

## Research Article

# Study on association of polymorphism of CYP450 2D6 with head and neck cancer and treatment response in patients receiving neoadjuvant chemotherapy paclitaxel, cisplatin, 5fu (TPF) followed by chemoradiation

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## ABSTRACT

**Background:** Aims of this study were to study the association of genetic polymorphism in CYP450 2D6 in patients of locally advanced head and neck cancer, and try to assess a correlation between this polymorphism & response to treatment. Need of the study was to find out a possible genetic level explanation for the different response achieved in patients with similar histopathology, stage, exposure to carcinogen & ethnicity undergoing similar treatment.

**Methods:** A study comprising of 150 patients & 150 controls was done to analyze the association between polymorphs of CYP450 2D6 with head & neck cancer and treatment response (TPF→CTRT). Two cycles of TPF (paclitaxel-175mg/m<sup>2</sup> D1, cisplatin 35mg/m<sup>2</sup> D2-D3 and 5Fu 1gm/m<sup>2</sup> D1-D3) were given followed by radiotherapy with concurrent cisplatin (40 mg/m<sup>2</sup>). The response to the treatment was assessed clinically, radiologically & by laryngoscopy-post treatment. Genotyping of the blood samples was done. Analysis of the association between genetic polymorphisms and risk of HNSCC was estimated by calculating crude odds ratio (OR). A P value of <0.05 was considered statistically significant. The statistical analysis was performed with the SPSS software package (version 11.0 for Windows; SPSS Chicago, IL).

**Results:** Patients with CYP 2D6\*1 showed good response to the therapy given, while CYP 2D6\*4 and \*10 were poor responders.

**Conclusion:** There is a strong association of polymorphs of CYP 2D6 with occurrence of head and neck cancer. Response to treatment (TPF→CT-RT) is polymorph graded. Our study thus provides an insight in to the concept of "Right therapy to the right patient".

**Keywords:** Polymorphism, CYP450 2D6, Chemoradiation

## INTRODUCTION

Head and neck cancer are a group of malignancies arising from the mucosal lining of upper aero digestive tract. It is the 5th leading cause of cancer by incidence and the 6th

leading cause of cancer mortality in the world. Most common histology associated is squamous cell carcinoma and rarely adenocarcinomas, adamantinoma, lymphoma, ameloblastoma and melanoma. The risk to developing these cancers is more in people consuming both then

those who use either tobacco or alcohol alone.<sup>1</sup> A heterogeneous neoplastic process is responsible in association with genetic variations and environmental toxins for the generation of various head and neck carcinomas. The presence of DNA sequence variations (polymorphisms) within critical genes will govern an individual's response to environmental toxins & chemicals. Genetic polymorphism affect almost all drug-metabolizing enzymes, leading to a wide variations in the enzyme activity ranging from absolute absence to high metabolizing capacity. The distribution of exposure risk in human populations as well as an estimation of risk due to exposure in prediction of an individual's risks due to exposure and also the response to treatment can be better understood by analyzing genetic polymorphism.

Cytochrome P450 (CYP) family of enzymes are the most important enzymes for metabolism of endogenous compounds, as well as environmental chemicals and many of the widely used drugs. There is a marked individual variation in the metabolic capacity of this system, leading to differences in the excretion rates and the final concentration of drug in the serum. Severe toxicity or therapeutic failure of medications as well as a possible increase in an individual's susceptibility to certain types of chemically induced cancers and other diseases can be due to genetic polymorphism of CYPs (Watanabe et al, 1998).

This work is an effort to bring forth the association of polymorphs of 2D6 (\*4 &\*10) with head and neck tumors and their treatment response to the induction therapy (TPF) followed by concurrent chemo radiotherapy.

