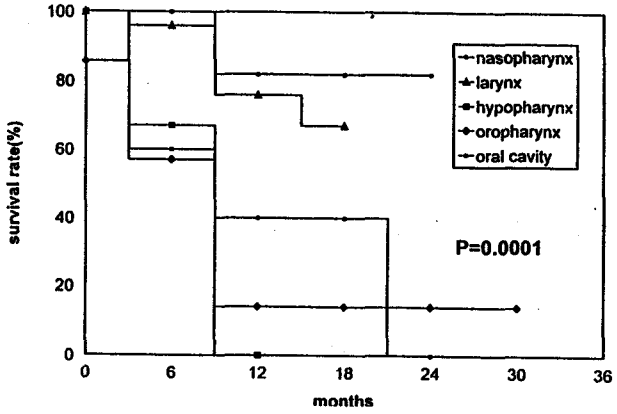

Fig. 3. Disease free survival by primary site.

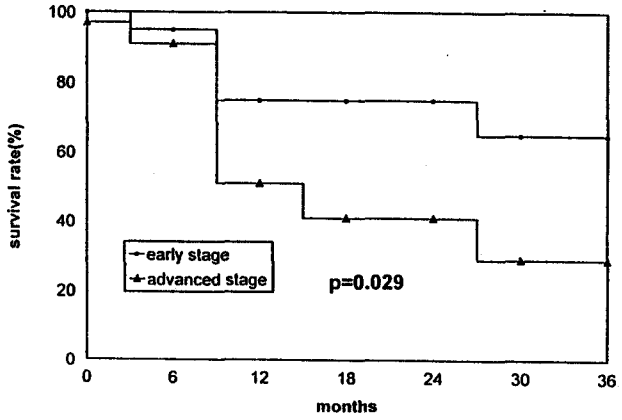

Fig. 4. Disease free survival by stage.

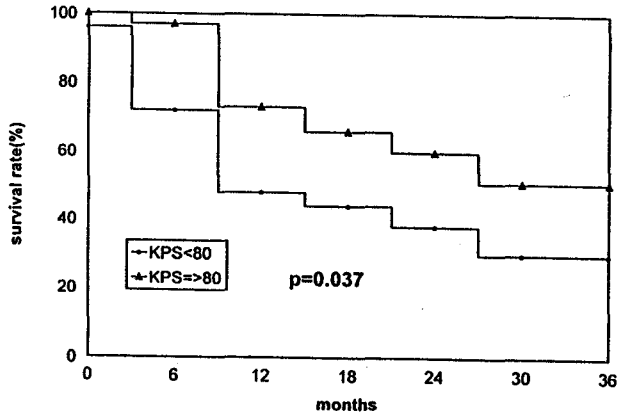

Fig. 5. Disease free survival by KPS.

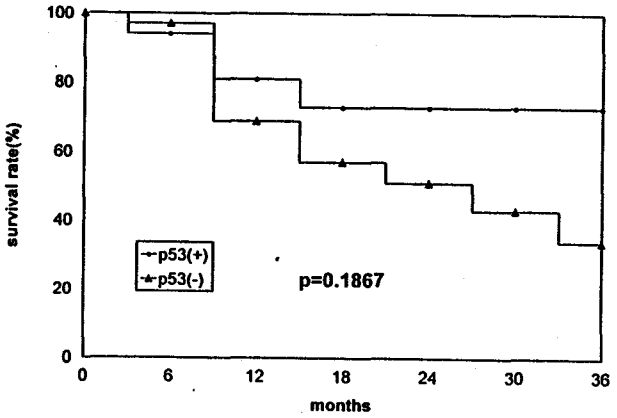

Fig. 6. Overall survival by p53 status.

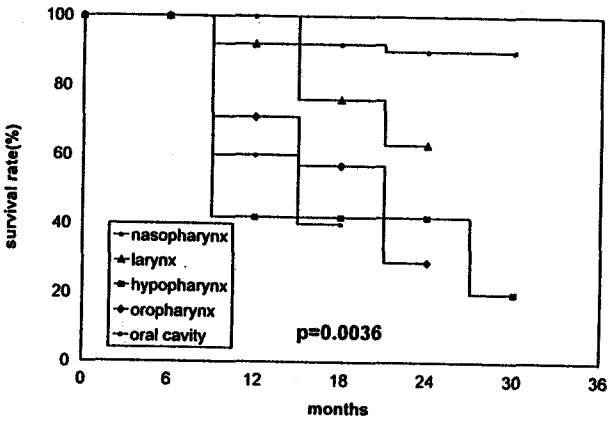

Fig. 7. Overall survival by primary site.

