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The Correlation between Primary Tumor Staging and Serum Tumor Markers in Testicular Cancer Patients: A Retrospective Single Center Study

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Abstract: Background Testicular cancer possesses good survival rate if it is managed well. The staging of testicular cancer plays important role to determine survival rate. The primary outcome of this study is to evaluate the correlation between primary tumor staging and serum tumor markers staging. The secondary outcome is to evaluate 2 years overall survival rate (OS). Methods We retrospectively included 122 testicular cancer patient's medical record. Data were collected from medical record system of Soetomo General Hospital during the period of 2015–2019. The ordinal data were analyzed using gamma correlation test. Overall survival rate was analyzed using survival analysis and Kaplan Meier statistic. Results Mean age of the subjects in this study was 29.96±16.68 years. There was moderate correlation between primary tumor staging and serum tumor markers staging ($r=0.491$; $p<0.001$). Correlation was also found between primary tumor staging with hCG level ($r=0.250$; $p=0.042$), LDH level ($r=0.432$; $p<0.001$). There was no significant correlation between primary tumor staging and AFP level ($r=0.180$; $p=0.148$). In terms of 2 years OS, seminoma pathology type was better compared to non-seminoma pathology type (HR=6.36; $p<0.001$) and primary tumor (T1) was better compared to T3 and T4 (HR=4.7 and 7.93; $p<0.001$). Clinical stage 1 was also better compared to clinical stage 2 (HR=2.584; $p=0.021$) and clinical stage 3 (HR 1.354; $p=0.478$) in terms of 2 years OS. Conclusion There was correlation between primary tumor staging and serum tumor markers. Pathological finding of seminoma, lower stage primary tumor and lower clinical stage were associated with better 2 years OS of testicular cancer patient.

Keywords: staging, testicular, cancer, overall survival

I. Introduction

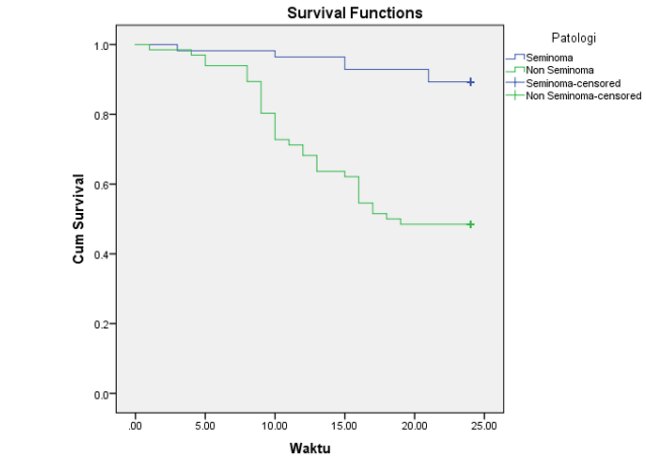
Testicular cancer is commonly found in men aged between 20-45 years old. This cancer is rarely found in people under 15 years old or above 60 years old. Testicular cancer accounts for 1-2% cancer on men and 5% of all urology tumors. The estimated new case number in America is 9 of 100.000 men each year. Around 90-97% of reported primary tumor are germ cell tumor (GCT) (seminoma and nonseminoma) while the rest is non-germ testicular tumor including Leydig cell, Sertoli cell, and gonadoblastoma [1–4]Testicular cancer has the best life expectancy among all if treated properly [3,4]. Serum tumor markers alpha fetoprotein, (AFP), beta human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH) represent valuable tools for the management of testicular cancer [5]. Serum tumor markers are able to help in diagnosis of GCT, predict tumor stage and to assess prognosis[6,7]. Moreover, it was found that not all testicular cancer cause elevations of these markers and it was influenced by histology and tumor burden[8]. To date, only few original data are available regarding the correlations of serum tumor markers with primary tumor staging. Information on survival of cancer patients represent an important indicator of cancer control. In order to plan health services, estimation in the number of alive survivors is required[9]. Previous research reported that histopathology type, age, and extent of disease are identified as prognostic factors in testicular cancers[10]. Several reports have provided survival rate in testicular cancers, however only few have reported survival data with differentiation between seminoma and non-seminoma patients. Also, only few data have reported survival rate in Indonesian patient. Therefore, our objectives in this study were: (1) to assess the correlations of primary tumour staging and serum tumour markers, and (2) to analyze the 2 years of overall survival rate in testicular patients.

