CORRELATION BETWEEN P53 PROTEIN EXPRESSIONS IN THE INCIDENCE OF METASTASIS IN WELL-DIFFERENTIATED THYROID CANCER

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ABSTRACT

Mostly well differentiated thyroid carcinoma has a good prognosis. Distant metastases is one of bad prognostic factor. Epidemiological studies provided that the mutant protein p53 play a role on thyroid carcinoma oncogenesis. Our objective is to know whether protein p53 is expressed in well differentiated thyroid carcinoma and how is the correlation of the protein p53 expression and the metastases in well differentiated thyroid carcinoma. Method that use in this study is cross sectional study, clinical data were noted from the medical record. Thirty paraffin blocks of thyroid carcinoma patients underwent surgery at Department of Surgery Dr Soetomo Hospital during January – December 2005 were stained with p53 imunohistochemical. Correlation of protein p53 expression and metastases in well differentiated thyroid carcinoma was analyzed. From the 30 samples, 28 (93.3%) showed protein p53 expression and 2 (6.7%) no protein p53 expression in imunohistochemical staining. There were metastases in 17 patients (57%), 11 patients (36.7%) with lymph node metastases, 4 patients (13.2%) with distant metastases and 2 patients (6.8%) with distant and lymph node metastases. There was a significant correlation between protein p53 expression and occurrence of distant metastases (p = 0.027), stronger expression of protein p53 showed higher occurrence of distant metastases. There was also a correlation between protein p53 expression and the patients ages (p>0.05). No correlation between protein p53 expression and extra capsular invasion, tumor size, and lymph node metastases. We concluded that protein p53 expression was found in almost well differentiated thyroid carcinoma (93.3%). So, there was a correlation between protein p53 expression and distant metastases in well differentiated thyroid carcinoma, but no correlation with lymph node metastases.

Keywords: Protein p53 expression, well differentiated carcinoma, metastases

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INTRODUCTION

Incidents of thyroid cancer in the world tend to increase. In Florida between 1990 and 2000 the number of patients with thyroid cancer was noted to increase two times, which is from 6 per 100.000 people in 1990 to 10.1 per 100.000 people in 2000 incident. Ηοδγσον & Βυττον 2004) 203 new cases were reported each year or 1.3 % of all new cancers in Finland. In England, thyroid cancer was 0.5 % of all cancers and cause approximately 0.5 % of all deaths caused by cancers.(Arja et al.. 2004)

Although the incidence rate is low, thyroid cancer has varied biological characteristics, from lesion with fine differentiation and good prognosis to anaplastic carcinoma with bad prognosis. Varied biological characteristics of thyroid cancer are one of many prognostic factors, and have become one consideration for clinicians to treat patients with thyroid cancers. This biological characteristic will determine the type and way of therapies to be applied.

Papillary and follicular thyroid cancers are cancers with fine differentiation, the most seen cases from all thyroid cancers. Prognosis for these cancers is usually good and mostly curable, but there are still cases with recurrence tendency and some even died because of it. Thyroid cancer can metastasize either through lymph vessels or blood vessels to distant organs. If the cancer has metastasized, the prognosis will become worse. That's why, it is important for clinicians to diagnose early and determine the right therapy. Some prognostic factors are used to handle this cancer.(Shah et al. 1992)

Based on data from retrospective study collected by National Cancer Institute from 1973 to 1995, several prognostic factors of thyroid cancer had been recognized and used such as age, sex, tumor size, histological type and grading, local invasion, multi centre, and metastases (Diana et al. 2000) . A lot of acronyms had been publicized such as, AGES which was Age, Grading, Extension, Size by Mayo Clinic in 1987, AMES which was Age, Metastases, Extension, Size by Lahey Clinic,

in 1988, MACIS which was Metastases, Age, Completeness of resection, Local invasion, Size by Mayo Clinic in 1993, and MSKCC (Memorial Sloan-Kettering Cancer Center) in 1995 which included age, tumor size, histological grading, histological type, extra thyroid invasion, and metastases (Diana et al. 2000)

With the development of bio molecular and immunohistochemical techniques these days, it was found that DNA ploidy, adenilatcyclase activities, and p53 gene mutation were also significant prognostic factors for thyroid cancer patients. Thyroid cancer patients with aneuploidy DNA have worse prognosis compared to patients with diploidy DNA because the tumor is more aggressive. While in patients with high response to adenilatcyclase, stimulation for the tumor's development will increase (Diana et al. 2000).