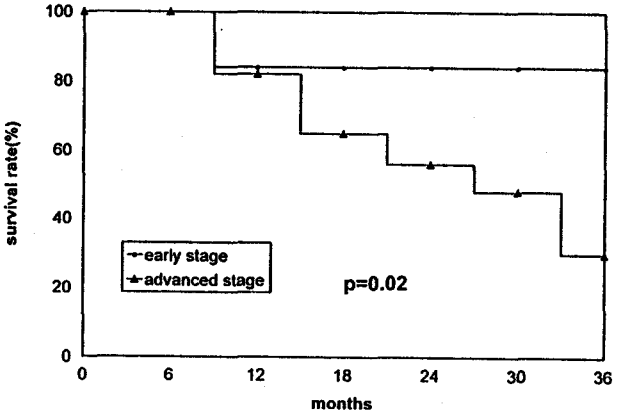

Fig. 8. Overall survival by stage.

Fig. 2~5 showed the disease free survival according to p53 status, primary site, stage tumor and performance status of patients, respectively. The disease free survival was not significantly affected by p53 status. Primary site and stage were significant prognostic implication for disease free survival by both univariate and multivariate analysis (Table 3).

Fig. 6~9 showed the overall survival rate according to p53 status, primary site, stage of tumor and performance status of patients, respectively. In univariate analysis, primary

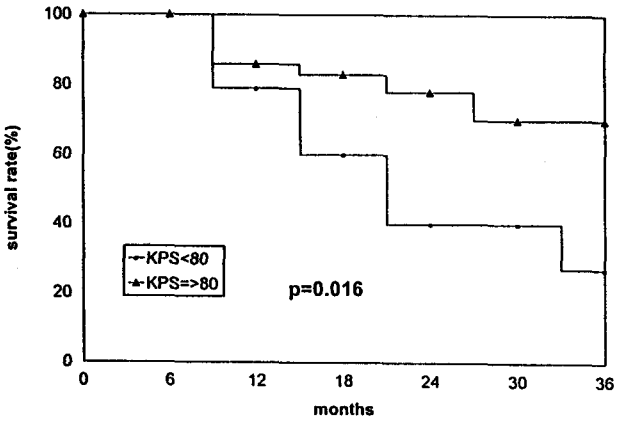

Fig. 9. Overall survival by KPS.

Table 3. Prognostic Factors

Parameter	Univariate analysis (*P*-value)	Multivariate analysis (*P*-value)
For Disease Free Survival Rate		
P53 status	0.3163	–
Primary site	0.0001	0.001
Stage	0.0283	0.0012
KPS	0.0365	0.0926
For Overall Survival Rate		
P53 status	0.1867	–
Primary site	0.0035	0.001
Stage	0.0204	0.007
KPS	0.016	0.091

site, stage and performance status were significant prognostic implication for overall survival. In multivariate analysis, primary site and stage had prognostic factors for overall survival (Table 3). Overexpression of p53 didn't have any prognostic implication for disease free survival and overall survival.

DISCUSSIONS

The p53 tumor suppressor gene has become one of the most extensively studied genes in both normal and tumor cells. However, the exact role of the p53 gene in the cellular response of normal and tumor cells to DNA damage is still unclear. In some cell types, the p53 gene mediates a permanent G1 cell cycle arrest following exposure to ionizing radiation.[3] However, in other cell types, radiation induces cellular apoptosis which can occur via both p53-dependent and p53-independent mechanisms.[2, 4]

The majority of laboratory studies which have investigated he intrinsic radiosensitivity of human and rodent tumor cell lines have conclude that cells with altered WTp53 function acquire increased clonogenic radiation survival in vitro. The exact reason for this is unclear, but may relate to the acquisition of mutant gene sequences that subsequently modify the repair of DNA strand breaks or the susceptibility for radiation induced apoptosis.[5]

In clinical work, the loss of p53 function has been shown to correlate with shortened survival in breast and lung carcinoma.[6~8] In addition, the accumulation of p53 as detected by immunohistochemical staining, has been shown to correlate with mutations in p53 gene and with poor prognosis in several other types of tumors.[9~11]