II. Medhods

This study is a retrospective cross-sectional which the data was collected from the medical records of dr. Soetomo General Hospital, Indonesia within the period of 2015-2019. The study was approved by the ethical committees of the hospital. A total of 122 testicular patients were included in our study (Table 1). Inclusion criteria was used to choose the study sample. The patient with confirmed histopathology of testicular cancer was included into our study. The exclusion criteria were if the patients had incomplete and insufficient data from their medical records. The informations collected were the degree of tumors, nodules, metastases, rate of tumor markers (LDH, hCG, AFP), stages, and histopathology types with gamma correlation test. Overall survival analysis was produced using Kaplan-Meier analysis.

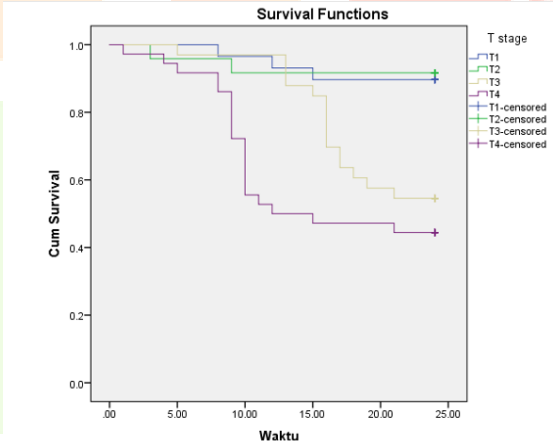
III. RESULT

The patients' age was between 1-68 years old with an average age of 29.96 ± 16.68 years old. There was a moderate correlation between primary tumor staging and serum tumor markers staging (r=0.491; p<0.001) (Table 2). Primary tumor staging also had correlation with hCG level, despite this was a weak correlation (r=0.250; p=0.042) (Table 3). The was correlation between primary tumor staging and AFP level although this correlation was not significant (r=0.180; p=0.148) (Table 4). There was also significant moderate correlation between primary tumor staging and LDH level (r=0.432; p<0.001) (Table 5). Compared to non-seminoma pathology type, seminoma pathology type was better in terms of 2 years overall survival rate (OS) (HR=6.36; p<0.001). Primary tumor (T1) was also better compared to T3 and T4 (HR=4.7 and 7.93; p<0.001) regarding 2 years OS. Clinical stage 1 was also better compared to clinical stage 2 (HR=2.584; p=0.021) and clinical stage 3 (HR 1.354; p=0.478) in terms of 2 years OS despite the correlation was not statistically significant.



Number of patient at risk						
Seminoma	56	55	54	52	52	50
Non seminoma	66	62	48	41	32	32

Figure 1. Kaplan Meier Statistics of Histopathological Type



Number of patients at risk						
T1	29	29	28	26	26	26
T2	24	23	22	22	22	22
T3	33	32	32	28	19	18
T4	36	33	20	17	17	16

Figure 2. Kaplan Meier Statistics of T Stage

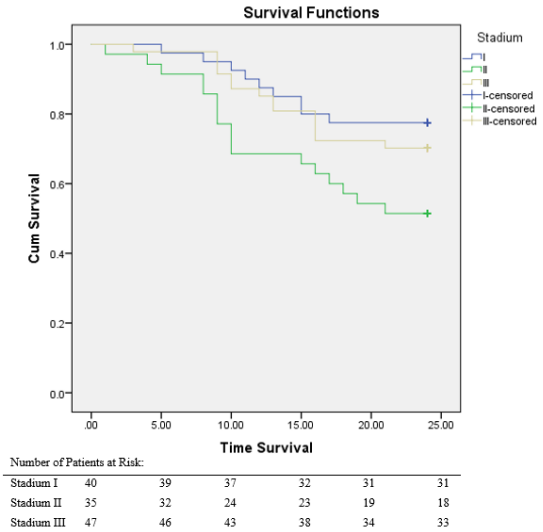


Figure 3. Kaplan Meier Statistics of Stadium

Table 1. Patients Characteristics

Characteristics	Frequency	Percentage
Age		
Mean	29.96 ± 16.68	-
Median	31 Years	-
Range	1-68 Years	-
T stage		
T1	29	(23.8%)
T2	24	(19.7%)
T3	33	(27.0%)
T4	36	(29.5%)
N stage		
N0	28	(23.0%)
N1	22	(18.0%)
N2	22	(18.0%)
N3	26	(21.3%)
Nx	24	(19.7%)
M stage		
M0	60	(49.2%)
M1	45	(36.9%)
Mx	17	(13.9%)
S stage		
S1	15	(12.3%)