Now there is a lot of studies about p53 protein expression in thyroid cancer, because p53 gene mutation holds important role in thyroid cancer carcinogenesis and p53 protein expression can reflect the patients' prognosis (Szybinski et al. 2001). P53 is a tumor suppressive gene which acts as gate keeper to oppose the formation of tumor.

Stopping cells proliferation cycle at phase G1 is done by normal protein p53. In thyroid cancer there is p53 gene mutation which causes p53 malfunction, and accumulation of mutated p53 protein in cancer cells can be detected by immunohistochemical examination because it is more stable and has longer half life (Pattiata et al. 1996).

Several studies previously done showed different results about p53 gene mutation and p53 protein expression in thyroid cancer. Kataki A (2003) reported that there was quite significant difference of p53 protein expression in which more expressions were found in badly differentiated and metastasized thyroid cancer.(Kataki et al. 2003) Godballe (1998) found that p53 expression had straight comparison with age, extra thyroid invasion, and distant metastases in thyroid cancer patients(Godballe et al. 1998).

However, according to Song Y (2000) and Szybinski (2001), the existence of p53 protein in thyroid cancer wasn't related with histological type, differentiation, or metastases. (Szybinski et al. 2001, Song et al. 2000) According to several studies above, it can be seen that there are still controversies about correlation between p53 protein expression and histological type and metastases of thyroid cancer, and also about p53 role as prognostic factors.

The objective of this study is to determine whether there is correlation between p53 protein expression and metastases incidence in finely differentiated thyroid cancers.

MATERIALS AND METHODS

This is a cross sectional study. The samples were paraffin blocks of thyroid cancer patients whose cancers either had metastasized to lymphoid glands or distant organs or didn't metastasize at all and had undergone surgeries in Dr. Soetomo General Hospital Surabaya January-December 2005, and either clinically or histopathologically showed finely differentiated thyroid carcinomas.

Clinical data were taken from medical documents in head surgery department of Dr. Soetomo General Hospital Surabaya. Patients who possibly had malignancies in other locations and/or had undergone either radiotherapy or chemotherapy before surgery were not included as samples. Immunohistochemical examination of p53 was done to as many as 30 paraffin blocks. After that, we also did correlation analysis between p53 protein expression and metastases incidence of finely differentiated thyroid carcinoma.

RESULTS

In period between January to December 2005, 30 samples were achieved. 80 % of the samples were females or 4 times more than males. The patients came from all ages, between 8 - 86 years old with mean 39.2 ± 18.2 years old. Half of the samples were 20 – 49 years old (table 1).

Table 1. Distribution of ages and sex in finely differentiated thyroid carcinomas

Age (Years)	Sex		Total(%)	
	Male (%)	Female (%)		
<20	1 (3.4)	3 (10.0)	4	(13.4)
20 – 49	2 (6.6)	13 (43.4)	15	(50.0)
50 – 69	2 (6.6)	8 (26.6)	10	(33.2)
≥ 70	1 (3.4)	0	1	(3.4)
Total	6(20.0)	24(80.0)	30	(100)

Histopathologic examination result showed more papillary type (70%) compared to follicular type (30%)(table 2). More than half of the specimens showed

capsular invasion (56.7%). More than half of the patients' cancers had metastasized (56.7%) either regional metastases (to the neck lymph vessels) or

distant metastases (table 3). Stage I was found the most (56,7%), no patients was in stage II, stage III was 23,3% and stage IV was 20% (figure 1).

