p-ISSN 2797-4189
e-ISSN 2797-457X

THE INDONESIAN JOURNAL OF CANCER CONTROL

Official Journal of The Indonesian Society of Oncology

InaJCC Vol.01 No.02 Page: 43-74

Jakarta, September–December 2021

p-ISSN 2797-4189
e-ISSN 2797-457X

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Jakarta, September–December 2021

Aims and Scope

Aims

The Indonesian Journal of Cancer Control aims to contribute towards better knowledge as a result of scientific studies that can be accessed by academic circles and researchers.

Scope

The Indonesian Journal of Cancer Control is a scientific quadrimester journal, managed by the Indonesian Society of Oncology. This journal is designed as a place of dissemination of information and scientific knowledge. It publishes original articles, case reports or case series, and review articles. These comprise of biomedical science, clinical medicine, public health science, and medical science education in the cancer field.

The Indonesian Journal of Cancer Control (InaJCC) is a quadrimester electronic journal, publishing papers in a wide spectrum of cancer control. The journal was launched in 2021 as the official publication of the Indonesian Society of Oncology and its first volume was published in 2021.

The InaJCC with its distinguished, diverse, and Indonesian & International-wide team of editors, reviewers, and readers, ensure the highest standards of research communication within the cancer control community across Indonesia as well as globally. The InaJCC accepts manuscripts on the whole spectrum of cancer control.

p-ISSN 2797-4189
e-ISSN 2797-457X

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Volume 1 **Number 2, September–December 2021**

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InaJCC The Indonesian Journal of Cancer Control

Editorial

Tobacco as cancer risk and the need for oncologists to be aware

Tobacco use is considered as one of the most serious – yet supposedly preventable – risk factor of cancer, casing the death of more than 8 million people in the world, in which more than 7 million are the direct result (1,2 million are attributed to second-hand smoke). With no threshold of safety to its exposure, this includes also various forms currently circulating in the market, i.e., various smokeless tobacco products, the so-called “safer alternatives”.

The clinical oncologist has traditionally been regarded as a “curative” person, expert in the use of means and technology in the fight against cancer; he or she is well-trained in the diagnosis and treatment of this deadly disease. But it is not enough. The incidence, and thus mortality, of cancer can only be brought down through a concerted effort in controlling through prevention and early detection.

And it is none more true than regarding the control of tobacco use.

With special emphasis on Indonesia, one of the highest users of tobacco in the world, oncologist should be well-informed and able to use their expertise, bringing the battle to the early

Leading cause of death, illness and impoverishment has been cited by the World Health Organization as consequences of tobacco use in mid and low-income countries like Indonesia, and oncologist should be aware and take part in the efforts to eliminate them.

Smokeless tobacco, for instance, is highly addictive and causes damage to health. Known to contain many cancer-causing toxins, its use increases the risk of cancers of the head, neck, throat, oesophagus and oral cavity (not to mention cancer of the mouth, tongue, lip and gums). The research by Samoedro in this edition of the InaJCC is an important article as it targets the young, a significant component of Indonesian society highly vulnerable to tobacco use. More research is need in this field, hopefully increasing awareness of oncologists – because the fight against tobacco is not only in the doctor’s examination room. Social media and community should also be the battlegrounds of the oncologist.
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Aru W Sudoyo

InaJCC The Indonesian Journal of Cancer Control

Original Article

Peripheral neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as prognostic factors in patients with nasopharyngeal carcinoma

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p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v1i2.50

Received: August 25, 2021
Accepted: December 10, 2021

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Abstract

Background: This study aimed to evaluate the prognostic value of pretreatment peripheral neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in nasopharyngeal carcinoma (NPC).
Methods: A total of 450 NPC patients in Dr. Sardjito hospital, Yogyakarta were recruited. Kaplan-Meier was used to analyze patients' survival while association of pretreatment NLR and PLR with overall survival (OS) were examined with Cox proportional hazards regression model (adjusted for age, gender, WHO pathological classification, clinical staging, and therapy).
Results: Cut-off values of 5.35 and 339.23 for pretreatment NLR and PLR respectively were used to sort NPC patients into high- and low-level groups. NLR and PLR are associated with tumor size (P=0.015 : P=0.012). High NLR and PLR are significantly associated with lower OS (median OS±SE high-level NLR vs. Low-level NLR: 20.18 ± 2.68 vs. 33.29 ± 2.38 months, P< 0.001; median OS±SE high-level PLR vs. low-level PLR: 20.29 ± 1.89 vs. 32.86 ± 2.27 months, P<0.001). NLR, clinical stage and therapy are independent prognostic factors in NPC (NLR: HR, 1.84; 95% CI, 1.26–2.7).
Conclusion: Pretreatment NLR is an independent prognostic factor and may serve as clinically useful biomarker for OS of NPC patients.

***Keyword**: nasopharyngeal carcinoma, neutrophil, lymphocyte, platelet, prognosis*

Abstrak

Latar belakang: Tujuan dari penelitian ini adalah untuk mengevaluasi nilai prognostik rasio jumlah neutrofil terhadap limfosit (NLR) dan rasio jumlah trombosit terhadap limfosit (PLR) darah tepi sebelum terapi pada karsinoma nasofaring (KNF).
Metode: Penelitian ini terdiri dari 450 pasien KNF di rumah sakit Dr. Sardjito. Analisis Kaplan-Meier digunakan untuk menghitung dan menggambarkan kurva kesintasan hidup pasien. Hubungan NLR dan PLR dengan kesintasan hidup (OS) diperiksa lebih lanjut dengan pemodelan regresi proporsional Cox, dengan penyesuaian usia, jenis kelamin, klasifikasi patologis WHO, stadium klinis, dan terapi.
Hasil: Nilai batas NLR dan PLR masing-masing adalah 5,35 dan 339,23, dan digunakan untuk membagi pasien KNF menjadi kelompok tingkat tinggi dan rendah. NLR dan PLR berhubungan dengan ukuran tumor pasien KNF (P=0.015: P=0.012). NLR tinggi berkaitan dengan kesintasan hidup yang pendek (median OS±SE NLR > 5,35 vs. NLR ≤ 5,35: 20,18 ± 2,68 vs. 33,29 ± 2,38 bulan, P < 0,001). PLR tinggi berkaitan dengan kesintasan hidup yang pendek (median OS±SE PLR > 339,23 vs. PLR ≤ 339,23: 20,29 ± 1,89 vs. 32,86 ± 2,27 bulan, P < 0,001). Analisis multivariat regresi proporsional Cox menunjukkan bahwa NLR, stadium dan terapi adalah faktor prognostik independen pada pasien KNF (NLR rasio hazard [HR], interval kepercayaan 95% [IK] untuk kesintasan hidup, HR, 1.84; 95% IK, 1.26–2.7).
Kesimpulan: NLR adalah faktor prognostik independen dan dapat berfungsi sebagai biomarker yang berguna secara klinis untuk menilai kesintasan hidup pasien KNF.

***Kata kunci**: karsinoma nasofaring, neutrofil, limfosit, trombosit, prognosis*

Background

Nasopharyngeal carcinoma (NPC) is a malignancy which originates from nasopharyngeal epithelium and is frequently found in the pharyngeal recessus (fossa Rosenmüller) located posteromedial to the ostium of Eustachian tube in the nasopharynx.[1] Generally, the prevalence of NPC is rare worldwide with a rate of less than 1/100,000 population.[2] The incidence of NPC in the world is approximately 86,000 per year with a mortality rate of 50,000 annually.[3] However, in certain countries, NPC is quite common. In Indonesia NPC is the fifth most frequently found head and neck cancer among males. The incidence of NPC in Indonesia is 6.6/100,000 population with a mortality rate as high as 4.3/100,000 population.[4]

Currently, prognosis evaluation of NPC is based on the cancer's stage (tumor size, involvement of lymph nodes and occurrence of distant metastasis).[5] Several molecular biomarkers, such as the Epstein-Barr virus' DNA in plasma had been found to have prognostic value [6,7]. However, their application in clinical setting is limited by high cost and technical requirements. Therefore, a novel low-cost prognostic biomarker is very much anticipated. Recent studies have shown that inflammatory cells play important roles in the occurrence and development of cancer.[8,9] In tumor microenvironment, inflammatory cells release multiple cytokines which promote cancer development while the body immune response system regulates the number and activity of lymphocytes to attack cancer cells.[9]

Neutrophil-to-lymphocyte ratio (NLR) is easily measured and reflected host inflammatory response. Previous studies have shown that NLR is a significant prognostic marker for several solid tumor, including lung cancer, hepatocellular carcinoma, breast cancer, gastric cancer and prostate cancer. [10,11,12,13,14]

Platelets play different roles in the body's physiological and pathological pathways. Concerning oncological process, platelets are involved in the metastasis of tumors.[15] Thrombocytosis has been identified as poor prognostic marker in solid tumors including oral and esophageal squamous cell carcinoma, bronchial and lung carcinoma, gastric cancer and breast cancer. [16,17,18,19,20] Hence, aim of this study is to evaluate the prognostic values of peripheral neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in NPC.

Methods

663 patients' data were collected during 2007-2015 from Dr. Sardjito Hospital data registry. Patients need to meet the following inclusion criteria: patient with newly diagnosed NPC and confirmed histologically who received therapy in Dr. Sardjito Hospital. Exclusion criteria, any of the following: missing data, history of other malignancy and history of infection or autoimmune disease. A retrospective analysis of 450 patients was performed for patients who fulfilled inclusion and did not meet exclusion criteria in Dr. Sardjito Hospital.

Routine blood count test was conducted prior to treatment initiation in these patients, which included neutrophil, lymphocyte and thrombocyte count. Laboratory data were obtained from medical record retrospectively from patient's medical record. The TNM staging used in this study was American Joint Cancer Committee (AJCC) sixth edition (Greene *et al*, 2002). Selected patients were monitored until death or for a minimum of 3 years. This study was approved by Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine Universitas Gadjah Mada, Yogyakarta.

NLR is defined by the absolute number of neutrophils divided by the absolute number of lymphocytes. PLR is defined by the absolute number of platelets divided by the absolute number of lymphocytes which obtained from routine blood count test before treatment initiation. The cut-off value of NLR and PLR is determined by analysis of receiver operating characteristic (ROC) curve and the value is expressed using the Youden index. Data were divided into 2 groups, which are high and low based on the cut-off value. Data frequency was recorded in form of proportion and then analyzed using chi-squared method. The endpoint of study was to evaluate overall survival (OS) of patients. OS is defined as the time from diagnosis to death, while patients who were still alive or loss to follow up were categorized into sensor group. The overall survival curve was estimated using Kaplan-Meier method and compared statistically using log-rank test. Univariate and multivariate analysis based on the Cox proportional regression model were conducted to identify prognostic factors. Other potential prognostic factors were used as modifiers in multivariate analysis including sex (male vs female), age (<50 years old vs ≥ 50 years old), histologic confirmation of nasopharyngeal carcinoma based on WHO (type I,II and III), clinical staging (I, II, III, IVA, IVB, IVC) and treatment (without treatment, chemo-therapy, radiotherapy and chemoradiotherapy). All

statistical analyses were 2-tailed with and p < 0,05 was determined statistically significant. All statistical analysis were performed using SPSS v16.0 (SPSS, Chicago, IL).

Results

There was a total of 450 NPC patients in this study with median age 49 years (minimum age 11 years, maximum age 76 years). The median survival rate of the 450 subjects is 29.7 months (95% CI (confidence interval): 26,02–33,39) with 3 years survival rate of 40.8%. Median follow up in this study is 30.3 months (95% CI: 27,9 - 32,7). Loss to follow up in this study is 34.7%.

The cut-off value of NLR, as determined by ROC curve, in this study is 5.35. Area under curve (AUC) is 0.56 with 95% CI: 0,51-0,6 and P = 0,048. The value 5.35 was chosen because it has the highest Youden index (index 0.143). This cut-off value of 5.35 has 35.2% sensitivity and 78.2% specificity. The cut-off value of PLR used in our study is 339.23 with AUC 0.55 (95% CI: 0,5-0,6 and P = 0,11). This value was chosen as it has the highest Youden index (index 0.11). This cut-off value of 339.23 has 28.7% sensitivity and 82.3% specificity.