S2	71	(58.2%)
S3	36	(29.5%)
Stadium		
I	40	(32.8%)
II	35	(28.7%)
III	47	(38.5%)
hCG (mIU/mL)		
<5000	72	(59.0%)
5000-50.000	34	(27.9%)
>50.000	16	(13.1%)
AFP (ng/mL)		
<1000	70	(57.4%)
1000-10.000	39	(32.0%)
>10.000	13	(10.7%)
LDH (U/I)		
<1.5 x N	32	(26.2%)
1.5-10 x N	68	(55.7%)
>10 x N	22	(18.0%)
Pathology		
Seminoma	56	(45.9%)
Nonseminoma	66	(54.1%)

Table 2. Correlation between T Stage and S Stage

T stage	**S stage**			**Correlation Coefficient**	**p value**
	S1	**S2**	**S3**		
T1	3 (10.3%)	24 (82.8%)	2 (6.9%)		
T2	5 (20.8%)	18 (75.0%)	1 (4.2%)	0.491	<0.001
T3	4 (12.1%)	16 (48.5%)	13 (39.4%)		*
T4	3 (8.3%)	13 (36.1%)	20 (55.6%)		

Table 3. Correlation between T Stage and hCG level

T stage	hCG level (mIU/mL)			Correlation Coefficient	p value
	<5000	5000-50000	>50000		
T1	20 (69.0%)	9 (31.0%)	0 (0%)	0.250	0.042*
T2	14 (58.3%)	10 (41.7%)	0 (0%)		
T3	18 (54.5%)	10 (30.3%)	5 (15.2%)		
T4	20 (55.6%)	5 (13.9%)	11 (30.6%)		

Table 4. Correlation between T Stage and AFP level

T stage	AFP level (ng/mL)			Correlation Coefficient	p value
	<1000	1000-10000	>10000		
T1	16 (55.2%)	13 (44.8%)	0 (0%)	0.180	0.148
T2	15 (62.5%)	4 (37.5%)	0 (0%)		
T3	22 (66.7%)	4 (21.2%)	4 (12.1%)		
T4	17 (47.2%)	4 (27.8%)	9 (25.0%)		

Table 5. Correlation between T Stage and LDH level

T stage	LDH level (U/I)			Correlation Coefficient	p value
	<1.5xN	1.5-10xN	>10xN		
T1	10 (34.5%)	17 (58.6%)	2 (6.9%)	0.432	<0.001 *
T2	10 (41.7%)	13 (54.2%)	1 (4.2%)		
T3	8 (24.2%)	19 (57.6%)	6 (18.2%)		
T4	4 (11.1%)	19 (52.8%)	13 (36.1%)		

Table 6. 2 Years Overall Survival of Testicular Cancer Patients

Characteristics	Status		2 years OS	HR	95%CI		p value
	Survive	Death			min	Max	
Total	82	40	67.2%				
Pathology							
Seminoma	50	6	89.3%				<0.001
Nonseminoma	32	34	48.2%	6.36	2.66	15.20	
T stage							
T1	26	3	89.7%				
T2	22	2	91.7%	0.81	0.13	4.88	<0.001
T3	18	15	54.5%	4.70	1.36	16.24	
T4	16	20	44.4%	7.93	2.35	26.78	
Stadium							
1	31	9	77.5%				
2	18	17	51.4%	2.584	1.15	5.80	0.021
3	33	14	70.2%	1.354	0.58	3.12	0.478