Table 2. Histopathologic distribution of finely differentiated thyroid carcinomas

Histology type	Capsular invasion		Total (%)
	+	-	
Papillary	11(36.7)	10(33.3)	21(70)
Folicullary	6(20.0)	3(10.0)	9(30)
Total	17 (56.7)	13(43.3)	30(100)

Table 3. Metastases distribution of finely differentiated thyroid carcinomas

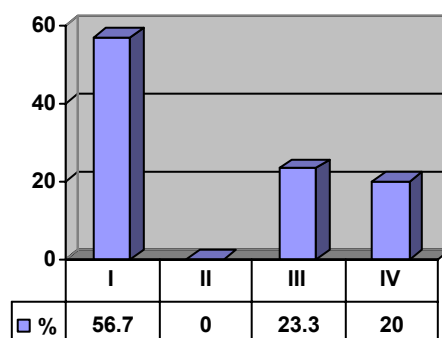| Histology type	Without metastases (%)	Metastases			Total (%)
		Regional (%)	Distant (%)	Regional + Distant(%)	
Papiler	7(23.3)	11(36.7)	2(6.6)	1(3.4)	21(70)
Folikuler	6(20.0)	0	2(6.6)	1(3.4)	9(30)
Jumlah	13(43.3)	11(36.7)	4(13.2)	2(6.8)	30(100)

Figure 1. Stages of finely differentiated thyroid carcinomas

The result of p53 protein expression was grouped into 4 cathegories which were cathegory 0 if there was less than 10% expression, expression between 11-30% was cathegory 1+, expression between 31-50% was

cathegory 2+, and expression above 50% was cathegory 3+ (figure 2). In this study we got more than half were positive 3 (56.7%) and negative expression was got in 6.7 %.

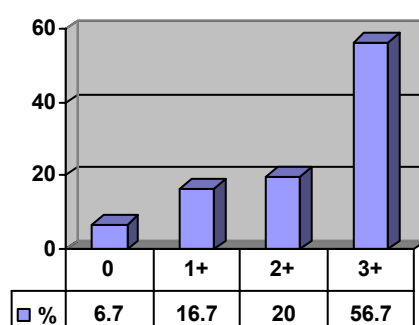|	0	1+	2+	3+
%	6.7	16.7	20	56.7

Figure 2. P53 protein expression of finely differentiated thyroid carcinoma

In the papillary type of thyroid cancer showed p53 expression category 3 + were 10 cases (47.6), categories 2 + as many as four cases (19%), category 1 + were 5 cases (23.8%) and 2 cases (9,5 %) showed expression of category 0 (figure 3).

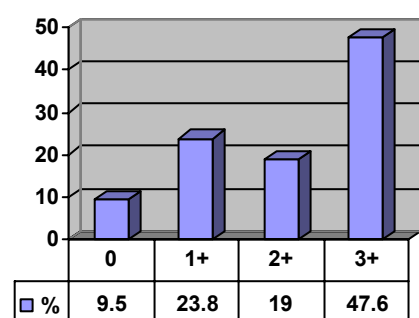|	0	1+	2+	3+
%	9.5	23.8	19	47.6

Figure 3. P53 protein expression of papillary type thyroid carcinoma

In the follicular type of thyroid cancer found that p53 expression showed category 3 + as many as 7 cases (77.8%), category 2 + were 2 cases (22.2%) and found no cases that showed category 1 + and 0 (figure 4).

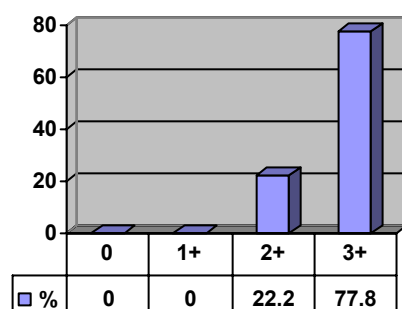|	0	1+	2+	3+
%	0	0	22.2	77.8

Figure 4. P53 protein expression of follicular type thyroid carcinoma

The mean expression of p53 protein in thyroid carcinoma differentiation between men and women was nearly equal. Statistical analysis with two independent samples t test showed p>0.05, which means there is no significant difference in mean p53 protein expression between male and female. Stage IV as much as 25% was found in only female patients and none on male patients. To know the stage distribution differences

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between patients of male and female performed statistical analysis with Mann-Whitney test. The analysis result, p>0.05, which means there is no difference between patients with disease stage distribution of men and women (table 4).