## METHODS

### *Study subjects*

A case control study was conducted at C. S. M. Medical University (formerly King George's Medical University, KGMU), Lucknow, India. Male cases suffering from HNSCC were included in this study. The study group comprised 150 cases with head and neck squamous cell carcinoma and equal number of healthy controls. The cases had squamous cell carcinoma of the oral cavity, oropharynx, the hypopharynx, the larynx and the cancer of the nasal cavity, nasopharynx, and paranasal sinuses which was confirmed by cytological or histopathological examinations. All the cases included in the study belonged to the same ethnic group (Indo-European community) of North India based on geographical location and linguistic basis. Controls were frequency-matched to cases by year of birth in 15-year classes. It was ensured that the controls also belonged to the same geographical location and socio-economic conditions. Based on medical check-up, controls were not found to suffer from any chronic disease. Informed consent of all the cases and control was obtained before inclusion in the study. Study was done after ethical approval from the

ethics committee. All study subjects completed a questionnaire covering medical, residential and occupational history. Information pertaining to dietary habits, family history of disease, smoking, tobacco chewing and alcohol drinking was also obtained in the questionnaire filled by the cases and controls as well. Individuals having regular smoking habits and smoking index (cigarettes/day  $\times$  365 days) of 730 or more were classified as smokers (Quinones, et al., 2001). Likewise, smokeless tobacco dose was estimated as 'chewing year' (i.e. CY = frequency of tobacco chewed .kept/day  $\times$  duration of year). Those who had CY of 365 or more were considered as tobacco chewers (Sikdar et al., 2003). Similarly cumulative exposure of alcohol drinking was derived by multiplying the total yearly consumption of alcohol (in L/year) by the duration of habitual alcohol drinking (in years). Those who had cumulative exposure of alcohol about 90 L were considered as regular alcohol users in our study (Hung et al., 1997).

### *Procedure and method*

For studying the polymorphism in Cytochrome P450 2D6 gene, patients suffering from Head & Neck Cancer, visiting OPD were included in the study. The clinical symptoms of the patients were recorded and blood samples was collected. 10ml of blood was drawn from cases and controls in the tube containing ACD solution, an anticoagulant and stored at 4°C till proceed for isolation of genomic DNA.

### *DNA isolation and CYP 2D6 genotyping*

Isolation of genomic DNA: Genomic DNA was isolated from whole blood for genetic analysis. The protocol for isolation of genomic DNA from whole blood by QIAamp spin columns of QIAGEN had already been standardized in our laboratory. DNA was isolated from 0.2 ml of blood following the recommended protocol. Molecular weight of genomic DNA isolated with this method ranges from 40 to 100kb with the A260/A280 ratio of 1.7-1.9. The isolated DNA was then directly used for PCR applications.

Blood from control healthy individuals was processed for isolation of genomic DNA using Flexi Gene DNA isolation kit (QIAGEN). The extracted DNA was quantified and checked for purity spectrophotometrically (CARY 300 Bio-UV/Visible Spectrophotometer).

### *Quantitative estimation of human genomic DNA*

Estimation was done through CARY 300 Bio-UV/visible spectrophotometer. For quantitating the amount of DNA, reading is taken at wavelength of 260 nm and 280 nm. The reading at 260 nm allows calculation of nucleic acid in the sample. An OD of 1 corresponds to ~50  $\mu$ g/ml for ds DNA. The ratio between the reading at 260 nm & 280 nm ( $OD^{260}/OD^{280}$ ) provides an estimate of the purity of

the nucleic acid. Pure preparation of DNA has OD<sup>260</sup>/OD<sup>280</sup> value of 1.8

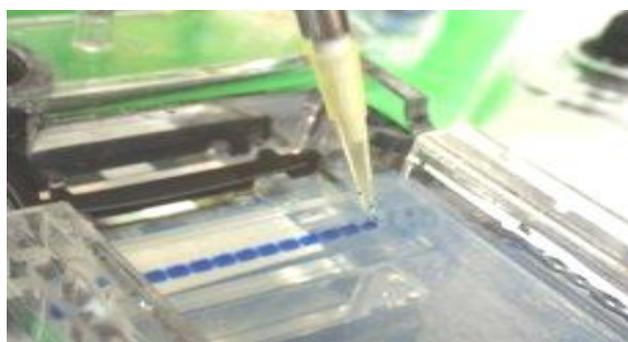
Using the formula for estimation of genomic DNA:

Conc. of genomic DNA (µg/ml) = OD at 260nm x DF x 50

Dilution Factor (DF) = Total volume / volume of DNA

**Qualitative analysis of human genomic DNA**

The integrity of genomic DNA was checked by running 0.8% agarose gel prepared in 0.5 x TBE buffer along with 4µl EtBr (10mg/ml). A proportion of 3µl of genomic DNA product and 2µl loading single dye Bromophenol Blue were mixed properly in Eppendorf and were loaded into the wells carefully and gel was run at 60 volts for around 30 min (Figure 1).