The association between NLR and PLR with clinical characteristic in patients with NPC is shown in Table 1. NLR and PLR were found to be significantly associated to tumor size (T) (P = 0,015: P = 0,012). Age, sex, histopathology, involvement of lymph node (N), distant metastasis (M) and clinical stage were found to be not associated to NLR and PLR.

Table 1. Association between NLR and PLR with clinical characteristics in patients with NPC

Characteristics		Case (%)	NLR			PLR		
			≤ 5.35	> 5.35	*P*	≤ 339.23	> 339.23	*P*
Age (year)								
	<50	51.1	168	62	0.412	180	50	0.553
	≥50	48.9	153	67		167	53	
Sex								
	Male	69.3	226	86	0.437	247	65	0.119
	Female	30.7	95	43		100	38	
Pathology								
	Type I/II	5.6	18	7	0.940	22	3	0.182
	Type III	94.4	303	122		325	100	
T class								
	Tis-T2	36.7	129	36	0.015	138	27	0.012
	T3-T4	63.3	192	93		209	76	
N class								
	N0-N1	33.6	110	41	0.614	119	32	0.543
	N2-N3	66.4	211	88		228	71	
Distant Metastatic								
	No	82.4	265	106	0.923	287	84	0.787
	Yes	17.6	56	23		60	19	
Overall Stage								
Stage	I	0.4	1	1	0.227	1	1	0.32
	II	5.7	23	3		24	2	
	III	20.8	72	22		76	18	
	IVA	19.3	59	28		65	22	
	IVB	36	110	52		121	41	
	IVC	17.8	56	23		60	19	
Therapy								
	None	12.6	30	27	0.002	39	18	0.003
	Chemotherapy	24.5	79	31		83	27	
	Radiotherapy	3.5	9	7		9	7	
	Chemoradiotherapy	59.4	203	64		216	51	

NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

Based on the univariate analysis with Cox regression, NLR has hazard ratio (HR) of 2.08 (95% CI: 1,56-2,7, P < 0,001) while PLR has HR of 2.02 (95% CI: 1,48-2,7, P < 0,001) for survival of NPC patients. High NLR is significantly associated to lower survival rate (median OS±SE NLR > 5.35 vs. NLR ≤ 5.35: 20.18 ± 2.68 vs. 33.29 ± 2.38 months, P < 0.001) (Figure 1). High PLR is significantly associated to lower survival rate (median OS±SE PLR > 339.23 vs. PLR ≤ 339.23: 20.29 ± 1.89 vs. 32.86 ± 2.27 months, P < 0.001) (Figure 2).

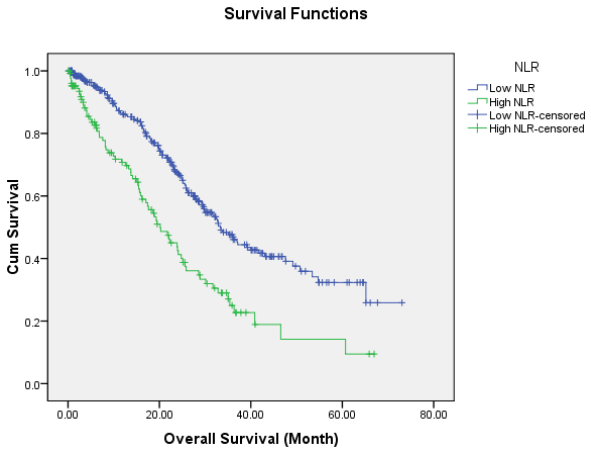

Figure 1. Kaplan Meier curve for NLR and survival rate

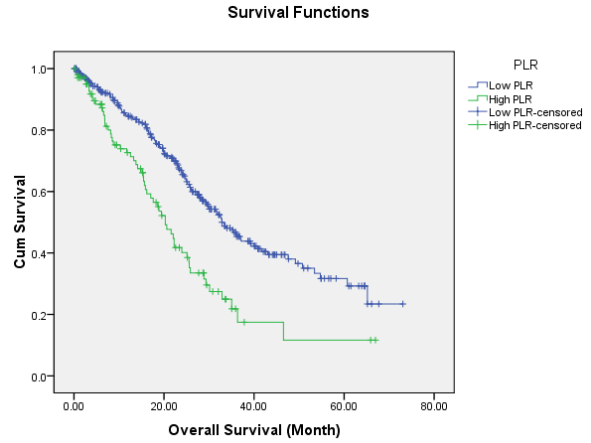

Figure 2. Kaplan Meier curve for PLR and survival rate

Based on the multivariate analysis with Cox regression, NLR, clinical stage and treatment are independent prognostic factors for overall survival of NPC patients (NLR's HR 1.84; 95% CI: 1.26 – 2.7). From multivariate analysis, PLR is not an independent prognostic factor for overall survival of NPC patients. (Table 2)

Table 2. Multivariate analysis on prognostic factors for overall survival of NPC patients

Endpoint	Hazard ratio (95% CI)	*P*
Overall survival		
Stage	1.245 (1.098-1.412)	0.001
Age (< 50 vs. ≥ 50)	1.26 (0.948-1.675)	0.111
Sex (Female vs. Male)	0.872 (0.641-1.185)	0.38
Therapy	0.629 (0.549-0.721)	<0.001
Pathology	1.568 (0.766-3.211)	0.218
NLR level (≤ 5.35 vs. > 5.35)	1.848 (1.261-2.709)	0.002
PLR level (≤ 339.23 vs.> 339.23)	1.11 (0.733-1.681)	0.623

Discussion

All cancer cells induce inflammation regardless before or after cancer development, which provides favorable condition for these cells.[21] Immune cells in the body participate in all stages of neogenesis and immuno-surveillance. This is illustrated by the fact that inflammatory microenvironment contributes in tumor initiation through mutation, genomic instability and epigenetic modification.[22]

Neutrophilia is associated with poor prognostic value in several cancers, such as lung cancer, melanoma and renal carcinoma.[23,24,25] Tumor-associated neutrophils (TANs) help tumor progression in multiple ways, one of which is by releasing matrix metalloproteinase-9 (MMP-9), cytokines (IL-1β, TNF-α, IL-6, and IL-12) dan arginase 1. TANs also produce reactive oxygen species (ROS) and serine proteases which facilitates tumor development.[26]

Acute inflammation can trigger antitumor immunity. Immunogenic cell death (ICD) as a result of injury, stress and certain chemotherapy may induce the expression of surface calreticulin and high-mobility group box 1 (HMGB1) protein in cancer cells, hence activating innate immunity via pattern recognition receptors (PRRs). Dendritic cell maturation and antigen cross-presentation, together with secretion of inflam-matory cytokines, can efficiently produce cytotoxic T cells, which triggers effective anti-tumor immunity responses.[21]

In this study, we found that higher stage of tumor size (T) is associated to higher NLR. High NLR signifies higher neutrophil count compare to lymphocyte in NPC patients. The increase in NLR is also significantly

associated to lower overall survival rate of NPC patients. The prognostic role of NLR in NPC patient is independent and is not affected by age, sex, stage, tumor histopathology, treatment and PLR of NPC patients.

A previous study had shown that NLR is a serum-based parameter which could reflect the immune response status of patients with solid tumor. NLR can represent the activity index of pro-tumor and anti-tumor in solid tumor patients.[27] NLR is relatively easy to obtain and cost efficient as it can be measured from routine blood count test result, which is carried out prior to treatment intiation. Hence, NLR can be used as biomarker to evaluate prognosis of NPC patients.

Thrombocytosis occurs in 10-57% of cancer patients.[28] Other studies had shown that thrombocyte count is inversely proportional to survival rate and thrombocytosis is known as a poor prognostic indication.[29,30,31] The main trigger of thrombocytosis in malignancy is the release of cytokines by cancer cells including IL-1, GM-CSF, G-CSF and IL-6, which stimulates thrombopoiesis through a mechanism dependent of thrombopoietin and affects growth and differentiation of megakaryopoiesis.[32,33]

Thrombocyte contributes to metastasis of cancer by facilitating migration of tumor cells, invasion and infiltration of blood vessels.[34,35] Tumor cells recruit thrombocytes before activating the thrombocytes' membrane which causes the release of their contents into peritumoral area, encouraging extravasation of tumor cells and eventually metastasis.[36]

In this study, we found higher stage of tumor size (T) is also associated to higher PLR value. High PLR signifies higher thrombocyte count compare to lymphocyte in NPC patients. In the univariate analysis, the increase in PLR is significantly associated to lower overall survival rate of NPC patients, however, the prognostic role of PLR in NPC patient is not independent and is affected by other prognostic factors including age, sex, stage, tumor histopathology, treatment and NLR of NPC patient.

The limitations of this study include the relatively high number of loss to follow up data and the fact that this research utilizes secondary data, which is very dependent on the completeness of medical record, such that any incomplete record will exclude a large number of patients as subject. However, this research has comparatively high number of subjects (450 NPC patients) which covers clinical stage I until IVC.

Conclusion

NLR is an independent prognostic factor dan can be used as biomarker to evaluate overall survival of NPC patients clinically. High NLR is associated to lower overall survival in many solid tumor patients including NPC patients. NLR can serve as a cost efficient and easily accessible prognostic biomarker. Further research should be conducted to measure the significance of NLR in treatment decision-making for solid tumor patients including those with NPC.

Acknowledgement

Authors thank to NPC registry team of RSUP Dr. Sardjito for providing data needed in order to establish this paper.

Conflict of Interest

The authors have no conflict of interest.

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InaJCC The Indonesian Journal of Cancer Control

Original Article

The reasons young smokers choose to use e-cigarette

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p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v1i2.52

Received: June 14, 2021
Accepted: November 25, 2021

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Abstract

Background: Electronic cigarettes (e-cigs) are battery-powered handheld devices that simulate tobacco smoking. Since its discovery in 2007, e-cigs have become a popular product in the market, especially among young smokers. With various programs that promote the dangers of smoking, the e-cigs industry takes this opportunity to offer products claimed to be alternatives to smoking with lighter side effects. The number of e-cigarette users is increasing exponentially.
Method: This research was done using a descriptive cross-sectional study design and it was conducted in Jakarta. The target population includes every e-cigs user that are accessible in Jakarta. Data were obtained through interviews conducted by two medical students on respondents in the electric smoker community scattered in several locations in Jakarta.
Results: From 937 subjects, the average age of respondents using e-cigs was 27.8±6.3 years old. Most of the users of e-cigs were male 95.8 %. Only 34.2% of 937 subjects were conventional smokers before using e-cigs, and it means more novice who immediately become smokers by using e-cigs (65. 8%). We have analyzed the reasons of 321 current smokers who had moved to become an electrical smoker; the most common reason was NRT (79.1%), followed by better taste (13.7%), trick (2.8%), and following the trend in youth (1.8%).
Conclusion: Electric cigarettes contain nicotine and other substances that endanger the health of the airway and can be a risk of lung cancer. The use of e-cigs as a transitional period for quitting conventional smoking is not the right choice.