Table 4. Distribution of P53 protein expression and stage of differentiation of thyroid cancer among both men and women

Variables	Sex		Statistic test	P value
	Male N=6	Female n=24		
P53 expression	55.0±34.5	55.3±25.4	t 2 sampel t=-0.23	0.981
Stage			Mann=Whitney Z=-0.870	0.384
I	4 (66.7%)	13 (54.2%)		
II	0 (0.0%)	0 (0.0%)		
III	2 (33.3%)	5 (20.8%)		
IV	0 (0.0%)	6 (25.0%)		

Results of correlation analysis showed that age. disease stage. and p53 protein expression correlated with each other. There was significant correlation between age and disease stage (p>0.05) with the strong correlation of 0.734 which means the higher the age the higher the stage of differentiation of thyroid cancer both suffered. There was significant correlation between age and p53 protein expression (p>0.05) with a strong correlation 0.674, which means the older the age the higher the expression of p53 protein, good differentiation of thyroid cancer. There was significant correlation between disease stage with p53 protein expression (p>0.05) with a strong correlation 0.551, which means the higher the stage of disease the higher the expression of p53. There was no significant correlation between the size of tumors with p53 protein expression (p>0.05) (Table 5).

Table 5. Correlation between age, disease stage, and P53 protein expression in both thyroid cancer differentiations

Variables	P53 expression	Disease stage
Age	r = 0.674 p = 0.0001	r = 0.734 p = 0.0001
Disease stage	r = 0.551 p = 0.002	-
Tumor size	r = 0.252 p = 0.179	-

To study the correlation between p53 protein expression metastases with simple logistic regression test. The mean expression of p53 protein in patients who have metastases was 61.2 ± 27.2%, higher than those who did not experience metastases of 47.4 ± 24.9%. Simple logistic regression test results obtained with p = 0.163 a strong correlation of 0.067 which means no significant correlation between p53 protein expression with metastases.

Table 6. Correlation between the expressions of p53 protein with a total incidence of metastases

P53 expressions	Total metastases		Total n (%)
	Positive n (%)	Negative n (%)	
0	1 (5.9)	1 (7.7)	2 (6.7)
+1	2 (11.8)	3 (23.1)	5 (16.7)
+2	3 (17.6)	3 (23.1)	6 (20.0)
+3	11 (64.7)	6 (42.6)	17 (56.7)
Total	17 (100.0)	13 (100.0)	30 (100.0)

Incidence of metastases can be separated into the lymph node metastases (KGB), neck and distant metastases. The mean expression of p53 protein in patients who experience neck lymph node metastases of 55.5 ± 28.9%, which is almost the same as patients who did not experience metastases of 55.1 ± 25.9%. Simple logistic regression test results obtained with p = 0.967 a strong correlation of 0.0001 which means no significant correlation between p53 protein expression with cervical lymph node metastases (table 7).

Table 7. Correlation between the expressions of p53 proteins with the incidence of cervical lymph node metastases

P53 expressions	Lymph node metastes		Total n (%)
	Positive n (%)	Negative n (%)	
0	1 (7.7)	1 (5.9)	2 (6.7)
+1	2 (15.4)	3 (17.6)	5 (16.7)
+2	3 (23.1)	3 (17.6)	6 (20.0)
+3	7 (53.8)	10 (58.8)	17 (56.7)
Total	13 (100.0)	17 (100.0)	30 (100.0)

The mean expression of p53 protein in patients experiencing distant metastases amounted to 83.3 ± 5.2%, which almost doubled compared with patients who did not experience distant metastases 48.2 ± 25.3%.

Simple logistic regression test results obtained with p = 0.027 a strong correlation of 0.370 which means there is a significant correlation between p53 protein expression with distant metastases (table 8).

Table 8. Correlation between the expressions of p53 proteins with the incidence of distant metastases

P53 expressions	Distant metastases		Total n (%)
	Positive n (%)	Negative n (%)	
0	0 (0.0)	2 (8.3)	2 (6.7)
+1	0 (0.0)	5 (20.8)	5 (16.7)
+2	0 (0.0)	6 (25.0)	6 (20.0)
+3	6 (100.0)	11 (45.8)	17 (56.7)
Total	6 (100.0)	24 (100.0)	30 (100.0)

The mean expression of p53 protein in the histopathological picture of capsule invasion of $51.8 \pm 28.5\%$, slightly lower than the absence of capsule invasion of $59.1 \pm 24.7\%$. Simple logistic regression test results obtained with $p = 0.420$ a strong correlation of 0.022 which means no significant correlation between p53 protein expression with invasion of capsule (table 9).