IV. Discussion

Testicular cancer is commonly found in men aged between 20-45 years old. Testicular cancer is considered to have the best life expectancy if treated properly [3,4]. The general symptoms found in testicular cancer is painless swelling testicle. The swelling generally occurs slowly, and people rarely complaint the weight sensation on testicle which leads to late diagnosis. Late diagnosis and therapy can predispose higher incidence of tumor spread. Delayed therapy is primarily due to patients' unawareness to undergo independent physical examination (IME) [11]. Therefore, tumor marker test can be a tool to make diagnosis, identify stages and prognosis. Some routine tumor marker tests are carried out to make a diagnosis and testicular cancer management, which are AFP, hCG and LDH [12]. Based on the results of this study, 29% of patients with testicular cancer and treated in Dr. Soetomo General Hospital were in primary tumor T4. Based on the laboratory examination results on 112 research subjects, most subjects have hCG level below 5000 mIU/mL, AFP level below 1000 ng/mL, and LDH level 1.5 – 10 times more than the normal level. The AFP level did not show consistent results toward primary tumor stage. This result was proved through the greatest rate of AFP 5000-10.000 ng/mL on patients with primary tumor T1, but the highest level of AFP <1000 ng/mL was on patients with primary tumor stage T3. The result supported the fact that there was insignificant correlation between primary tumor stages and testicular cancer with AFP level. The prior studies proved that the AFP produced by the yolk sac mainly increased on embryonal and teratoma cancer [13]. The increased AFP level generally occurs in nonseminoma, but not in seminoma [3]. For this reason, our results could be influenced by the use of seminoma and nonseminoma mixed sampling. The increased AFP level can also be a false positive if a liver failure occurs due to chemotherapy treatment [13]. Therefore, only taking the AFP level test is not valid enough to predict the overall testicular cancer stage. Based on the result of this study, it was found that patients with primary tumor T1 mainly had hCG level less than 5000 mIU/mL, while the patients with primary tumor T4 had the highest hCG level more than 50.000 mIU/mL. A significant correlation was found between primary tumor stage and hCG serum on testicular cancer patients. Although consistent results and significant correlation were found between primary tumor stage and hCG level, the correlation coefficient of the test results showed that the r was 0.250 which implied that the correlation was weak. A similar study explains that in general, patients with seminoma will have increased hCG, but the hCG will increase only in 15-20% cases in advanced tumor stage [14]. The hCG level test holds limitation in its sensitivity and specificity in identifying the stage of testicular cancer because this tumor marker can also increase to other malignancy, such as neuroendocrine, bladder, kidneys, and lungs [13]. A detailed anamnesis is required before interpreting the hCG level increase since certain conditions such as hypogonadism might induce hCG production from hypophysis as a compensation mechanism causing false positive [13]. Therefore, hCG single examination is inadequate to predict the stage of testicular cancer. The LDH test showed a quite consistent results to testicular cancer primary tumor stage. Patients with primary tumor T1, T2, and T3 mostly had LDH level 1.5-10 times more than normal and patients with stage T4 cancer mainly had LDH level 10 times more than normal. Theoritically, LDH level was in concordance with testicular cancer primary tumor stage which our analysis test also revealed

a significant correlation between primary tumor stage of testicular cancer and LDH level with correlation coefficient of 0.432. Therefore, the correlation of staging and testicular cancer with LDH was higher than hCG and AFP. However, just like AFP and HCG, the LDH test produces also limitation regarding its sensitivity and specificity. False positive may appear from the increased LDH due to the condition of thalassemia, leukemia, and heart attack [13]. Additionally, our statistical analysis on tumor marker level showed results that were in concordance with LDH examination. We found a significant correlation test between primary tumor stage of testicular cancer and tumor marker level with r correlation coefficient of 0.491. Therefore, tumor marker level has the strongest correlation in predicting testicular cancer primary tumor stage compared to other single tumor marker tests. Histopathology test plays an important role in determining the therapy and prognosis of testicular cancer. This had been revealed through the study results that the patients' overall survival in two years was higher on seminoma histopathology type with the survival rate of 89.3% compared to non-seminoma histopathology type, which only by 48.2%. Besides, the multivariate analysis produced a significant result on overall survival for two years, with hazard ratio 6.36 times higher in non-seminoma cases than seminoma. This results are in accordance with the previous study which explains that seminoma has higher survival rate [3]. Based on the stages, this study revealed that stage 1 had the largest life expectancy by 77.5%. Multivariate analysis showed that HR level was 2.584 times higher on stage 2 than stage 1. While for stage 3, the HR level was 1.354 compared to stage 1 although this result was not statistically significant. Prior studies stated that the survival rate of five-year free tumor was 98% for stage I and 92% for stage IIA if testicular cancer was treated properly [3]. This study also revealed that cancer staging held an important role in determining testicular cancer prognosis, in accordance with other malignancy. This result was proved with Kaplan-Meier curve, the lowest on T4 compared to stage T1, T2, and T3. Besides, multivariate test showed a hazard ratio by 7.93 times on T4 stage compared to T1. Therefore, tumor marker level is essential and can be used to predict patient's prognosis in the future. The results of this study strengthen the established research that the changes in tumor marker level are useful in evaluating therapeutic response in any clinical scenario. In addition, serum tumor marker test is also useful to make risk stratification, and holds a crucial role in patient's surveillance strategy with GCT[15].

V. Conclusion

There is a correlation between primary tumor staging and serum tumor markers. Histopathological finding of seminoma, lower stage primary tumor and lower clinical stage were associated with better 2 years OS of testicular cancer patient.

VI. Acknowledgment

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