Keywords: *e-cigarette, young smoker, reasons*

Abstrak

Latar belakang: Rokok elektrik (*e-cig*) merupakan alat portable untuk merokok yang dioperasikan menggunakan baterai. Ditemukan sejak tahun 2007, dan rokok elektrik ini menjadi popular di pasaran, terutama pada kalangan perokok generasi muda. Berbagai program dan penyuluhan berhenti merokok serta kampanye bahaya rokok konvensional membuat industri rokok elektrik mengambil kesempatan mempromosikan produk mereka yang diklaim sebagai alternatif dari merokok konvensional dengan efek samping dan risiko yang lebih ringan. Pengguna rokok elektrik meningkat secara eksponensial
Metode: Penelitian ini dilakukan dengan desain potong lintang dan dilakukan di Jakarta. Populasi target dari penelitian ini adalah pengguna rokok elektrik yang dapat diakses di Jakarta. Data diambil melalui wawancara oleh 2 orang mahasiswa pada komunitas perokok elektrik di beberapa lokasi di Jakarta
Hasil: Dari 937 responden rerata usia 27,8±6,3 tahun. Sebagian besar pengguna rokok elektrik adalah laki laki 95,8%. Hanya 34,2% responden mengaku menggunakan rokok konvensional sebelum menggunakan rokok elektrik. Dan sebagian besar 65,8% perokok pemula langsung menggunakan rokok elektrik. Dan dari 321 perokok mengemukakan alasan terbanyak pindah menjadi perokok elektrik adalah sebagai pengganti rokok konvensional (NRT) (254 reponden 79,1%), kedua rasa rokok elektrik yang lebih enak 44 responden (13,7%), trick (permainan asap) 9 responden (2,8%), karena trend dikalangan muda 6 responden (1,8%)
Kesimpulan: Rokok elektrik mengandung nikotin dan substrat lain yang dapat mempengaruhi kesehatan paru dan memiliki risiko terkena kanker paru. Penggunaan rokok elektrik sebagai alternatif transisi sebelum berhenti merokok bukan pilihan yang tepat

Kata kunci: *rokok elektrik, perokok muda, alasan*

Background

Tobacco smoking is one of the world's largest health problems. Over the course of the 20th century, it killed around 100 million people, most of them in today's rich countries. The health burdens of smoking are now moving from high-income to low-to-middle income countries; some estimates have suggested that one billion people could die from tobacco over the 21st century.[1-3] Indonesia is the country with the largest cigarette consumption in the world, which is in the third place after China and India. Tobacco consumption has increased significantly, due to factors increasing household income, population growth, low cigarette prices and mechanization of the kretek industry. The prevalence of male adult smokers has increased from year to year. Likewise, the proportion of female adult smokers have increased. Very concerning 32.1% students have used smoky tobacco products. According to the Global Youth Tobacco Survey report 2014, adolescents under the age of 15 years old, 43.2% start smoking and 11.4% at 14-15 years old.[3]

In this modern era, the development of technology produces a trend and a new way of smoking in the form of electronic cigarettes (e-cigs). Electric cigarettes are innovations from conventional cigarettes and equally produce aerosol substances. In conventional cigarettes, the aerosol substance is smoke as a result of the combustion process, whereas in electric cigarettes there is steam as a heating process.[4] Electric cigarette does not contain smoke, tar or carbon monoxide like conventional cigarettes. that is what causes the wrong perception in the community that e-cigarettes are relatively safer even though there are still many other toxic substances.[5] The main toxic substance in e-cigs that is also found in conventional cigarettes is nicotine.[6] Smokers are starting to switch to e-cigs because not only is it more modern and varies in flavor, e-cigs are believed to be one of the nicotine therapy methods to overcome their dependence.[7]

Smoking and lung cancer in younger population. In many countries we see a significant rise, peak and then decline in lung cancer death rates in the 20th century. In the United States, the death rate peaked in the 1980s in men. In Spain this peak was later, only in the 1990s.These trends are driven by the trends in smoking. Smoking is the biggest risk factor for lung cancer and we see that the trends in lung cancer follow those in smoking with a lag of around 20 years. In 2017, it has been shown that 7 million people globally died a premature death because of smoking. The fact that smoking causes lung cancer is the major reason for the high death toll of smoking.[8,9] Interesting and important thing is, research from Europe and Japan has shown a trend of increasing incidence of lung cancer in young adults [9,10] The incidence of early-onset lung cancer differs according to geographical region and over time. In a cohort study in China, the incidence of lung cancer in the young population (aged 18-35 years) was 1.37%.[11]

The main prevention efforts for cancer, especially lung cancer is not to be exposed to cigarette smoke and prevent the increasing number of smokers. The effort is not easy because it involves many sectors that sometimes conflict with each other. In recent years, efforts have begun to aggressively attract more beginner smokers by using e-cigs. Because the use of e-cigs is still relatively new, there are not much data that states the number of e-cigs users in Indonesia. Moreover, this research was conducted to find out the characteristic and reasons young people use e-cigs.

Methods

This research was done using a descriptive cross-sectional study design and it was conducted in Jakarta. The target population in this research includes every e-cigs user in Jakarta the accessible population. Data obtained through interviews conducted by 2 medical students on respondents in the electric smoker community scattered in several locations in Jakarta.

Results

In this study, we have found that of the 937 respondents using e-cigs was young. It was found that most of the users of e-cigs were male and the most of them novice smoker.

Table 1. General characteristics of research subjects

Variables	N	%
Gender		
Male	898	95.8
Female	39	4.2
Age (years old)		
Mean	27.8 (SD 6.3)	
Range	18 - 57	
Occupation		
Student	212	22,.6
Public employee	40	4.2
Entrepreneur	403	43
Private employee	216	23
Others	66	7
Education		
Elementary diploma	8	0.8
Junior high school diploma	28	3.0
High school diploma	448	47.8
Associate degree	73	7.8
Bachelor's degree	356	38.0
Master's and Doctoral degree	24	2.6
Income		
<IDR. 3.500.000,00	186	19,8
>IDR. 3.500.000,00	751	80,2

Table 2. History of cigarette

	N	%
History Smoker		
Yes	321	34.2
No	616	65.7
Type of E-cigs		
Mechanical vaporizer	170	18.1
Electric vaporizer	671	71.6
Others	96	10.2
Duration of E-cigs usage		
< 3 months	51	5.4
3-6 months	72	7.7
6-12 months	103	10.9
>12 months	711	75.9

Table 3. The reason of current smoker changes to use electric cigarette

	N (n= 321)	%
NRT	254	79.1
Taste	44	13.7
Smoke trick	9	2.8
Trends	6	1.9
Others	8	2.5

Discussion

Electronic cigarettes are battery-powered handheld devices that simulate tobacco smoking. E-cigs heat a solution (i.e., e-liquid/e-juice) containing a mixture of propylene glycol, vegetable glycerin, concentrated flavors, and optionally, variable concentrations of nicotine into inhalable vapor. Electronic cigarettes use is commonly referred to as "vaping", and e-cig users are interchangeably termed "vapers". Since its discovery in 2007, e-cigs have become a popular product in the market, especially among smokers and the younger generation. With various programs that promote the dangers of smoking for both modern smokers and nonsmokers, the e-cigs industry takes this opportunity to offer products that are claimed to be alternatives to smoking with lighter side effects. The number of e-cigarette users is increasing exponentially. In 2016, the sales of e-cigs increased 14 times from 2008.[12,13] In this study, of the 937 subjects studied, the average age of respondents using e-cigs was 27.8±6.3 years old. It was found that most of the users of e-cigs were male with a rate of 95.8%. Very surprising only 34.2% of 937 subjects were conventional smokers before use e-cigs, and it means more novice who immediately become smokers by using e-cigs (65.8%). Electronic cigarette users vary in terms of age with a fairly high number in the group of young adults. It shows the success of the businessman with his incessant so that in a short time be able to instill an image that is right for the younger generation about the coolness of using e-cigs According to the results of Corey et al, the use of e-cigs in the United States among adolescents and young adults increased 9-fold from 2011 to 2015.[11] Similar results related to gender in the use of e-cigs were also found in the study of Pineiro et al, where out of all respondents 66.8% of the subjects were male. Judging from the level of education, high school graduates obtained as the highest proportion, followed by undergraduates as the top 2 groups.[12] Compared to a study conducted by the American Heart Association (AHA) in 2018, the results found showed a similar pattern. Judging from the level of education, even though both are in the top 2 positions, undergraduates are obtained as the group with the highest proportion followed by high school graduates. This component can be affected by various variables including one of the factors of different levels of education in developed and developing countries. In addition to reviewing age groups and education levels, financial levels include factors that affect an individual's ability to buy and consume e-cigs. Judging from their work, respondents with the highest proportion are classified as entrepreneurs and are followed by private

employees and students. In the study, it was found that around 80% of the subject's income was above the minimum wage set at IDR 3,500,000.00. When compared with studies in the United States, the highest proportion was found in the income group of $ 20,000 - $ 44,999 per year, or roughly with multipliers of IDR 14,000.00 per dollar, then a figure of around IDR .23,000,000 - 52,500,000.00 per month.[13] Of course, many factors affect the income of respondents, especially comparing developed and developing countries. But what the researchers want to emphasize is that the average respondent has enough income to be able to buy and consume e-cigs regularly, with a variety of prices that are adjusted to the selection of types, liquids, and the number of e-cigs used.

To find out the reasons for choosing e-cigs in this study, respondents may only choose one reason. In This study, only a small portion of them claim to use e-cigs because they follow trends 16 of 937 (1.7%), are attracted by taste 161 of 937 (17.2%), or because they can play a smoke trick for fun 32 of 937 (3.4%). The mostly reasons for choosing e-cigs were related to the nicotine content which was said to be lower than conventional cigarette, and can be a method for nicotine replacement therapy 719 of 937 (76.7%). There seems to be no discrepancy between the reasons for choosing electric cigarettes because the number of respondents who were conventional smokers before were 321 of 937. It is possible for novice smokers the reason for choosing it is because the nicotine content in electric cigarettes over conventional cigarettes is lower, rather than choosing the smoking cessation method as in previous conventional smokers. There may be misperceptions about NRT in novice smokers because it only applies to current smokers who intend to stop smoking. One way is through the NRT method in the transitional transition process. To make it clearer we analyzed only those groups that had previously used conventional cigarettes. The reasons 321 conventional smokers who had moved to become an electrical smoker, the most of reason were NRT 254 (79.1%) as the reason for the method of stop smoking with the NRT method is stronger. Followed by reasons were of the taste, smoke trick, trend, and other (Table.3). Electric cigarette enters the market as a healthier alternative to smoke with minimal impact on health. But, the statements about e-cigs have lower nicotine compositions than tobacco cigarettes are still being debated. One component that is the main focus is the content of nicotine as an addictive substance which is the main factor for cigarette users to have an addiction. Besides, different combustion methods also affect the distribution of nicotine itself. Although it varies and depends on the type of e-cigs, the nicotine compositions in e-cigs are generally lower than in tobacco cigarettes. The Department of Pulmonology and Respiratory Medicine Universitas Indonesia have done a study. The study had shown that the urinary cotinine (uCOT, product of nicontine metabolism) and nicotine dependence level on the regular e-cigs male user was significantly correlated, of which age, nicotine level, and flavor of e-cigs liquid significantly influenced in the uCOT. The uCOT of regular e-cigs male user was significantly higher than non-smoker.**[14]**

The important issues that are hidden from e-cigs users are other carcinogenic substances that trigger cancer such as cigarette smoke.[15] Cigarette smoke is a complex mixture of chemicals including multiple genotoxic lung carcinogens. The classic mechanisms of carcinogen metabolic activation to DNA adducts, leading to miscoding and mutations in critical growth control genes, applies to this mixture but some aspects are difficult to establish because of the complexity of the exposure.[16,17] The question of whether the use of e-cigs has a lower risk for cancer such as statements that say e-cigs has a lower carcinogen content. An animal study, the carcinogenicity of e-cigs was tested in mice. They found that mice exposed to e-cigs for 54 weeks developed lung adenocarcinomas (9 of 40 mice, 22.5%) and bladder urothelial hyperplasia (23 of 40 mice, 57.5%). These lesions were extremely rare in mice exposed to vehicle control or filtered air. Current observations that e-cigs induces lung adenocarcinomas and bladder urothelial hyperplasia, combined with our previous findings that e-cigs induces DNA damage in the lungs and bladder and inhibits DNA repair in lung tissues, implicate e-cigs as a lung and potential bladder carcinogen in mice. While it is well established that tobacco smoke poses a huge threat to human health, whether e-cigs poses any threat to humans is not yet known and warrants careful investigation.[17]

Conclusion

This study reveals that young people use e-cigarettes due to misinformation regarding their safety. Low nicotine content and its role as a transition towards cessation of smoking seem to underline their reasons for its use.

It is only through correct information and open communication that the younger generation can be made to understand that e-cigs is not the right way to stop smoking so that prevention efforts for lung cancer can be done earlier. Although the jury is still

out regarding its carcinogenicity, e-cigs still contain carcinogen which can be a trigger for cancer, especially lung cancer.