Table 9. Correlation between the expressions of p53 protein with capsular invasion

P53 expressions	Capsular invasion		Total n (%)
	Positive n (%)	Negative n (%)	
0	2 (11.8)	0 (0.0)	2 (6.7)
+1	3 (17.6)	2 (15.4)	5 (16.7)
+2	4 (23.5)	2 (15.4)	6 (20.0)
+3	8 (47.1)	9 (69.2)	17 (56.7)
Total	17 (100.0)	13 (100.0)	30 (100.0)

The mean expression of p53 protein in the histopathological picture of follicular type of $70.0 \pm 17.3\%$, higher than the papillary type is $48.9 \pm 27.9\%$. Simple logistic regression test results obtained with $p = 0.062$ a strong correlation of 0.141 which means no significant correlation between p53 protein expression with histology type of differentiation of thyroid carcinoma is good (table 10).

Table 10. The correlation between p53 protein expression with histology type of differentiation of thyroid carcinoma either

P53 expressions	Histology type		Total n (%)
	Papillary n (%)	Follicularly n (%)	
0	2(9.5)	0 (0.0)	2(6.7)
+1	5(23.8)	0 (0.0)	5(16.7)
+2	4(19.0)	2(22.2)	6(20.0)
+3	10(47.6)	7(77.8)	17(56.7)
Total	21(100)	9(100)	30(100)

DISCUSSION

Of the 30 blocks of paraffin well differentiated thyroid cancer is examined in this research, the papillary and follicular types each have 21 (70%) and 9 (30%). This is consistent with the literature that the type of papillary thyroid cancer is the most types of follicular type, followed by a second sequence of all thyroid carcinomas. (Davies 1993) age of patients most in this study group the age range 20-49 years (50%). There were three patients (10%) aged <20 years.

Of sex, good differentiation of thyroid cancer was found more in women (80%) than men (20%). This is in accordance with the literature that says that more women suffer from thyroid carcinoma, especially due to hormonal factors, which is one reason for the occurrence of thyroid carcinoma (Davies 1993, Fraker et al. 2001). Of the 30 patients studied, found metastases in 17 women (57%) and it was found that as many as 14 people papillary type (82%). This is consistent with the literature that the papillary type of thyroid cancer metastases and more often provide 63-80% of the papillary type of thyroid cancer patients have undergone mikrometastase. (Lin 1999)

Six patients had metastases found three patients (10%) with papillary thyroid cancer and three patients (10%)

with follicular thyroid cancer. And from three patients with papillary thyroid cancer, papillary thyroid cancer, all of which are follicular type. This is in accordance with the literatures that papillary thyroid cancer follicular type has aggresivitas larger than pure papillary type of thyroid cancer. (Fraker et al. 2001, Jean 1998)

All the paraffin blocks examined p53 protein expression using immunohistochemical techniques and the result is a positive expression of 3 (severe) of 17 (56.7%), positive 2 (moderate) as many as six (20%) and positive one (mild) 5 (16.7%). Only found two cases (6.7%) showing negative p53 protein expression (zero). This shows that in almost all good differentiation of thyroid cancer mutation of p53 protein resulting in its function as a suppressor gene is not going well. Mutated p53 protein which plays a role in the process of carcinogenesis of thyroid carcinoma (Kummar et al. 2005, Soares et al. 2004).

In this study, 17 (56.7%) patients with thyroid cancer who had experienced good metatase neck lymph node metastases or distant metastases. This shows that thyroid cancer patients for treatment to Dr Soetomo most advanced stage. Naguib (1992) report of 1599 patients who came to his clinic for about 50 years, found that 58% of patients already have lymph node metastases either the neck or distant organs (Naguib et al. 1992).

It was found in 11 cases (64.7%) showed positive expression of p53 protein 3, a positive two to three cases (17.6%), positive one in two cases (11.8%) and 0 in one case (5.9%). Simple logistic regression test results obtained with p = 0.163 a strong correlation of 0.067 which means no significant correlation between p53 expression with metastases. These results are consistent with Song Y (2000) and Szybinski (2001), they found no significant correlation between metastases and p53 protein expression. (5.9) This can happen because many other factors that could cause such metastases adenilatsiklase activity , DNA aneuploidy, and others (Diana et al. 2000).