**Figure 1: Pipetting the DNA samples in agarose gel electrophoresis.**

**Procedure protocol**

Two cycles of TPF (paclitaxel-175 mg/m<sup>2</sup> D1, cisplatin 35 mg/m<sup>2</sup> D2-D3 and 5Fu 1gm/m<sup>2</sup> D1-D3 ) were given followed by radiotherapy (70Gy in 35# @ 2 Gy/#, 5#/week) with concurrent cisplatin (40 mg/m<sup>2</sup>). The response to the treatment was assessed clinically, radiologically & by laryngoscopy at 1,3,6 & 12 month after completion of treatment.

**RESULTS**

A total of 150 patients were enrolled for the study. 10 patients defaulted the treatment and were excluded while analyzing the treatment response. The distribution of demographic variables and putative risk factors of HNSCC is summarized in Table 1.

Table 2 summarizes the genotypic frequencies of CYP 2D6\*4 in the control & cases respectively. The frequency of heterozygous genotypes (wt/mt) of CYP 2D6\*4 polymorphism was found to be higher in the cases (18 %) when compared to the controls (10%). This increase in frequency resulted in an increased OR (2.04) in cases which was found to be statistically significant. Likewise, the frequency of homozygous genotype (mt/mt) was

slightly higher in cases (14.67%) when compared to controls (13.33 %) that resulted in an increase in risk OR (1.25) which, however, was not found to be statistically significant.

**Table 1: Distribution of demographic variables and putative risk factors of HNSCC cases.**

Characteristics	Controls n (%)	Cases n (%)
Subjects	150	150
Age (Mean ± SD)	45 ± 11	46±9
Non-tobacco chewers	111 (74.0%)	73 (48.66%)
Tobacco chewers	39 (26%)	77 (51.33%)
Non-smokers	110 (73.33%)	60 (40%)
Smokers	40 (26.66%)	90 (60%)
Non-alcohol users	115 (76.66%)	70 (46.66%)
Alcohol users	35 (23.33%)	80 (53.33%)

**Table 2: Distribution of CYP 2D6\*4, genotypes among HNSCC cases and healthy controls.**

Genotype frequency	Control n=150 (%)	Cases n=150 (%)	OR value	P value
wt/wt	115 (76.67%)	101 (67.33%)	1 (ref)	-
wt/mt	15 (10%)	27 (18%)	2.04 (1.03-4.06)	0.03
mt/mt	20 (13.33%)	22 (14.67%)	1.25 (0.64-2.42)	0.50

Table 3 summarizes the genotypic frequency of heterozygous genotypes (wt/mt) of CYP\*10 polymorphism & it was found to be higher in the cases (20 %) when compared to the controls (6.67 %). This increase in frequency resulted in an increased OR (3.6) in cases which was found to be statistically significant. Likewise, the frequency of homozygous genotype (mt/mt) was slightly higher in the cases (7.33 %) when compared to controls (6 %) that resulted in an increase in risk OR (1.4) which, however, was not found to be statistically significant.

**Table 3: Distribution of CYP 2D6\*10, genotypes among HNSCC cases and healthy controls.**

Genotype frequency	Control n=150 (%)	Cases n=150 (%)	OR value	P value
wt/wt	131 (87.33%)	109 (72.67%)	1 (ref)	-
wt/mt	10 (6.67%)	30 (20%)	3.6 (1.68-7.70)	0.000
mt/mt	9 (6%)	11 (7.33%)	1.4 (0.58-3.67)	0.40

The effect of interaction of the risk modifiers such as tobacco chewing, with the CYP 2D6 genotypes in the control and cases are summarized in Table 4. The number

of individuals with variant genotypes of CYP 2D\*4 was significantly increased in cases (36.36%), who were regular tobacco chewers as compared to the controls (10.26%) with similar habit of tobacco chewing. The increase in the frequency resulted in several fold statically significant increase in the OR (4) amongst the tobacco chewing cases. As observed with CYP 2D6\*4

the frequency of individuals who were regular tobacco chewers with variant genotypes of CYP 2D\*10 was also increased significantly in cases (35.06%). When compared to the controls (23.08 %) the increase in the frequency resulted in 2-3 fold statistically significant increase in the risk (Table 4).