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InaJCC The Indonesian Journal of Cancer Control

Case Report

Late relapse in hormone receptor (+) HER2 (-) early breast cancer: Case report

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p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v1i2.53

Received: August 25, 2021
Accepted: December 3, 2021

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Abstract

Background: Hormone-receptor (HR) positive breast cancers represent the majority of all breast cancers (BC). Adjuvant endocrine therapy is effective for nearly all women with ER+ and/or PgR+ tumors. Tamoxifen taken for five years has been the standard adjuvant endocrine treatment. However, despite receiving this treatment, >50% ER+ patients relapse and died from breast cancer 5–10 years after diagnosis.
Case: 50-year-old female with distant relapse BC. November 2008, radical mastectomy of the right breast. Invasive ductal carcinoma grade III T2N1M0 (stage IIb) ER+ (90%), PgR+ (90%), HER2-. Chemotherapy, radiotherapy, and Tamoxifen 2009-2014. Disease-free survival (DFS) : 8 year. January 2017, presented with cough. Chest x-ray: nodule in left lung, transthoracal biopsy: metastatic carcinoma from the breast, ER+ (50%), PgR-, HER2-.
Discussion: Identification of subpopulations likely to benefit from extended endocrine therapy is crucial. For high-risk ER+ patients, ten years endocrine therapy is an option. Evaluation of adverse event, long-term toxicity and risk of recurrence is vital. Discordant hormonal status between primary and metastatic site tumor has been reported 6-40%. Decision to change treatment based on this finding is still limited.

Keywords: *late relapse, early breast cancer, hormone receptor positive.*

Abstrak

Latar Belakang Kanker payudara reseptor hormon positif merupakan bagian terbesar kanker payudara di seluruh dunia (60% -75% ER +, 65% PgR +). Terapi endokrin ajuvan sangat efektif dan sesuai untuk hampir semua wanita dengan tumor ER + dan / atau PgR +. Selama beberapa dekade, tamoxifen yang dikonsumsi selama 5 tahun adalah pengobatan endokrin adjuvan standar, tetapi lebih dari separuh pasien dengan kanker payudara ER + akan kambuh dan meninggal akibat kanker payudara pada 5-10 tahun setelah diagnosis meskipun sudah diberikan terapi endokrin selama 5 tahun.
Kasus: Dosen wanita berusia 50 tahun dengan kanker payudara kambuh lambat. November 2008, dilakukan mastektomi radikal pada payudara kanan, hasil patologi anatomi : karsinoma duktal invasif grade III T2N1M0 (stadium IIb) ER + (90%), PgR + (90%), HER2-, kemudian kemoterapi (Docetaxel + Cyclophosphamide) dilanjutkan radioterapi dan diberikan Tamoxifen (2009-2014). Kesintasan hidup bebas penyakit : 8 tahun 1 bulan. Pada Januari 2017, pasien batuk. Rontgen dada menemukan nodul pada paru kiri dengan efusi pleura minimal, hasil biopsi transthoracal : metastasis karsinoma dari payudara, ER + (50%), PgR-, HER2-.
Diskusi: Identifikasi subpopulasi yang cenderung mendapat manfaat dari terapi endokrin yang diperpanjang dan yang tidak mendapat manfaat adalah penting. Durasi pemberian terapi endokrin penting untuk pasien ER+ dengan risiko tinggi. Pemberian terapi selama 10 tahun saat ini menjadi salah satu pilihan. Sangat penting mempertimbangkan toksisitas jangka panjang dan risiko tingkat kekambuhan. Pada pasien kanker payudara stadium awal reseptor hormon positif premenopause, pemberian terapi supresi ovarium dan exemestane mengurangi risiko kekambuhan dibanding terapi supresi ovarium dan tamoxifen. Dibandingkan dengan pemberian tamoxifen saja, terapi supresi ovarium terkait dengan peningkatan gejala menopause, disfungsi seksual, dan penurunan kualitas hidup. Biopsi pada tempat metastasis yang dapat diakses direkomendasikan untuk dilakukan. Hasil biopsi bisa ada ketidaksesuaian status hormon antara tumor primer dan metastasis dilaporkan 6-40% namun bukti penelitian masih kurang mendukung apakah mengubah terapi antikanker berdasarkan perubahan status reseptor mempengaruhi hasil klinis.

Kata kunci: *kambuh lambat, kanker payudara dini, reseptor hormon positif.*

Background

Global Cancer Report (GLOBOCAN) has reported the increasing number of cancer patient, particularly for breast cancer. In 2012, incidence of breast cancer has reached for 48.998 annually, with mortality cases of 19.750 annually. Moreover, in 2020, the incidence of breast cancer is projected to increase in a number of 58.799 of cases annually, with mortality of 23.836 of cases annually.[1]

Hormone-receptor positive breast cancer is a major type of breast cancer (60 – 75% is estrogen positive, and 65% is progesterone positive). Endocrine therapy is an effective adjuvant treatment for most breast cancer with both estrogen and progesterone positive. For latest decades, tamoxifen therapy for five years is still being drug of choice for hormone positive breast cancer.[2]

This case report will discuss about late relapse which is frequent among hormone-receptor positive breast cancer, which the late relapse is defined as recurring event after five years from initial treatment.[3] This case will also review about the effectivity of extending tamoxifen for ten years, clinical marker of late relapse, and the concordance status of hormone receptor between primary tumor and metastatic lesion.

Case Illustration

A 50-years old lecturer woman was known to have a distant metastasis of breast cancer. In November 2008 (42 years old), the patient complained with right breast lump which later underwent radical mastectomy on her right breast. Pathological anatomy examination concluded ductal infiltrative carcinoma grade III with estrogen receptor positive (ER 90%), progesterone positive (PR 90%), and Her-2 negative. The stage was concluded as stage IIb T2N1M0 of breast cancer. The patient then received systemic chemotherapy with docetaxel and cyclophosphamide, followed by radiotherapy. After chemo-radiotherapy, she had received hormone therapy with tamoxifen for five years from 2009 and 2014. During hormonal therapy, she underwent surveillance with relatively good compliance. In addition, she also had good quality of life without any significant adverse events of a five years tamoxifen.

In January 2017, the patient complained dry cough which did not improve but the activity level was still unrestricted. Thoracic X-Ray was evident left pulmonary nodule with minimal pleural effusion and later confirmed with PET scan which was shown a hypometabolic multiple nodules in left lung and left pleural effusion with a solid component and mild metabolic activity. A trans-thoracic fine biopsy through the pulmonary nodule concluded neoplastic cells of breast cancer. Immunohistochemistry examination showed ER positive (50%), PR negative, and Her-2 negative (figure 1, 2, and 3). The patient was still in a good performance status (ECOG 0) and subsequently received second line treatment with eribulin.

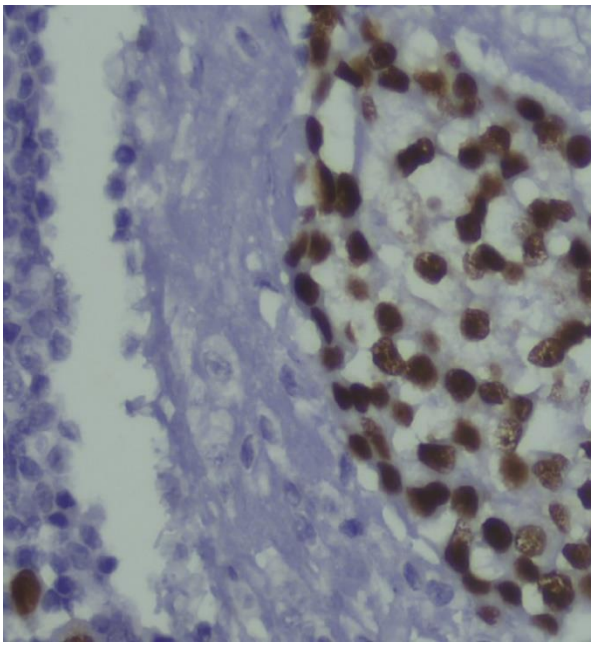

Figure 1. Immunohistochemical examination showing 50% ER positive tumor cells

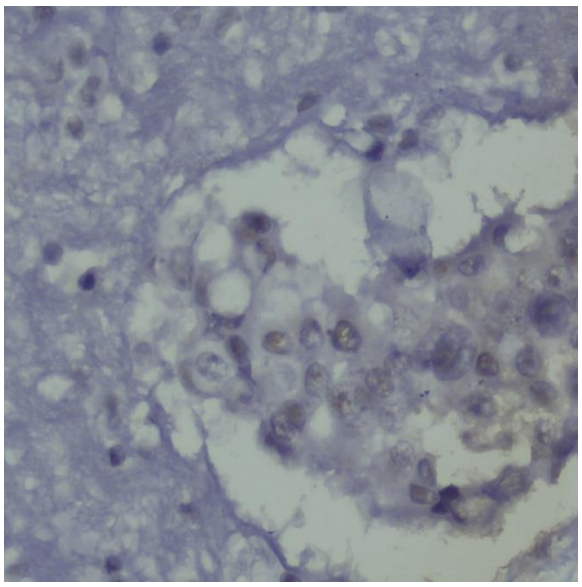

Figure 2. Immunohistochemical examination showing PR negative tumor cells

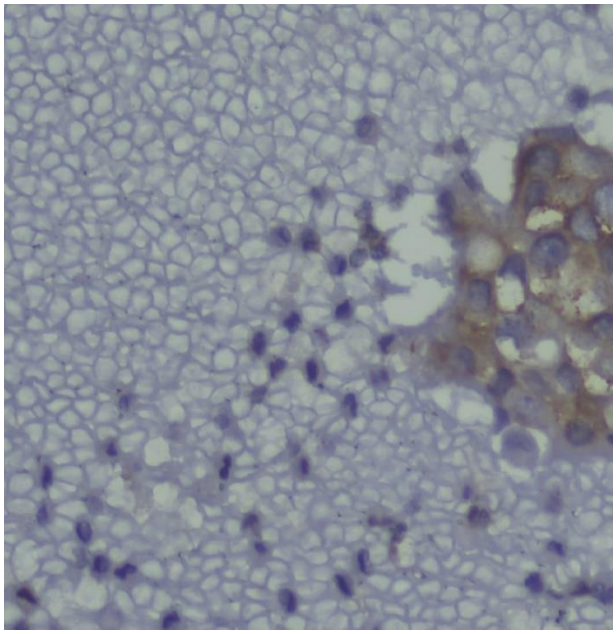

Figure 3. Immunohistochemical examination showing Her-2 negative tumor cells

Discussion

Breast cancer is heterogeneous disease with varying pattern of recurrence. It also has been evidenced as a spectrum of disease with several subtypes such as luminal, Her2, and basal.[4] The onset of late recurrence is also varies in each subtype. For instance, ER negative/Her2 positive breast cancer is known for a three times higher risk of relapse for initial 5-7 years of disease compared with ER positive.[5] Nevertheless, the latter type tends to have higher risk of relapse after 5-7 years among all age groups compared with ER negative.[6]

According to the presented case supplemented with other study results showed that the duration of endocrine treatment is an important aspect for ER positive breast cancer prognosis due to higher risk of late recurrence. The ATLAS study compared a group of ER positive breast cancer with five years and ten years of tamoxifen, later evidenced a significant reduction in mortality with superior reduction in ten years of tamoxifen. A ten years duration of tamoxifen significantly decreased relapse case compared with five years arm (617 in 3428 subjects vs 711 in 3418 subjects, p = 0002), cancer-specific mortality reduction (331 vs 397 of dead cases, p = 0,01), and reduction of overall mortality (639 vs 722 of dead cases, p = 0,01). However, the adverse events were known to increase in ten years tamoxifen arm, particularly among postmenopausal women. The ATLAS study showed that ten years tamoxifen decreased half of overall mortality for 10-14 years after the diagnosis.[7]