In this study, 13 patients (43.3%) had cervical lymph node metastases. JD Lin (1999) reported over 18 years, from 910 cancer patients thyroid differentiation both get 134 (14.7%) patients had cervical lymph node metastases. While some other researchers who perform prophylactic neck dissection found that 27-82% of thyroid cancer patients both have experienced differentiation micro neck lymph node metastases (Lin et al. 1999).

The mean p53 expression in patients experiencing cervical lymph node metastases of 55.5 ± 28.9%, which

is almost the same as patients who did not experience metastases of 55.1 ± 25.9%. Results of simple logistic regression p = 0.967 can be derived with the strong correlation of 0.0001 which means no significant correlation between p53 expression with cervical lymph node metastases.

This indicates that although the expression of p53 protein does not mean that the higher incidence of lymph node metastases of the neck will be higher as well. These results are in accordance with a study by Song Y (2000), Szybinski (2001), whereas no correlation between p53 protein expression with the incidence of cervical lymph node metastases in patients with good differentiation of thyroid carcinoma (Szybinski et al. 2001, Song et al. 2000).

Prognostic influence of neck lymph node metastases is still unclear. Some studies suggest that cervical lymph node metastases did not affect survival rates but the effect on tumor recurrence rates (Lin et al. 1999). In this study, six patients (20%) had suffered metatastase much on other organs, namely in the lung (3 patients), iliac bone (one patient) and frontal bone (2 patients). Of the six patients experiencing metasase found three patients (10%) with papillary thyroid cancer follicular type and 3 patients (10%) with follicular thyroid cancer.

The mean p53 expression in patients experiencing distant metastases by 83.3 ±5.2%, which almost doubled compared to patients who did not experience metastases of 48.2 ± 25.3%. Simple logistic regression test results obtained with p = 0.027 a strong correlation of 0.370 which means there is a significant correlation between p53 expression with distant metastases. This is according to a study by Godballe (1998) that showed a correlation between p53 protein expressions with differentiation of thyroid cancer metastases is much better.

The greater expression of p53 protein, the greater the possibility of metastases of thyroid cancer has experienced far (Godballe et al. 1998). The existence of distant metastases also showed that the prognosis of thyroid cancer patients will get worse and the heightens mortality. (26) On this study, 21 patients (70%) types of papillary thyroid cancer and 9 patients (30%) follicular type. Of the 21 patients with papillary thyroid cancer was found three patients (14.2%) were papillary thyroid cancer follicular type, and all had 3 + expression of p53 protein. The mean expression of p53 in thyroid cancer follicular type of 70.0 ± 17.3%, higher than the papillary type is 48.9 ± 27.9%

This is consistent with the literature that the follicular type of thyroid cancer have a mutation of the p53

protein is greater than papillary. (Godballe et al. 1998, Soares et al. 1994) But from the results of tests performed simple logistic regression p = 0.062 obtained with the strong correlation of 0.141 which means no significant correlation between p53 expression with histological type of thyroid carcinoma differentiation either.

In Section Surgery Dr Soetomo to determine the differentiation of thyroid cancer prognosis is a good prognostic factor according to Ames criteria consisting of age (Age), distant metastases (Metastases), capsule extensions (Extention) and tumor size (Size). It says a good prognostic factor when patients age<40 years for men and <50 years for female patients, did not experience distant metastases, tumor size <5 cm and tumor extension did not hold out the thyroid capsule.

These prognostic factors in addition to determining the prognosis, can also be used to determine the type of operation to be performed. Differentiation of thyroid cancer patients with good prognostic factors of all, need not be total tiroidektomi, hemitiroidektomi done enough so that the patient does not need to take thyroid hormone preparations lifetime. This is according to research reported by Hay ID (1998) on the differentiation of thyroid carcinoma with good prognostic factors did not show recurrence rate hemitiroidektomi different to that of the total tiroidektomi. (Hay et al. 1998).