**Table 4: Interaction between CYP 2D6 genotype and tobacco chewing and risk to HNSCC.**

Genotype	Tobacco chewers					Non-tobacco chewers				
	Control n=39	Cases n=77	OR	CI 95%	P value	Control n=111	Cases n=73	OR	CI 95%	P value
<b>CYP 2D6*4</b>										
Wild type	35 (89.74%)	49 (63.64%)	1 (ref)	-	-	90 (81.08%)	53 (72.6%)	1 (ref)	-	-
Variant	04 (10.26%)	28 (36.36%)	4.00	1.2-12.5	0.01	21 (18.92%)	20 (27.4%)	1.66	0.84-2.4	0.176
<b>CYP 2D6*10</b>										
Wild type	30 (76.92%)	50 (64.94%)	1 (ref)	-	-	80 (72.07%)	48 (65.75%)	1 (ref)	-	-
Variant	9 (23.08%)	27 (35.06%)	1.80	0.74-4.33	0.187	31 (27.93%)	25 (34.25%)	1.34	0.71-2.54	0.36

Cigarette smoking also increased the risk to HNSCC in the cases (44.44 %) with CYP 2D6 polymorphism when compared to the smokers in the controls (20%). The OR associated with cigarette smoking increased several fold in the patients with a variant genotypes of CYP 2D6 which was found to be statically significant (pvalue-

0.000). As observed with CYP 2D6\*4 variants, the number of cases with the variant genotypes of CYP 2D6\*10 was also increased amongst smokers (33.33%) as compared to the controls (12.5 %). Further, this increase was associated with an increased risk OR (3.5), which was found to be statically significant (Table 5).

**Table 5: Interaction between CYP 2D6 genotype and smokers and risk to HNSCC.**

Genotype	Smokers					Non-smokers				
	Control n=40	Cases n=90	OR	CI 95%	P value	Control n=110	Cases n=60	OR	CI 95%	P value
<b>CYP 2D6*4</b>										
Wild type	32 (80%)	50 (55.56%)	1 (ref)	-	-	87 (79.09%)	40 (66.67%)	1 (ref)	-	-
Variant	8 (20%)	40 (44.44%)	3.20	1.32-7.40	0.00	23 (20.91%)	20 (33.33%)	1.89	0.93-3.83	0.07
<b>CYP 2D6*10</b>										
Wild type	35 (87.5%)	60 (66.67%)	1 (ref)	-	-	90 (81.82%)	43 (71.67%)	1 (ref)	-	-
Variant	5 (12.5%)	30 (33.33%)	3.50	1.24-9.64	0.01	20 (18.18%)	17 (28.33%)	1.77	0.84-3.73	0.12

Our data further showed that the frequency of the individuals with variant genotypes of CYP2D6\*4 and who were regular alcohol user significantly increase in the cases (33.75 %) when compared to the controls (11.43 %). this increase in frequency was associated with almost 4 fold increase in the risk OR (3.94) to HNSCC in the cases with variant genotypes, the number of cases with variant genotypes of CYP2d6\*10also increased amongst alcohol users with variant genotypes of CYP2D6\*10 when compared moreover, this increase in

the risk was also found to be statically significant OR (2.9) (Table 6).

A follow up study was also carried out in 140 patients to investigate the effect of treatment on the patients with different genotypes of CYP 2D6. The response was based on WHO criteria (50% reduction in the size of tumor in size-CR & 50% & above response-PR) as judged by clinical parameters, imaging (CT/MRI) and laryngoscopy. Amongst the patients with wild type

genotypes of CYP 2D6 (CYP 2D6\*1), 73.08% responded to the treatment of the given regimen (TPF→CT-RT)

while 26.92% showed no response and the variant (\*4,\*10) showed poor response.