Ovarian Function Suppression (OFS) treatment has a significant role in reducing recurrence rate among early hormone receptor positive breast cancer in premenopausal women. According to TEXT and SOFT study, it has been evidenced that adjuvant endocrine treatment in form of OFS and exemestane significantly reduced recurrence rate compared with OFS and tamoxifen. However, OFS plus tamoxifen insignificantly reduced recurrence rate compared with tamoxifen only. Compared with tamoxifen only, the combination of OFS and tamoxifen increased the menopausal symptoms substantially, sexual dysfunction, and decreased the quality of life.[8,9]

It is essential to know precisely the risk stratification of breast cancer recurrence and predict survival of hormone-receptor positive breast cancer. According to St Gallen's International Conference of Breast Cancer in 2009, nodal status, tumor size, grade and histological type, peritumoral vascular invasion, HER2 and hormone receptor status are categorized as the most useful clinical markers for management of breast cancer.[10] Registry data reported by Danish Breast Cancer Cooperative Group (DBCG) showed similar mortality as general population among 3,197 of hormone receptor positive and early stage breast cancer patients with aged of 60 years or older, small tumor size (≤10 mm), no lymph node involvement, and favorable grade of ductal or lobular carcinoma.[11]

From the presented case, it has been known the concordance expression of hormone receptor between the primary site and metastatic lesion, which were ER positive and Her-2 negative. There are many potential benefits to perform biopsy for metastatic lesion, such as concluding the diagnosis, excluding the possibility of any other primary tumor, and confirming the concordance expression of hormone receptor status between primary and metastatic lesion. Indeed, it has been reported discordance rate between primary and metastatic lesion in 6-40% of cases.[12] Moreover, the discordance rate of hormone receptor expressions for ER, PR, and Her-2 are 20%, 33%, and 8% respectively.[13] The BRITS and DESTINY study showed the result of biopsy causes management changes in 14.2% of cases but the clinical effect was still unknown.[14] Exposure of previous treatment can change the molecular profile of metastatic tumor cells, including in breast cancer, and may induce drug resistance which makes the subsequent treatment challenging.[15]

Conclusion

It is important to identify subgroup of early-stage, hormone-receptor positive breast cancer patients who might benefit from extended endocrine therapy to prevent the late recurrence. Therefore, clinical markers such as age, nodal status, tumor size, and histopathology could be utilized to stratify the risk. Extending the endocrine therapy for ten years to ER+ with high risk breast cancer patients may reduce the risk of late recurrence. Effectiveness of ovarian function suppression (OFS) treatment is potentiated by combination with exemestane in premenopausal breast cancer patients. Weighing the side effects and long-term toxicity against the recurrence risk is essential. Re-biopsy of recurrent metastatic lesion in breast cancer is beneficial albeit lacking evidence to change treatment when found any discordant expression of hormone receptor which actually aims to improve patient outcomes.

Acknowledgement

Authors would like to thank the Department of Anatomical Pathology of FKKMK UGM / Sardjito General Hospital for providing and documenting biopsy and IHC photos in this case.

Conflict of Interest

The authors have no conflict of interest to declare.

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InaJCC The Indonesian Journal of Cancer Control

Case Report

Endometrial cancer after tamoxifen-containing adjuvant treatment for breast cancer

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p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v1i2.49

Received: August 25, 2021
Accepted: December 17, 2021

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Abstract

Background: Breast cancer is the most predominant cancer among women globally, including in Indonesia, and has been recognized as a heterogeneous disease. Hormone-receptor positive breast cancer is the major subtypes of breast cancer which expresses estrogen and/or progesterone receptors and has unique characteristics of favorable prognosis despite predisposes to have a higher risk of late recurrence. Tamoxifen is a selective estrogen receptor modulator (SERM) which has become a drug of choice for adjuvant hormonal therapy to reduce the recurrence risk of hormone-receptor positive breast cancer in pre- or postmenopausal women. Therefore, current clinical guidelines recommend to extend the duration of tamoxifen to increase the benefit of reducing the risk of recurrence. On the other hand, the long-term side effects of tamoxifen are also increasing, including the incidence of tamoxifen-induced endometrial cancer.
Case: This case report presents a clinical case of endometrial cancer emerged in a survivor of hormone-receptor positive breast cancer who previously underwent tamoxifen adjuvant therapy.
Discussion: Eventually, this case report may increase awareness of secondary malignancy and review the incidence, underlying mechanism, risk factors, prevention measures, and current management of tamoxifen-induced endometrial cancer.

Keywords: *breast cancer, tamoxifen, endometrial cancer, estrogen receptor, hormonal therapy*

Abstrak

Latar Belakang: Kanker payudara merupakan kanker terbanyak pada wanita di seluruh dunia, termasuk di Indonesia, dan telah dikenal sebagai suatu penyakit yang heterogen. Kanker payudara hormon reseptor positif yang mengekspresikan baik reseptor estrogen dan/atau progesteron merupakan subtipe mayor dari kanker ini dengan karakteristik unik berupa prognosis yang lebih baik tetapi di sisi lain memiliki risiko rekurensi lambat yang cukup tinggi. Tamoxifen merupakan agen modulator anti-estrogen selektif yang menjadi salah satu pilihan utama sebagai terapi hormonal ajuvan untuk menurunkan kejadian kekambuhan pada kanker payudara bertipe hormon reseptor positif baik pada wanita pre- atau pascamenopause. Oleh karena itu, *guidelines* klinis terkini merekomendasikan untuk memperpanjang durasi pemberian tamoxifen untuk semakin menurunkan risiko rekurensi tersebut. Di sisi lain, efek samping jangka panjang akibat tamoxifen juga berisiko meningkat, termasuk di antaranya kejadian kanker endometrium yang diinduksi oleh tamoxifen.
Kasus: Laporan kasus ini menyajikan suatu kasus kanker endometrium yang muncul pada penyintas kanker payudara bertipe hormon reseptor positif dan sebelumnya menjalani terapi ajuvan tamoxifen.
Diskusi: Hal tersebut untuk meningkatkan kewaspaadan akan risiko keganasan sekunder serta membahas kembali mengenai insidensi, mekanisme, faktor risiko, pencegahan, dan manajemen terkini seputar kanker endometrium yang diinduksi tamoxifen.

Kata Kunci: *kanker payudara, tamoxifen, kanker endometrial, reseptor estrogen, terapi hormonal*

Background

Global cancer report in 2018 has highlighted breast cancer as the most predominant cancer among women with incidence number reached to two million cases (24.2%) and mortality rate of six hundred thousand cases.[1] Moreover, breast cancer has been marked as cancer with the highest incidence in Indonesia, with 58000 of new cases and 22000 of dead cases. In addition, the case fatality rate of breast cancer in Indonesia has reached 38.9%, higher than other Southeast Asian countries such as Thailand, Philippines, and Malaysia, which count of 38.1%, 32.5%, and 38.1% respectively.[1] The high case fatality rate is apparently contributed by several factors, including initial presentation of most patients with advanced-stage, suboptimal treatment compared with international standards, and a growing number of younger breast cancer cases.

In the early of 2000, breast cancer has been known as heterogeneous disease, both molecularly and genetically. This has brought breast cancer to be classified into 4 distinct subtypes which are luminal A or B, triple-negative, and human epidermal growth factor receptor-2 (Her-2) overexpressed.[2] Each subtype has different characteristics that requires differential approach.[3] Luminal or hormone-receptor positive breast cancer is the major subtype of breast cancer in which estrogen and/or progesterone become oncogenic drivers.[4] This predominant subtype has a unique biological features, in particular for favorable prognosis but higher rate of late recurrence (after five years of disease). Therefore, recurrent disease is also marked as a critical problem in this subtype without failing to notice the patient's survival.

Tamoxifen has been a pivotal drug as adjuvant hormone therapy for early-stage of breast cancer, both in pre-menopause and post-menopause women, alongside with aromatase inhibitors, and gonadotropin-releasing hormone (GnRH) agonist [2,3]. Several meta-analyses have mentioned tamoxifen to effectively prevent breast cancer recurrence.[5,6] However, late recurrence rate remains high even after a 5-year use of tamoxifen which initiates other trials to extend hormone treatment duration for 10 years to reach an optimum benefit.[6–9] Furthermore, tamoxifen response among young women (<35 years) in term of recurrent reduction is considered deficient and the incident of long-term adverse events such as venous thromboembolism and endometrial cancer is regarded as high.[6,10]

In order to improve awareness of the endometrial cancer risk among tamoxifen user women in breast cancer, this study reported a clinical case of endometrial cancer in a patient previously treated with tamoxifen for breast cancer and reviewed for incidence, risk factor, proposed mechanism, and management, along with preventive measures.

Case Illustration

In the mid of 2002, a 42-year-old, pre-menopause woman came to Sardjito General Hospital and complained about a lump palpated in left breast for 5 years. Initially, the lump only felt pain in each of her period, but later progressed into a constant pain. Mass diameter of approximately 2-2.5 cm. With a favorable initial Karnofsky performance status of 90%, lumpectomy was then performed and biopsy concluded as ductal infiltrative breast cancer. Mammography of her right breast found insignificant findings. The breast cancer was then concluded as stage IIIA T3N1M0. Subsequently, the patient received adjuvant chemotherapy with CAF regiment (Cyclophosphamide, Doxorubicin, and Fluorouracil) for 6 cycles. After adjuvant chemotherapy, the patient underwent routine follow-up of abdominal and breast sonography which was found to be normal.

The patient has remained disease-free for three years until she complained a new lump on her left breast. The lump was then evaluated by sonography which was suggested as a residual mass, and performed fine-needle aspiration biopsy (FNAB) which was found malignant cells, giving a conclusion of relapsing breast cancer. A modified-radical mastectomy (MRM) procedure was performed, with the biopsy resulted in moderate differentiation of ductal infiltrating carcinoma. No metastases were found in the contralateral breast or other organs. Immunohistochemistry examination resulted positive expression of estrogen and progesterone receptors in approximately 35% of the tumor cell population, but negative in Her-2 (figure 1, 2, and 3). The patient then received second-line chemotherapy with paclitaxel and carboplatin for 6 cycles and radiotherapy with total dose of 30 Gy. After chemoradiotherapy, patients were initiated tamoxifen adjunctive therapy for 5 years (2006-2011). Routine control was performed including breast and abdominal sonography which resulted insignificant result, and assessment of CA 15.3 and CEA level reached within normal range. Abdominal sonography surveillance during tamoxifen therapy found no abnormalities in the uterus including the size of uterus. Patient was again declared to achieve disease-free after the first episode of relapse.

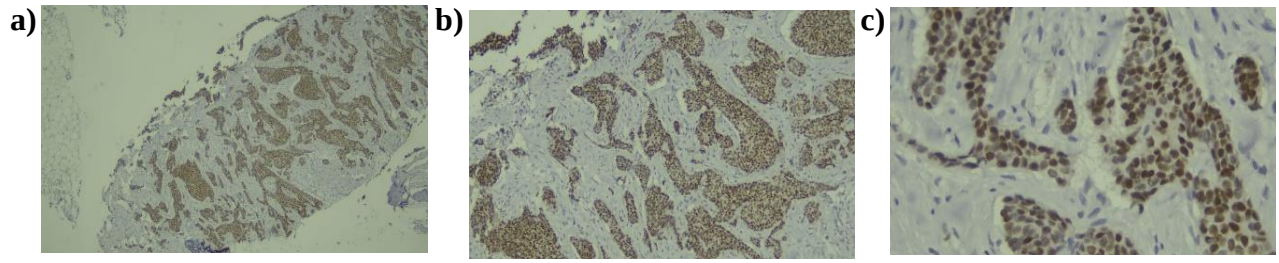

Figure 1. Estrogen receptor showed positive expression in ± 35% of tumor cells in breast cancer case, (a) low magnification, (b) medium magnification, (c) high magnification.