Whether or not the presence of MTp53 is prognostic factor in squamous cell carcinoma of head and neck remains undefined. Studies supporting this hypothesis include Shin et al., who reported the overexpression of p53 by immunohistochemical staining in primary head and neck squamous cell carcinoma was significantly predictive of shorter survival because of its association with earlier development of both tumor recurrence and second primary tumors after receiving definitive local therapy in M.D. Anderson Cancer Center.[12] Koch et al also reported that mutation of p53 gene by direct sequence analysis was associated with an increase risk of locoregional failure in patients with head and neck squamous cell carcinoma who are treated with radiation therapy.[13]

Contrary to these, several publications have reputed the prognostic significance of p53 overexpression. Awwad et al demonstrated that the p53 accumulation as detected by immunohistochemical staining in a group of head and neck carcinomas was not predictive of patient's poor survival and disease free survival. This study showed that the TNM stage was only significant prognostic factor and smoking status had significant association with p53 accumulation.[14] Kokoska reported that nuclear accumulation of p53 protein was not predictive of tumor response or recurrence in the patients with T1 or T2 glottic carcinoma treated with primary radiotherapy. Histologic differentiation was the only significant predictor of outcome in this patient population.[15] Recently Pai et al also demonstrated that mutant p53 protein detected by immunohistochemistry was not predictive as a prognostic factor for clinical outcome following radiation therapy for early stage glottic carcinoma.[16] This is general agreement

with other recently published studies of head and neck cancer patients treated with radiation therapy. Our study also demonstrated that the p53 overexpression didn't have any predictive value for locoregional control or survival. Primary site and stage had prognostic significance for survival.

In our study, overexpression rate of p53 was 67.3% and significant correlation with primary tumor site. Other head and neck cancer studies reported p53 overexpression in 44~83% of laryngeal,[17, 18] in 20~80% of oropharyngeal,[15, 39, 49] and in 42~73% of oral cavity carcinomas.[18, 19] In comparing results from different centers, it seems there is no consisitant correlation between labeling and tumor site. The reason for the differences in results from different centers are difficult to explain because multiple factors may be involved, such as differences in studied populations and staining techniques. Immunohistochemical detection of antigen will be influenced by many variables, such as the absolute level of the antigen, affinity and concentration of antibody, duration of incubation, sensitivity of detection system, and the consequences of fixation.[20]

Aberrant p53 can be detected by several methods, including DNA sequencing and immunohistochemical staining with specific commercially prepared p53 monoclonal antibodies. The latter represents relatively inexpensive and rapid technique. Malignant cells possessing abnormal p53 protein will stain positive owing to the fact that MT p53 protein has a longer half-life than WT p53 and, thus stains more readily. However, the positive detection of accumulated p53 protein by immunohistochemical analyses does not always predict the expression of MTp53 protein.[21, 22] In addition, discordance between the result of DNA sequencing and immunohistochemistry has been documented in various tumors.[23, 24] This suggests that non-mutational mechanisms of p53 protein accumulation may exist. Furthermore, aberrant p53 proteins can be undetectable by immunohistochemistry when they are the result of: nonsense or frameshift mutations of the p53 gene, incorrect RNA transcription from the p53 gene, interactions between p53 protein and viral proteins which degrade WTp53 protein and structural rearrangements of the p53 gene.[25~27] As a result, the predictive value for immunohistochemistry in the detection of MTp53 protein may be low in some human tumors dependent on cell type, the nature of the aberrant protein, and cellular protein-protein interactions.[26]

Alsner et al recently evaluated the prognostic value of p53 status by immunohistochemistry and gene sequencing. (exon 5~9) p53 mutation were found in 32/68 patients by sequencing and two-thirds of the tumors expressed p53 activity on immunohistochemistry. There was no significant correlation between p53 expression and p53 mutation by sequencing. They concluded that p53 mutation is strong marker of prediction of locoregional control and disease-specific survival. They also suggested that the better understanding of role of p53 pathway in head and neck cancer treated with radiotherapy and biochemical evaluation of the consequence of different type of p53 mutations were required to further explore the prognostic potential of this marker.[28]