**Table 6: Interaction between CYP 2D6 genotype and alcohol use and risk to HNSCC.**

Genotype	Alcohol users					Non-Alcohol users				
	Control n=35	Cases n=80	OR	CI 95%	P value	Control n=115	Cases n=70	OR	CI 95%	P value
<b>CYP 2D6*4</b>										
Wild type	31 (88.57%)	53 (66.25%)	1 (ref)	-	-	101 (87.83)	55 (78.57%)	1 (ref)	-	-
Variant	04 (11.43%)	27 (33.75%)	3.94	1.26-12.34	0.01	14 (12.13%)	15 (21.43%)	1.96	0.89-4.37	0.09
<b>CYP 2D6*10</b>										
Wild type	29 (82.86%)	50 (62.5%)	1 (ref)	-	-	90 (78.26%)	60 (85.71%)	1 (ref)	-	-
Variant	6 (17.14%)	30 (37.5%)	2.9	1.07-7.79	0.03	25 (21.74%)	10 (14.29%)	0.6	0.269-1.33	0.20

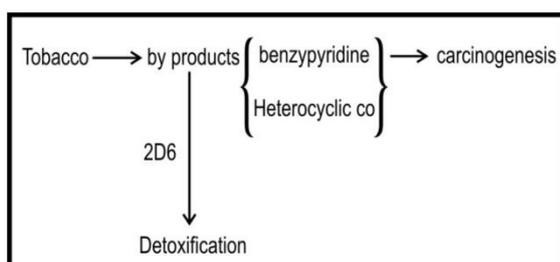
**Table 7: Treatment responses in patients of HNSCC with genotype of CYP 2D6\*4 and CYP 2D6\*10.**

Genotype	Cases (n=140) (%)	Response -rs (%)	Non-response -rs (%)	P value
CYP 2D6*1	52 (37.14%)	38 (73.08%)	14 (26.92%)	1 (Ref)
CYP 2D6*4	46 (32.86%)	17 (36.96%)	29 (63.04%)	0.00
CYP 2D6*10	42 (30%)	18 (42.86%)	24 (57.14%)	0.00

**DISCUSSION**

The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism. CYP 2D6 is a member of the cytochrome P450 superfamily of enzymes. It is known to metabolize as many as 20%-25% of commonly prescribed drugs. The gene is highly polymorphic in the population; varying from poor metabolizer to ultra-rapid metabolizers. Its polymorphism has been studied for number of sites other than head and neck in the past.

Proposed association as derived from the study for the development of carcinoma in patients who smoke & chew tobacco:



Benz pyridine is a byproduct of tobacco chewing material. Heterocyclic compounds are present in tobacco smoking products (Cigarette, Bidi). The polymorphs (variants) of 2D6 are thus more susceptible to carcinogenesis, since they do not detoxify the byproducts of tobacco.

Some of the other studies done in the past too have showed the association of polymorphs of 2D6 with different cancers.

Alcohol acts as a solvent for the penetration of various carcinogens through the mucosa of upper aero digestive organs.<sup>2</sup> The primary metabolite of ethanol-acetaldehyde, forms DNA adducts with DNA in human cells *in vitro* thus giving a plausible explanation for the carcinogenic effect of alcohol.<sup>3</sup> Production of reactive oxygen species and nitrogen species is a possible mechanism of alcohol related carcinogenesis.<sup>4</sup> Heavy alcohol use might lead to nutritional deficiencies by reduced intake of foods rich in micronutrients, by impaired intestinal absorption, and by changes in metabolic pathways.<sup>5</sup> Alcohols affect absorption and metabolism of vitamin B<sub>12</sub> and vitamin B<sub>6</sub>, resulting in changes in DNA methylation pathways. Deficiency in vitamin A has also been proposed as an alcohol mediated carcinogenesis. Metabolism of vitamin A is changed by chronic alcohol intake.<sup>6</sup> Alcohol consumption can reduce immune surveillance, thus favoring cancer development and metastatic potential.<sup>7</sup>

Sobti et al.<sup>8</sup> in 2006 have suggested that the CYP17 A2/A2, CYP1B1 Val/Val, and CYP 2D6 genotypes may be associated with an altered risk of prostate cancer. study by Gajecka M<sup>9</sup> for CYP 1A1\*1/\*4, CYP 2D6\*4/\*4, NAT 2\*4/\*6A genotypes, as well as the CYP 1A1\*4, CYP 2D6\*4 and NAT 2\*4 alleles, found significantly higher frequencies in cases than in controls indicating their role as "risk-elevating" factors in laryngeal SCC. Study by Zienolddiny<sup>10</sup> indicate that several SNPs in the