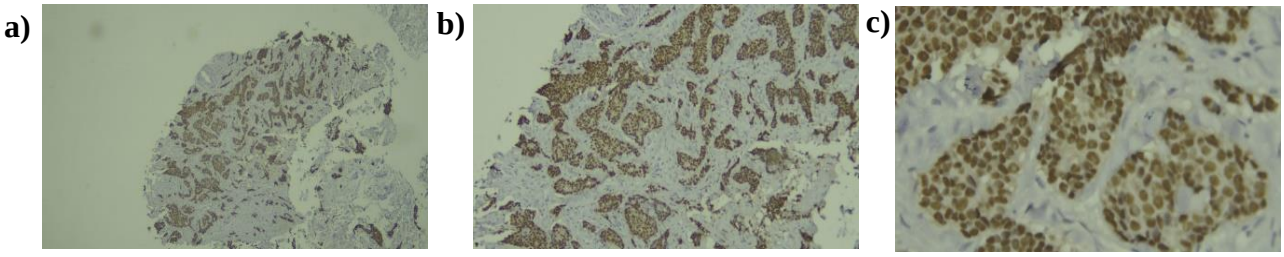

Figure 2. Progesterone receptor showed positive expression in ± 35% of tumor cells in breast cancer case, (a) low magnification, (b) medium magnification, (c) high magnification.

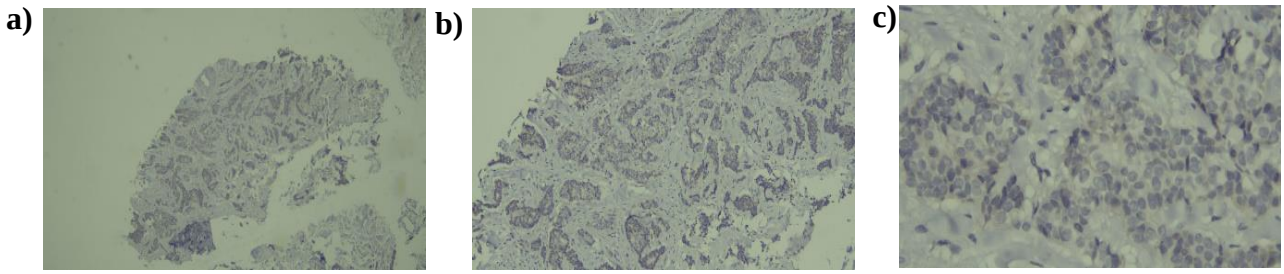

Figure 3. Her-2 Receptor showed negative expression among tumor cells in breast cancer case, (a) low magnification, (b) medium magnification, (c) high magnification.

Within a year after previous use of five-year tamoxifen, the patient, who at the time has achieved post-menstrual status, complained episode of heavy vaginal bleeding for 5 months, with gynecological evaluation was found a lesion on the cervical portion. Pap smear examination showed low-grade squamous intraepithelial lesion (LSIL) and continued with cervical biopsy concluded endometrioid carcinoma nuclear grade 3. During this moment, the Karnofsky performance status was 90%. Total Abdominal Hysterectomy and Bilateral Salpingo-oophorectomy (TAH-BSO) procedure were then performed on the patient. Uterine biopsy showed a poorly differentiated adenocarcinoma which invaded into myometrium, without the involvement of adnexa and omentum (figure 4), and later concluded as stage II T2N0M0 of endometrial carcinoma. Patient received 6 cycles of adjuvant chemotherapy with carboplatin. After chemotherapy, the patient underwent surveillance of abdominal and breast sonography, in addition to assessment of CEA, CA 125, and CA 15-3 which fell within normal range. Patient has remained in disease-free for breast cancer and endometrial cancer until her last recent visit in February 2020 (8 years for endometrial cancer, 15 years for breast cancer).

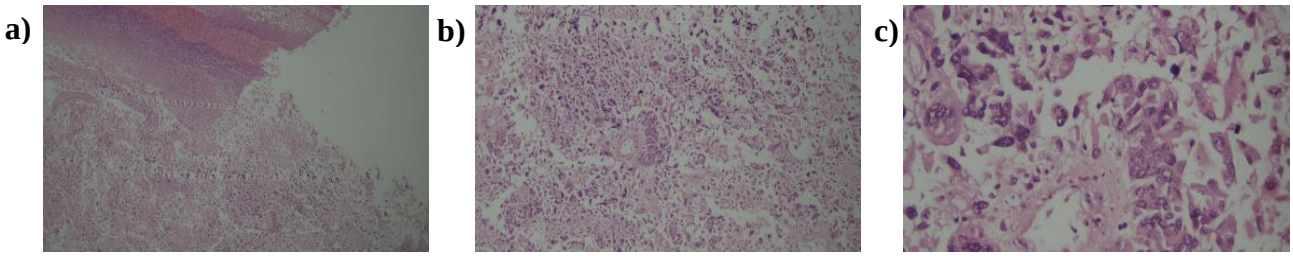

Figure 4. Pathological examination of uterine showed poorly differentiated adenocarcinoma, (a) low magnification, (b) medium magnification, (c) high magnification.

Discussion

The incidence of endometrial cancer among breast cancer patients with known using tamoxifen for hormonal treatment is considered rare and varies within studies, for about 2-8 per 1000 women.[6,11,12] Indeed, there is no specific study on the incidence of endometrial cancer related to tamoxifen in Indonesia. The estimated risk of endometrial cancer in breast cancer patients with tamoxifen use is also wide-ranging with a significant result reported by prospective study of tamoxifen (RR 2.53; 95% CI 1.35-4.47). Moreover, the risk is considered to be higher among patient over 50 years (RR 4.01; 95% CI 1.70 - 10.90).[12] On the other hand, most retrospective studies do not provide significant results for tamoxifen as a risk factor associated with endometrial cancer, seemingly due to limited number of endometrial cancer events compared with prospective studies.[11,13]

Tamoxifen is a selective estrogen receptor modulator (SERM) which has been proved to effectively reduce breast cancer recurrence and the risk of contralateral breast cancer events significantly. Five years of tamoxifen therapy could reduce the risk of relapse after 10 years by 37% among women aged 50-59 years, and as much as 54% among women aged 60-69 years.[14] In breast tissue, tamoxifen will provide anti-estrogen effects by blocking estrogen receptors (ER), thereby inhibiting the growth of estrogen-dependent breast neoplastic cells. On the other hand, the agonistic effects of estrogen would be seen in other tissues that also have estrogen receptors, including endometrial tissue which is stimulating both benign and neoplastic transformation.[15]

Tamoxifen selectively induces estrogen receptors with different characteristics between alpha estrogen receptors (α-ER) and beta (β-ER). The underlying mechanism of tamoxifen in breast cancer originates from the antagonistic effect of α-ER on breast tissue, but its agonistic effect via endometrial β-ER is related to hyperplasia and malignancy, even atypia in the endometrium.[16] Heterogeneity of this effect cannot be explained yet, but a proposed theory states that it depends on endogenous estrogen circulation. In an estrogen-rich environment, tamoxifen could act as a primary antagonist, while in an environment lacking of estrogen, the primary effect tends to be agonistic rather than antagnositic.[14,15,17]

Use of tamoxifen for three years or more is known to have a significant risk of endometrial cancer (OR 2.94; 95% CI, 2.13-4.06) which represents prolonging duration of estrogenic stimulation to endometrium.[18,19] In addition, women older than 35 years are also posed a higher risk of endometrial cancer (OR 4.08; 95% CI 1.67 - 9.93). However, other factors such as previous hormone exposure, hypertension, and diabetes insignificantly increase the incidence of endometrial cancer among breast cancer patients receiving tamoxifen.[18] In line with previous statement, both age factor and duration of tamoxifen therapy, which are confirmed within this case, are presumed to increase the patient's risk of endometrial cancer.

Heavy vaginal bleeding or menorrhagia is the main symptom and accounts for 62% of endometrial carcinoma among previous use of tamoxifen which was also presented in this case.[19] On the other hand, abnormality or any changes in term of uterine enlargement is rarely presented in tamoxifen-induced endometrial carcinoma. Instead, the previous sign is frequently presented in more benign cases such as leiomyomatosis, adenomyosis, and uterine polyp as also being other implications of tamoxifen-driven estrogenic stimulation in endometrium.[19–21] Thus, it seems to be fairly difficult to conduct surveillance of endometrial cancer among tamoxifen user sonographically.

The endometrial cancer presented in this case was staged as FIGO II and T2N0M0. The management was conducted with total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO),

followed by adjuvant chemotherapy with carboplatin for six cycles. NCCN Guidelines has recommended surgical procedure in resectable endometrial cancer, followed by adjuvant radiotherapy by using extended-beam radiotherapy (EBRT) with or without systemic chemotherapy in FIGO stage II.[22] Generally, endometrial cancer is classified into two Bokhman's subtypes. The first type which is often referred as endometrioid, which is occurred in this case, is an estrogen-dependent and has more favorable prognosis with 5-year overall survival (OS) of around 85%. In contrast, the second type, known as non-endometrioid types (including, serous and clear-cell) is more estrogen-independent type and frequently has worse prognosis with 5-year OS of around 55%.[23]

Extending tamoxifen duration from five to ten years has been shown to reduce breast cancer recurrence, for which NCCN guidelines has considered extending hormonal treatment for pre- and postmenopausal women with breast cancer.[7–9,24,25] Nevertheless, the consequence is also detrimental which is reported by other studies regarding the doubling risk of endometrial cancer when tamoxifen is extended to another five years.[24] Therefore, any measures to prevent or decreasing the cancer risk is invaluable in this scenario.

At present, the consensus issued by ESMO-ESGO-ESTRO still does not recommend routine surveillance of endometrial cancer other than routine gynecological care in pre-menopausal tamoxifen user women. However, postmenopausal women using tamoxifen are expected to be informed regarding long-term adverse events and also the cancer risk with providing to report any symptoms and signs that are correlated with endometrial hyperplasia or cancer such as vaginal bleeding.[26,27] Other clinical evidence of any measure to reduce the risk of endometrial cancer is still absent. For instance, a trial to combine tamoxifen and medroxyprogesterone has not been proven to effectively protect against endometrial carcinoma due to lower incidence of endometrial cancer than expected which is unable to make a robust conclusion.[28]

The evaluation of endometrial cancer among pre- and postmenopausal women is different. Generally, it requires transvaginal ultrasonography (TVS) and/or endometrial sampling. Women on tamoxifen therapy who have abnormal uterine bleeding (AUB) or are known to have endometrial thickening sonographically require pathological evaluation of the uterus. Endometrial thickness ≤ 4 mm based on TVS results in postmenopausal woman is sufficient to exclude endometrial cancer. However, a thickness of more than previous cut-off in post-menopausal women who are known as tamoxifen users is recommended to have an endometrial biopsy rather than TVS alone. Due to limitation of endometrial biopsy in detecting focal pathology, it is necessary to do a hysteroscopic endometrial biopsy along with TVS.[29]

Conclusion

Tamoxifen is still being drug of choice as hormonal therapy that is effectively reducing recurrence risk for hormone-receptor positive breast cancer. Due to this success, tamoxifen therapy has been extended from five to ten years. However, recent finding notifies for the doubling risk of endometrial cancer along with extension of tamoxifen therapy. Therefore, the risk must be properly handled, including screening, diagnosis, and management of endometrial cancer among women using tamoxifen. Clinical evidence in preventing the risk of endometrial cancer is still demanding to mitigate the risk along with arising practices of extending tamoxifen duration among breast cancer survivor.

Acknowledgement

Authors would like to thank the Department of Anatomical Pathology of FKKMK UGM / Sardjito General Hospital for providing and documenting biopsy and IHC photos in this case.

Conflict of Interest

The authors have no conflict of interest to declare.

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InaJCC The Indonesian Journal of Cancer Control

Review Article

Lung cancer and the new paradigm: A personal journey with a chronic disease

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p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v1i2.51

Received: August 28, 2021
Accepted: October 23, 2021

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Abstract

Cancer is a global health problem affecting all countries. Lung cancer is the most complicated cancer due to the involvement of various genes and intracellular processes in its carcinogenesis. It is the third most common cancer found in Indonesia after breast cancer and cervical cancer, and its impact on the patient, family, and national health burden could not be underestimated. Significant advancements have been achieved in the diagnostic procedures and treatment modalities of lung cancer. However, solving the lung cancer problem in Indonesia require a holistic solution, and good collaboration between specialists as a multidisciplinary team is crucial. The new paradigm of lung cancer views this disease as a chronic disease and offer more optimistic target of treatment to control the disease and to have good quality of life. Objective measurement of premature death can be used as a parameter to assess the achievement of lung cancer program nationally. Strict control of risk factors and early screening for high-risk groups are essential for lowering premature deaths. For the future, stem cell therapy is a promising modality in the treatment of lung cancer. Studies are currently planned for the discovery of lung cancer stem cell and the therapy that target it.