Age is one of the important prognostic factors in differentiation of thyroid cancer well. Many studies have shown that there is a direct relationship between age of patients with thyroid cancer mortality in both differentiation. (Davies 1993, Cady et al. 1979) In this study, 15 patients (50%) are in the age range 20-49 years and patients aged over 50 years as many as 11 people (36.6%). Several papers mention that age <40 years in men and <50 years in women having a good prognosis. (Davies 1993)

Spearman correlation test results showed a significant correlation between age and p53 expression (p>0.05) strong correlation of 0.674 with a mean age of the older the patient the higher the p53 expression of thyroid cancer. Godballe (1998) also reported that of 211 patients with thyroid cancer showed good differentiation was significant correlation between p53 with patient age. (Godballe et al. 1998)

The existence of extensions out of the capsule of thyroid tumors showed high aggresivity of the tumor, therefore the invasion outside the capsule affects the prognosis of patients with good differentiation of thyroid cancer. The invasion came out of this capsule will be more

meaningful if the tumor is also an invasion of blood vessels (angioinvasi). (Diana et al. 2000)

In this study, tumors from 17 patients (56.7%) have experienced the invasion of the capsule. The mean expression of p53 protein in the histopathological picture of capsule invasion of 51.8 ± 28.5%, slightly lower than that in the absence of capsule invasion of 59.1 ± 24.7%. Simple logistic regression test results obtained with p = 0.420 a strong correlation of 0.022 which means no significant correlation between p53 protein expression with the invasion of the capsule. These results indicate that tumor invasion through the capsule was not influenced by the size of a mutated p53 proteins in both differentiation of thyroid cancer.

Beahrs (1984) found that tumor size affects the differentiation of thyroid cancer prognosis good. Patients with smaller tumor size is said to have a good prognosis because these tumors have a low aggresivitas properties, and vice versa on thyroid cancer with large tumors have a high aggresivitas. (Beahrs 1984) at Ames as a cut-off criteria of tumor size was 5 cm. In contrast to the results we get, in this study we found nine patients (30%) with tumor size <5cm, but metastases have experienced either neck lymph node metastases or distant organ metastases.

ven a patient with thyroid cancer "occult" metastases has experienced far into the frontal bone. Davies (1993) suggested that 13-28% of patients who experienced cancer metastases of thyroid differentiation of both primary tumor which turned out to have "occult". Large size of thyroid cancer will provide local complications such as airway obstruction which would cause mortality of patients. (Davies 1993, Goldman et al. 1980) Spearman correlation test results showed there was found no significant correlation between the size of tumors with p53 protein expression (p> 0.05).

CONCLUSION

From this research we can conclude that, expression of mutated p53 protein was found in good differentiation of thyroid cancer (papillary type and follicular type). We found no correlation between p53 protein expression with the occurrence of extra-capsular invasion and tumor size in both thyroid cancer differentiation. There is a correlation between p53 protein expression with differentiation of thyroid cancer patients aged well. The older the age, the higher expression of p53 protein is mutated.

Found no correlation between the expression of p53 proteins with the incidence of cervical lymph node

metastases of thyroid cancer better differentiation. There is a correlation between expression of p53 proteins with the incidence of distant metastases of thyroid cancer better differentiation.

The stronger expression of p53 protein is mutated, the more likely a good differentiation of thyroid cancer had distant metastases. Follicular thyroid cancer types showed the frequency of p53 protein expression 3 + category is greater than the type of papillary thyroid cancer (77.8% vs 47.6%)

For further research it is expected that the research on the expression of p53 protein that the examination performed before surgery by taking the material through the Fine Needle aspiration (Fna). We hope there is continued research on the cut-off levels of p53 expression associated with differentiation of thyroid cancer metastases in both

REFERENCES

Hodgson NC, Button J. Thyroid cancer : Is the incidence still increasing ?. Ann Surg Oncol 2004; 11:1093-1097

Arja Jukkola, Risto Bloigu, Tapani Ebeling. Prognostic factors in differentiated thyroid carcinoma and their implications for current staging classifications. Endocrine Related Cancer 2004; 11:571-579.

Diana SD, Ian DH, Hay MB. Prognostic indicators in differentiated thyroid carcinoma. Cancer Control 2000; 7: 229-239

Shah JP, Loree TR, Dharker D, et al. Prognostic factors in differentiated carcinoma of the thyroid gland. Am J Surg 1992; 164 : 658-61.