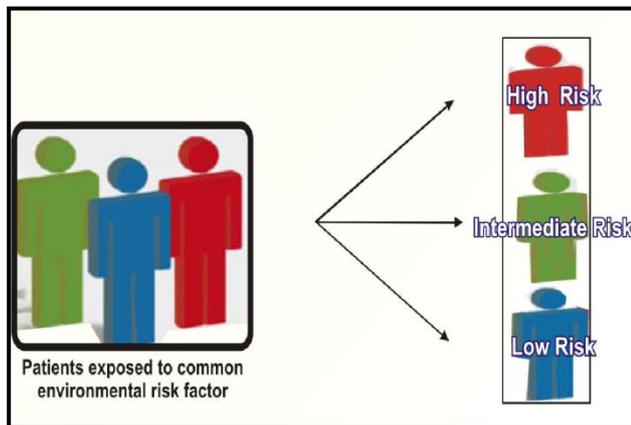
phase I genes, CYP 1B1, CYP 2D6, CYP 2E1 and CYP 3A4, are associated with the risk of NSCLC. Abdel-Rahman<sup>11</sup> suggested that the predisposing CYP 2D6 gene increase the risk for bladder cancer among Egyptians.

Study by Leonor Gomes et al.<sup>12</sup> suggested an association of the CYP 2D6\*1 allele and the susceptibility to pituitary adenomas. An association with a protective effect against papillary thyroid cancer has been found with the homozygous mutant CYP 2D6 genotype and similar results have been reported for tumors at other sites, such as lung cancer and leukaemia.<sup>13</sup> Ladona et al.<sup>14</sup> reported a significant association between the heterozygous CYP 2D6 genotype and breast carcinoma risk among postmenopausal patients. De Jong et al.<sup>15</sup> found that homozygous mutant CYP 2D6 genotype increased the risk of breast carcinoma. Study published in 1996 by Bouchardy et al.<sup>16</sup> found that the effect of tobacco smoking on lung cancer risk rose with increasing CYP 2D6 activity.

**CONCLUSION**

The present study concludes:

1. There is a strong association between polymorphs of cytochrome P450 2D6 with head and neck cancer, majorly having habit of smoking, tobacco chewing and alcohol drinking. Hence patients with 2d6 variants are having a strong propensity of getting carcinoma of head and neck if they indulge into habits of chewing or smoking tobacco and alcohol drinking.

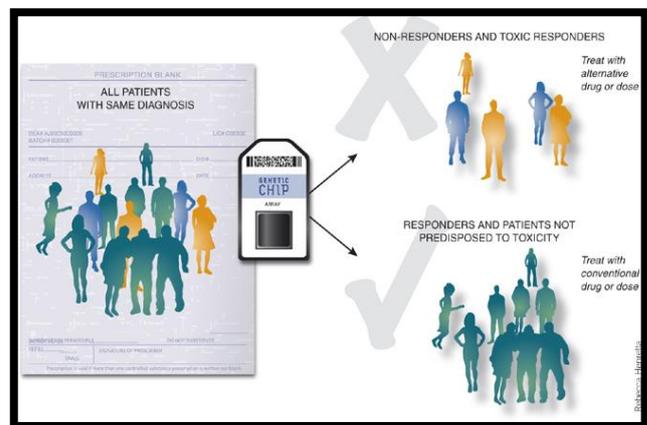


**Figure 2: Risk stratification among patients exposed to same environmental risk factor.**

Also we depict from our study, as has been shown in Figure 2 too, the fact that the people who are exposed to same environmental toxin can be segregated into person who is at major risk, intermediate risk & low risk of getting the disease (head & neck malignancy) and hence appropriate steps of education & prevention can be taken at a very early stage.

2. 2D6\*1 showed good response to TPF→CTRT but polymorphs 2D6\*4, 2D6\*10 are poor responders. Hence, the response to the therapy (TPF→CTRT) is variant dependent.

The statement means that people with head and neck malignancy with 2D6 genotype can be segregated into people who will respond to TPF→CTRT and people who will not, as from our study we know that 2D6\*1 carrying patients will get a definite benefit from TPF→CTRT while patients with \*4 & \*10 are having a very less chances of getting the response to the TPF→CTRT regimen. Hence as has been depicted in figure no.3 that using the amplichips we can know the genotype of the patient and appropriate therapy for the patient can be decided at a very early stage.