Keywords: *lung cancer, paradigm, chronic disease*

Abstrak

Kanker merupakan masalah kesehatan global yang memengaruhi semua negara. Kanker paru-paru merupakan kanker yang paling rumit karena adanya keterlibatan berbagai gen dan proses intraseluler dalam karsinogenesisnya. Kanker paru adalah kanker tersering ketiga di Indonesia setelah kanker payudara dan kanker serviks, dan dampaknya terhadap pasien, keluarga, serta beban kesehatan nasional tidak bisa diremehkan. Berbagai kemajuan telah dicapai dalam prosedur diagnostik dan modalitas terapi, namun untuk menyelesaikan masalah kanker paru-paru di Indonesia dibutuhkan solusi yang holistik. Kolaborasi yang baik antar spesialis sebagai tim multidisiplin juga penting. Paradigma baru kanker paru-paru memandang penyakit ini sebagai penyakit kronis, dan memberikan target tata laksana yang lebih optimistis untuk mengendalikan penyakit dan memiliki kualitas hidup yang baik. Pengukuran objektif kematian prematur dapat digunakan sebagai parameter dalam menilai capaian program nasional pengendalian kanker paru-paru. Pengendalian yang ketat terhadap faktor risiko serta skrining dini pada kelompok berisiko tinggi berperan penting dalam mengurangi angka kematian prematur. Untuk masa depan, terapi sel punca merupakan modalitas yang menjanjikan untuk tata laksana kanker paru-paru. Berbagai penelitian sedang direncanakan untuk menemukan sel punca kanker paru-paru dan terapi yang menargetkannya.

Kata kunci: kanker paru, paradigma, penyakit kronis

This article is translated from the author's professorial inauguration speech on March the 13th 2021 at FMUI Salemba campus, Jakarta

Background

A simple and concise title, but the word “paradigm” has quite a broad and deep meaning. Paradigm is a set of assumption, concept, values and practice which are applied in viewing the reality to understand the problem of lung cancer. Through this speech, I attempt to get us back to the basic and principles of lung cancer treatment, by altering the lung cancer stigma which has always been referred as the cancer with the worst prognosis and the most common cause of death from cancer. That stigma leads to the patients and their doctor to lose hope, while inaccurate information and miscommunication encourage most patients to seek alternative treatments and becoming the victim of irresponsible nonmedical treatments.

Cancer will always be a global health problem affecting all countries irrespective of the developed, developing, or underdeveloped country criteria. Cancer is not exclusively a problem of low-income or middle-income countries, but also high-income countries. The differences are only in the prevalence and prognosis of each cancer cell type, which are highly associated with the demographic characteristics, life style and health care system of a country. Cancer is a disease caused by the uncontrolled growth of abnormal cells inside the body which spread and damage body tissues. Cancer cell growth is affected by many factors and prolonged time is needed to finally be able to diagnose it clinically. Generally, cancer is divided into solid tumor and hematologic malignancy. Solid tumor is a cancer that originate or differentiate from the epithelial tissue of human organs. Although considered the same cancer cell type, cancer in different body organs may show diversity in genetical and molecular biology levels.

Science has developed rapidly including the knowledge about malignancy and cancer, especially after the Polymerase Chain Reaction (PCR) technique was founded by Kary Banks Mullis. Since its first application approximately 37 years ago, PCR technology has revolutionized several molecular biology aspects in the world. Due to that phenomenal invention in 1993, the inventor of PCR was awarded the Nobel prize in Chemistry. That method has slowly unraveled the mystery of carcinogenesis, including the problem of cancer cell’s unresponsiveness towards anti cancer therapy. Genetic and molecular diversities will affect the different treatment and prognosis of each cancer type. For example, breast cancer adeno-carcinoma, servical cancer adenocarcinoma or lung adenocarcinoma have different method of determining the progress of the disease when it is found, called staging system. These types and molecular differences also enable the therapeutic modality choice that is expected to be the best for the patients. These are what drive the development of targeted therapy and changes the method of cancer treatment using individual approach or personal medicine for each cancer patient.

The Problem of Lung Cancer

Lung cancer is the most complicated cancer due to the involvement of various genes (multi-genes) and intracellular processes (multi-processes) in its carcino-genesis. This is understandable as the respiratory tract and lung are connected and exposed directly to the atmosphere, and we normally bring the air with all its contents into the respiratory tract and lung for respiration by inhaling and exhaling 16-20 times every minute. The anatomical position of the respiratory system makes lung cancer very difficult to detect during its early stage.

I remember that in 2004 my mentor, Prof. dr. Anwar Jusuf, SpP(K), expressed his many hopes for the development of lung cancer treatment in his professorial inauguration speech. It has been 16 years since then, and part of that challenge has been answered along with the development of knowledge regarding cancer. Nowadays, the new generation of cancer therapies used in therapy guidelines or chemotherapy regimens offers more options, with easier administration, less side effect, and better therapeutical response.

However, the progress of knowledge that influence clinical implication makes me realize that the knowledge about cancer, especially lung cancer, is like a never-ending story. The more we discover abnormalities, the more we are forced to seek the answer on what affect it. Therefore, I was relieved when Prof. Anwar, as the Head of the Department of Pulmonology and Respiratory Medicine FMUI back then, once asked me, a staff in the Oncology Division since 2000, to also explore other lung diseases. I declined because I was going to focus in thoracic malignancies. (Prof. Anwar maybe forgot, but I declined because we discussed it on the way to an event at Dharmais Cancer Hospital for a Lung Cancer study group activity every Wednesday morning in my tiny red Ceria car).

The year 2018 was an exceptional year for us who were involved in cancer problem in Indonesia. When Prof. Dr. dr. Nila Djuwita Anfasa Moeloek, SpM(K), an oncologist, was appointed as the Minister of Health, cancer problem was given special attention by the formation of the National Cancer Control Committee (NCCC) / *Komite Penanggulangan Kanker Nasional (KPKN)*, which was first chaired by Prof. Dr. dr. Soehartati A. Gondhowiardjo, Sp.Rad(K),Onk.Rad. We certainly agreed and realized that to effectively unravel the problem and determine the priority scale for cancer control, good and accurate data were needed. We, the members of NCCC, together with the Ministry of Health and Dharmais Cancer Hospital, developed and renewed the national cancer registry system, which encompasses many regions according the the international standard. This task was led by dr. Evlina Suzanna, SpPA. This effort has paid off, as we now have an estimation of cancer data profile in Indonesia which can be accessed as it was listed in the global registry written and published by the World Health Organization (WHO) in Globocan 2018, and is updated every year.[1]

Cancer problem in Indonesia is pictured (Figure 1) in this 2020 statistical data published in early 2021.[2] Lung cancer is the third most common cancer found in Indonesia after breast cancer and cervical cancer. According to gender, lung cancer is the most common cancer in males, followed by colorectal cancer and liver cancer. In females, lung cancer is not included in the five most common cancer. This is in contrast with the global data of 19.3 million new cases, the top three cancer types are female breast cancer (11.7%), lung cancer (11.4%) and liver cancer (11.0%). Similar to Indonesia, lung cancer is the most common cancer found in males globally, followed by prostate cancer and colorectal cancer. Another difference is that lung cancer in females is the second most common cancer globally following breast cancer.[3,4]

Summary statistic 2020

	Males	Females	Both sexes
Population	137 717 861	135 805 760	273 523 621
Number of new cancer cases	183 368	213 546	396 914
Age-standardized incidence rate (World)	138.9	145.4	141.1
Risk of developing cancer before the age of 75 years (%)	15.0	14.9	14.9
Number of cancer deaths	124 698	109 813	234 511
Age-standardized mortality rate (World)	96.3	75.9	85.1
Risk of dying from cancer before the age of 75 years (%)	10.5	8.3	9.4
5-year prevalent cases	389 640	556 448	946 088
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Lung Colorectum Liver Nasopharynx Prostate	Breast Cervix uteri Ovary Colorectum Thyroid	Breast Cervix uteri Lung Colorectum Liver

Figure 1. Cancer statistics in Indonesia 2020.[2]

Those statistical data are not merely numbers. Based on those estimated figures, we can learn so much regarding the factors that affect those differences. Those data will provide us academics, with our responsibility as researchers, and the government as regulators with the necessary tools to establish priority scale which enables more effective lung cancer control program and well-targeted health service.

Are the data published by the WHO represent the real practical condition? The Oncology Division, Department of Pulmonology and Respiratory Medicine FMUI, located

at Persahabatan National Respiratory Referral Hospital (RSUP Persahabatan), has the annual report. The lung cancer characteristics data in 2017-2019 (Table 1) represents the national characteristic, considering the abundance of referral cases from all regions of Indonesia.[5] Lung cancer is more often found in males, in reproductive age (40-65 years old) and the majority of cases were discovered on its late stage.[5]

Table 1. Characteristics of lung cancer patients at RSUP Persahabatan, Jakarta, year 2017-2019

Characteristic	Total	(%)
Gender		
• Male	1,513	66.89
• Female	749	33.11
Age		
• Median	60	
• Rate	21-98	
Cancer cell type		
• Adenocarcinoma	1,455	64.32
• Squamous cell carcinoma	596	26.35
• Others	211	9.33
Stages of disease		
• Early stages (stage 1 and 2)	31	4.64
• Late stages (stage 3 and 4)	2,157	95.36

However, several issues were not revealed by these statistics. Lung cancer is not a communicable disease, but causes disruption or social impacts that could not be underestimated. The fact that the morbidity and mortality rates of lung cancer are still high surely creates problems not only for the family and social environment. It must be understood that cancer treatments are generally expensive, thus causing financial problem for the family and contributing to the national health burden. The National Social Security on Health or Badan Penyelenggara Jaminan Sosial (BPJS) Kesehatan currently cover at least eight catastrophic diseases, such as heart disease, cancer, stroke, kidney failure, thalassaemia, haemophilia, cirrhosis hepatitis and leukaemia. The three most costly diseases for BPJS Kesehatan amongst those eight are heart disease, cancer and stroke.[6]

We should be grateful that Indonesia is one of the countries, maybe the only one, that have a National Health Insurance / Jaminan Kesehatan Nasional (JKN) with its BPJS Kesehatan program which insure the cost of lung cancer management, starting from diagnosis to treatment. The BPJS system supports many lung cancer patients, however this service platform is not yet perfect as it oftenly causes late payments due to the convoluted nature of the system. Therefore, BPJS needs to listen to suggestions from us clinicians and patients as their consumers, so that lung cancer treatment will be more effective and efficient with the aim of providing the optimal management.

Until today, we at RSUP Persahabatan and other academic hospitals in Indonesia that have similar department can say that molecular-level diagnostic procedure is a challenge for us to provide individual therapy. The loss of the country's foreign exchange to other countries associated with health service in Indonesia is a concern for us. This problem is not as simple as blaming the clinicians, because clinicians only play a small part in our whole health service system. Therefore, once again we appeal to the new BPJS board of directors to listen to our suggestions for a better system. Let us leave the old expression that "using BPJS is exhausting, complicated, and annoying" as a past hoax, and let us help lung cancer patients that could not afford to pay more at private hospital only for convenience. The government, in this case BPJS, must change because all the Indonesian people are constitutionally obligated to participate in this health insurance system.