Szybinski P, Nowak W, Stachura J et al. Expression of protein p53: the marker of low neoplatic cell differentiation in thyroid carcinoma. Wiad Lek 2001; 54 Suppl 1 :88-94

Pattiata R. The p53- tumor supressor gene. In : Indon J Pathol Vol 6. Jakarta : P.T. Repro International ; 1996.p. 7-12

Kataki A, Sotirianakos S, Memos N et al. P53 and C-FOS overexpression in patients with thyroid cancer: an imunohistochemical study. Neoplasma 2003 ; 50 :26-30.

Godballe C, Asschenfeldt P, Jørgensen KE, et al. Prognostic factors in papillary and follicular thyroid carcinomas: p53 expression is a significant indicator of prognostic. Laryngoscope 1998; 108 : 243-9.

Song Y, Wang L, Huang G, Yuan S, Xiao L. Relationship of p53 gene mutation with pathological characteristics and prognosis of thyroid carcinoma. Hua Xi Yi Ke Da Xue Xue Bao 2000; 31: 298-299, 314

Davies C. Surgery of Thyroid Cancer. In : Lynn J, Bloom SR (eds). Surgical Endocrinology. Oxford: Butterworth-Heinemann;1993. p. 240-257

Reksoprawiro S. Karsinoma Tiroid. Deteksi Dini dan Penanganannya. Warta Ikabi 1997;10:140-154.

Fraker DL, Skarulis M, Livolsi V. Thyroid tumors. In: DeVita VT Jr, Hellman S, Rosenberg SA, (eds), Cancer: Principles and Practice of Oncology. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001. p 1740-1762

KazakovVS, Demidchik EP. Thyroid cancer after Chernobyl. Nature 1992;359:21

Mc Henry C, Jarosz H, Calandra D. Thyroid neoplasia following radiation therapy for Hodgkin's lymphoma. Arch Surg 1987;122:684-686.

Martin Jean. Review Articles : Papillary and follicular thyroid carcinoma. New Engl J Med. 1998; 338: 297-306

JD Lin, MJ Liou, TC Chao. Prognostic variables of papillary and follicular thyroid carcinoma patients with lymph node metastases and without distant metastases. Endocrine Related Cancer 1999; 6: 109-115.

Goldman JM, Goren EN, Cohen MH, et al. Anaplastic thyroid carcinoma: long-term survival after radical surgery. J Surg Oncol 1980; 14 : 389-394.

Hay ID, Grant CS, Bergstralh EJ, et al. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? Surgery 1998; 124 : 958-64; discussion 964-6.

Cady B, Sedgwick CE, Meissner W. Risk Factor analysis in differentiated thyroid cancer. Cancer 1979;43: 810-820

Giuffrida D, Gharib H. Current diagnosis and management of medullary thyroid carcinoma. Ann Oncol 1998; 9 : 695-701

Thyroid. In: American Joint Committee on Cancer.: AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer; 2002. p 77-87.

Stratton M.R. The p53 gene in human cancer. In: Yamold J.R, Stratton MR, Mc Millian T.J.(eds) Molecular Biology for Oncologists, 2th ed. Great Britain: Chapman 7 Hall :1996. p. 92-101.

Kumar, Abbas, Fausto. Neoplasia. In : Kumar V, Abbas AK, Fausto N. Robbins and Cotran (eds). Pathologic Basic of Disease. 7th ed Philadhelphia: Elsevier Inc;2005.p. 288-339.

Soares P, Camaselle TJ, Sobrinho SM. Immunohistochemical detection of p53 in differentiated, poorly differentiated and undifferentiated carcinomas of the thyroid. Histopathology 1994; 24 :205-210

Gown AM, Leong A. Immunohistochemistry of "solid" tumor : poorly differentiated round cell and spindle cell tumors II. In : Leong AS, (ed). Applied

Immunohistochemistry for surgical pathologist. Great Britain: Edward Arnold ; 1993.p. 97-98

Naguib AS, Pamela NS, Robert CH. The Results of various modalities of treatment of well differentiated thyroid carcinoma: A Retrospective review of 1599 patients. J Clin Endocrinol Metab 1992; 75:714-720.

Yamashita H, Noguchi S, Murakami N. Extraxcapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. Cancer 1997;80:2268-72.

Beahrs,OH. Surgical treatment for thyroid cancer. Brit J Surg 1984; 71:976-979.