**Figure 3: Right therapy to right patient.**

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*Ethical approval: The study was approved by the ethics committee of KGMU, Lucknow, UP, India*

**REFERENCES**

1. Sankaranarayanan R, Masuyer E, Swami Nathan R, Ferlay J, Whelan S. Head and neck cancer: a global perspective on epidemiology and survival. *Anticancer Res.* 1998;18:4779-86.
2. Wright AJ, Ogden GR. Possible mechanisms by which alcohol may influence the development of oral cancer: a review. *Oral Oncol.* 1998;34:441-7.
3. Vaca CE, Nilsson JA, Fang JL, Grafstrom RC. Formation of DNA adducts in human buccal epithelial cells exposed to acetaldehyde and methylglyoxal in vitro. *Chem Biol Interact.* 1998;108:197-208.

4. Molina PE, Hoek JB, Nelson S et al. Mechanisms of alcohol induced tissue injury. *Alcohol Clin Exp Res.* 2003;27:563-75.
5. Lieber CS. Relationship between nutrition, alcohol use and liver disease. *Alcohol Res Health* 2003;27:220-31.
6. Leo MA, Lieber CS. Alcohol, vitamin A, and beta-carotene: adverse interactions, including hepatotoxicity and carcinogenicity. *Am J Clin Nutr* 1999;69:1071-85.
7. Cook RT. Alcohol abuse, alcoholism, and damage to the immune system: review. *Alcohol Clin Exp Res.* 1998;22:1927-42.
8. Sobti RC, Onsory K, Al-Badran AI, Kaur P, Watanabe M, Krishan A, Mohan H. CYP 17, SRD 5A2, CYP 1B1, and CYP 2D6 gene polymorphisms with prostate cancer risk in North Indian population. *DNA Cell Biol.* 2006 May;25(5):287-94.
9. Gajecka M, Rydzanicz M, Jaskula-Sztul R, Kujawski M, Szyfter W, Szyfter K. CYP 1A1, CYP 2D6, CYP 2E1, NAT2, GSTM1 and GSTT1 polymorphisms or their combinations are associated with the increased risk of the laryngeal squamous cell carcinoma. *Mutat Res.* 2005 Jul;574(1-2):112-23.
10. Zienolddiny S, Campa D, Lind H, Ryberg D, Skaug V, Stangeland LB, Canzian F, Haugen A. A comprehensive analysis of phase I and phase II metabolism gene polymorphisms and risk of non-small cell lung cancer in smokers. *Carcinogen.* 2008 Jun;29(6):1164-9.
11. Abdel-Rahman SZ, Anwar WA, Abdel-Aal WE, Ghoneim MA, Au WW. The CYP 2D6 extensive metabolizer genotype is associated with increased risk for bladder cancer. *Cancer Lett.* 1997 Oct;119(1):115-22.
12. Leonor Gomes. CYP 2D6 genetic polymorphisms are associated with susceptibility to pituitary tumors. *Acta Med Port.* 2005;18:339-44.
13. Lemos MC, Cabrita FJ, Silva HA, Vivian M, Placido F, Regateiro FJ. Genetic polymorphism of CYP 2D6, GSTM1 and NAT2 and susceptibility to haematological neoplasia. *Carcinogen.* 1999;20:1225-9.
14. Ladona MG, Ablidua RE Ladero JM, Roman JM, Plaza MA, Agundez JAG, Munoz JJ, Benitz J. CYP 2D6 genotypes in Spanish women with breast cancer. *Cancer Letters.* 1996;99:23-8. Blot WJ, McLaughlin JK, Winn DM. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res.* 1988;48:3282-7.
15. De Jong MM, Nolte IM, Te Meerman GJ, Van der Graaf WT, Oosterwijk JC, Kleibeuker JH, Schaapveld M, de Vries EG. Genes other than BRCA1 and BRCA2 involved in breast cancer
16. Bouchardy C, Benhamon S, Dayer P. The effect of tobacco on lung cancer risk depends on CYP 2D6 activity. *Cancer Res.* 1996;56:251-3.

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