The disparity in the conclusion reached by a number of clinical studies raises the question as to what endpoints are required to evaluate critically the role of WTp53 protein function as a determinant of radioresponse. As mentioned above, there are a number of mutational and nonmutational mechanism by which WTp53 protein function can be altered. These changes may, or may not be detected by immunohistochemistry or DNA sequencing studies.[24, 26] For example, eventhough gene sequencing analysis can provide a sensitive assay for the presence of a MTp53 gene sequence,[22, 24, 29] they can not determine the cellular function of encoded p53 protein. This may not an important factor since in that the expression of MT p53 protein may not necessarily abrogate the radiaiton induced G1 checkpoint or other p53-mediated activities.[30, 31] In future, the simultaneous documentation of cell cycle check point control and relative expression levels of variety proteins may attainable by the use of multi-parameter flowcytometry. This technique could be used as a means of directly testing the relationship between the expression of protein involved in cell cycle control and local tumor control following fractionated radiation treatment.[32]

Of particular interest to our study is the role of p53 in radiation therapy-induced cell death. Using animal models, Clarke et al[1] and Lowe et al[2] demonstrated that immature mouse thymocytes lacking normal p53 function were resistant to the cytotoxic effect of ioninzing radiation. This suggested that the mechanism of radiation-induced cell death is through apoptosis and that p53 is necessary for apoptosis. This mechanism of resistance is also noted in human cell lines.[4] Thus came about the hypothesis that tumor cells possessing mutated p53 were unable to undergo programmed cell death after radiation-induced DNA damage and conferred resis-

tance to clinical radiation therapy. This is hypothesis tested in our study, with attention focused on squamous cell carcinoma of head and neck cancers. In our studies, significant percentage of patients population showed p53 overexpression. This didn't predict local control or survival rate in patients treated with curative radiation therapy.

Seong et al recently reported that the development of apoptosis required upregulation of both p53 and p21 (WAF1/CIP1) as well as a decrease in bcl-2 /bax ratio and an increase in in bcl-2/bax ratio prevented apoptosis in the presence of upregulated p53 and p21 (WAF1/CIP1). These finding suggested that the involvement of multiple oncogenes in apoptosis regulation in vivo and demonstrated the complexity that may be associated with the use of a single oncogene assessment for predicting the outcome of cytotoxic therapy.[33]

We concluded that p53 overexpression detected by immunohistochemical staining should not be used as a prognostic factors or predictor of treatment outcome in squamous cell carcinoma of head and neck cancer until further studies can substantiate its prognostic significance.

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국문 초록

두경부종양 환자에서 p53의 과발현과 방사선치료결과

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목 적 : 실험적으로 p53 종양억제유전자는 세포의 방사선에 대한 반응을 조절하는 것으로 알려져 있는데, 임상에서 p53의 변화와 방사선치료 후의 예후와의 상호관련성은 아직 명확하게 규명되지 않은 상태이다. 이에 두경부종양환자에서 흔히 관찰되는 p53의 변화가 방사선치료결과에 어떤 영향을 미칠 수 있는지를 알아보고자 하였다.

재료 및 방법 : 두경부종양으로 진단되어 근치적 방사선치료를 받은 55명의 환자를 대상으로 임상결과를 후향적으로 분석하였다. 각 환자의 치료전 종양조직의 paraffin section을 human p53단백질에 대한 monoclonal antibody (D-07)로 면역조직화학염색하여 labeling Index (number of labelded nuclei/total number of counted nuclei x100)를 구하여, 임상결과와 연관지어 분석하였다.

결 과 : 전체환자의 67.2%에서 p53의 기능이상을 시사하는 과발현 소견을 보였다. 원발병소에 따른 과발현 빈도는 oral cavity, larynx, hypopharynx, nasopharynx순으로 각각 100%, 76%, 67%, 67%, 38%로 나타났다. 흡연자가 비흡연자에 비해 유의하게 높은 과발현 빈도를 보였다 (78.6%, 30.8%). 원발병소, 병기 및 Karnofsky performance status가 방사선치료에 대한 반응율과 유의한 연관을 보였으며, p53의 과발현여부는 치료반응율에 유의한 영향을 미치지 못하는 것으로 나타났다. 무병생존율 및 전체생존율에 영향을 미치는 인자는 원발병소와 병기였고, p53의 과발현여부는 유의한 연관을 보이지 못하였다.

결 론 : 근치적 방사선치료를 받은 두경부종양 환자에서, 면역조직화학염색에 의한 p53의 과발현율은 원발병소, 병기 및 흡연여부와 유관하였으며, 과발현여부가 치료반응율 및 생존율에 유의한 영향을 미치지 못하였다.

핵심 단어 : p53, 방사선치료, 두경부종양