Without putting unnecessary burden to the government, we have implemented quality and equality improvement in synergical cooperation or collaboration with our peers in other specialties involved in lung cancer management. In 1992, I started my residency and witnessed my teachers, Prof. dr Anwar Jusuf, Sp.P(K), Prof. dr. Ismid D. Busro, Sp.BTKV(K), Prof. dr. Nirwan Arief, Sp.P(K), dr. Sutjahjo Endardjo, Sp.PA(K) and dr. Suginem Mujiantoro, Sp.Rad.Onk, as the multidisciplinary team (MDT) routinely held discussion in the lung cancer conference at RSUP Persahabatan every Thursday noon. Then in 2004, the seniors instructed me, Dr. dr Ahmad Hudoyo, Sp.P(K), dr Agung Wibawanto, Sp.BTKV(K), Dr. dr Aziza G. Icksan, Sp.Rad(K), dr Juniarti Sp.Rad.Onk, dr. Heriawaty Hidajat, Sp.PA and many other next generation clinicians to form a study group (Indonesian Association for the Study on Lung Cancer or InSCLC) that specifically discuss about the Indonesian version of lung cancer management. In 2005, this study group published a recommendation and it became the first national lung cancer management guideline, which is updated every 5 years. The InSCLC has developed significantly with the active involvement of Pumonary and Respiratory Medicine specialists, Anatomical Pathology specialists, Radiotherapy specialists, Radiology specialists and other specialists, not only at RSUP Persahabatan, but also in the national scope

by actively working with those who are involved in lung cancer management in Pulmonology and Respiratory Medicine academic centre hospitals. Good collaboration between specialists as a multidisciplinary team (MDT) is crucial for lung cancer management. We have also widened our focus to other thoracic malignancies such as mediastinal tumor, lung metastases, chest wall tumor and mesothelioma. In 2019, InSCLC changed its name to Indonesian Association for the Study of Thoracic Oncology (IASTO) to answer and provide solutions according to the development of knowledge and experience in the field.

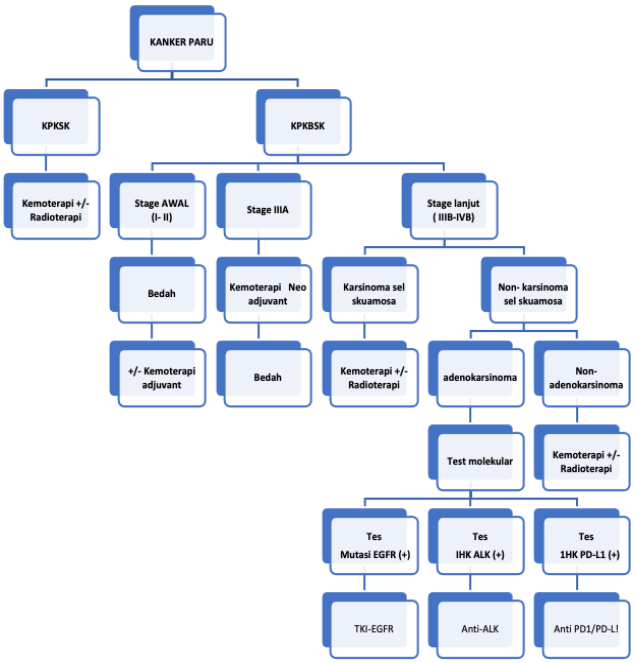

Figure 2. Diagram of lung cancer management according to cell type and molecular examination.[12]

With the advancement of our ability in diagnostic procedural techniques, as well as undergoing numerous researches and participating in clinical trials on new drugs for lung cancer, we are now entering the targeted therapy era. Studies in gene mutation (EGFR) and gene products (ALK, PD-L1) needed for targeted therapy have been done, albeit with limited research fund.[7-9] Our contribution on clinical trials of new drugs can serve as proofs that the management that we provide to our patients is on the same level with other countries.[10-12] Unfortunately, the opportunity to be involved in clinical trials on new cancer drugs are now slimmer due to the government regulation of material transfer agreement (MTA). It is not an exaggeration to hope for a joint decree involving three ministries (Health, Education and Research) to open up more opportunities to be involved in multicenter clinical trials, not only to provide solution for health problems, but also to produce more reputable international publications representing our beloved Universitas Indonesia. Multicenter studies may also provide opportunities for patients to get access to drugs currently in trials. We are quite envious with the perks obtained by overseas researchers and patients due to the easiness of procedure for clinical trial.

I am grateful to be a part of this revolution in lung cancer knowledge which influence lung cancer management rapidly. The year 1992-1994 are my early years in studying, understanding and performing therapies. We were quite proficient in performing diagnostic procedures during our second semester. Due to the presence of Prof. dr. Nirwan Arief, Sp.P(K) and Prof. dr. Menaldi Rasmin, Sp.P(K), and also the dynamic collaboration with our peers in Radiology and Thoracic Surgery, the time limit of 2 weeks for diagnosis was usually achieved. Chemotherapy administration is a required competency for Pulmonology residents, not simply deciding the regimen type, but also preparing the drug and evaluating the result. However, there were only few cancer patients undergoing therapy, due to financial problem and the lack of health insurance system for lung cancer patients, as well as the bad stigma of lung cancer.

In the year 1994-1999, I started a new journey in cancer field, one which was made possible by Prof. dr. Faisal Yunus, PhD, Sp.P(K) and Prof. Michio Yamakido, MD, PhD. Armed with scholarship from Monbusho, Japan, I enlisted in a postdoctorate program in the Second Department of Internal Medicine, School of Medicine Hiroshima University, Japan. All praise to God, I was at “the right time, the right person and the right place”. As a researcher, it was a great experience because I did not need to consider the fund limit for materials and facilities. The number of lung cancer patients also kept increasing which provided me with sufficient specimens for research materials. The year 2000 is the year when I started to work at RSUP Persahabatan, as well as the increase of lung cancer patients visiting the hospital and the implementation of ASKES insurance system for government employees, resulting in more lung cancer cases receiving better treatment. The incorporation of new generation anti-cancer therapies in the guidelines or chemotherapy regimens for lung cancer enabled us to choose the best regimen for a cancer patient. The protocol for chemotherapy administration, the overall mild side effects and the

better survival rate of lung cancer patients receiving treatments all showed promising results.

Around the middle of the year 2005, lung cancer management has entered the era of targeted therapy. We were involved in a multi center clinical trial for an orally-administered lung cancer therapy. Since returning from Japan, we adjusted with the available facilities and fund, and we kept doing molecular epidemiology studies to assess the characteristics of lung cancer patients in Indonesia. By the end of 2020, the types of cancer therapy have increased with more specific indications. If in the end of the nineties we dwelled on whether a new lung cancer patient may survive for one year, nowadays we can easily discuss the variety of therapeutic modalities for lung cancer patients, especially in the last five years when BPJS Kesehatan enabled the access to several types of targeted therapy.

The New Paradigm of Lung Cancer

If the beginning of my speech was more of a reflection and complaint, then for the next part I would like to propose an idea for thought on what should be done. In my opinion, solving the lung cancer problem in Indonesia require a holistic solution. Hence, I remember an old phrase which in its native language reads “baraja ka nan manang, baguru ka nan pandai”. It means, we do not need to be reluctant to learn from others who are successful. Therefore, we can adopt the good things and adjust the bad ones for a better result suitable with our condition.

We do not need to use the gloomy vibe of whether lung cancer can be cured or not anymore. With the new paradigm, we can offer more enlightening options, and the target of our treatment is to control the lung cancer. Palliative approach in lung cancer patient management will provide optimistic targets, for example, for elderly patients who wish to have grandchildren, which God willing can be achieved by helping their children to get married. Some patients may want to witness their children graduating as specialists, or having the opportunity to perform the Hajj pilgrimage, or any other optimistic targets. We should certainly avoid giving false promise or unrealistic target, such as completely eliminating the cancer without any surgery. The target for terminal stage lung cancer patients is to control the disease and to have good quality of life.

It is time for us to apply other parameters to assess the achievement of lung cancer program nationally. One of which is to use premature death on lung cancer that can be measured objectively. Lung cancer premature death is death that occurred before the average death rate of a certain population. Developed countries set the age limit of 75 years as the threshold to measure premature death and estimating the risk of lung cancer patient before 75 years. Indonesia can use the age limit of 65 or 70 years, considering the data by Statistics Indonesia (Badan Pusat Statistik / BPS) in 2020 that the life expectancy at birth of Indonesian people is 71.47 years. In Australia, lung cancer was the second most common cause of premature death in 2012, with three of five (59%) premature deaths caused by lung cancer occurred in males. However, these figures showed significant drop of 45% in the last three decades from 1982-2012.[13]

Figure 3. Premature deaths due to lung cancer in Austrialia, according to gender and age group in 2012.[13]

Learning from other countries that have succeeded in decreasing the lung cancer premature deaths, lung cancer management in Indonesia really needs improvement. Upstream, we have to recognize and control the risk factors. The main risk factor for lung cancer is cigarette smoke exposure.[5] Without serious control of risk factors, the number of cancer patients will never decrease. We have not been controlling the main risk factor seriously. Indonesia is still one of the countries that has not yeen ratified the tobacco control treaty due to economic considerations while also positioning the tobacco industry as an important foreign exchange contributor. Nevertheless, we should appreciate some attempts that have been made in the regulation of non-smoking area in public

spaces and raising the customs and price of cigarette. What is lacking is a firm and strict regulation to limit the increasing numbers of beginner and teenager smokers. Setting the age limit of smoking will raise the age of being diagnosed with lung cancer. Right now, the majority of lung cancer patients were diagnosed at the age of 40-65 years (66.18%), > 65 years (29.18%) dan < 40 years (4.47%), as the consequences of starting to smoke at a very young age. Downstream, we need to urge high-risk groups for lung cancer to get screening. Table 2 shows the percentage of lung cancer risk factors.[13]

Table 2. Risk factors for lung cancer at RSUP Persahabatan, Jakarta, year 2017-2019

Risk Factors	Total	(%)
Cigarette smoke exposure		
• **Yes**		**91.4**
(Active or former smoker)	1,435	(63.44)
(Passive smoker)	633	(27.98)
• Non-smoker	108	4.77
• N/A	86	3.83
Tuberculosis		
• **Yes**	675	**29.84**
• No	1,508	66.72
• N/A	79	3.44
Family history of cancer		
• **Yes**	204	**9.02**
• No	2,013	88.99
• N/A	45	1.99
Environment (workplace, home, etc.)		
• **Yes**	345	**15.26**
• No exposure	1,512	66.84
• N/A	405	17.90

The biggest risk for lung cancer is cigarette smoke exposure, however there are other factors that need attention. History of lung tuberculosis as a risk factor needs further studies, as presently lung cancer diagnosis is more of a factor that delay the diagnosis (underdiagnosis), but a study has found correlation between them.[14] The risk of lung cancer according to family history has not yet been proven, but may become a factor that increases one's susceptibility.[15] Similar statement can be concluded with carcinogen exposure at workplace.[16]

The high-risk groups for lung cancer include people over 45 years old and smokers, or ex-smokers for less than 10 years that do not exhibit any symptoms. The suggested screening tests are low-dose thoracal CT scan. Those who are high risk and have symptoms, should actively perform early detection. The discovery of lung cancer in early stage and undergoing surgery will give long survival rate, or even complete cure. With the correct therapeutic modality, we hope to be able to increase the five-year survival rate percentage. It is promising that by choosing the right regimen and anticancer drugs in late stage lung cancer, the efficacy rate is better.

Conclusion

In my opinion, advocating prevention by risk factor control will not succeed if it is only rhetorical. Therefore, we need to provide scientific evidences to encourage the public and the government as regulators regarding the risk factor control. Currently, the outcome of risk factor control was not satisfying, as it is incredibly difficult to educate people regarding the danger of smoking. Studies showed that several genes were involved in the early process of lung cancer formation. Inhibition in the molecular level needs to be considered to prevent lung cancer in smokers (chemoprevention), while keeping in mind that cigeratte smoke is like a double-edged knife, not only because of the carcinogens contained inside but also by causing continuous irritation on the respiratory tract epithelium that may become precursor of lung cancer.

Even though recent treatments for lung cancer showed better result, there is still one dream that we are trying to achieve. Together with our colleagues in the Human Cancer Research Center cluster at IMERI, we are planning to conduct studies to discover lung cancer stem cells. Stem cell therapies have been applied for other diseases successfully at FMUI, but not yet in lung cancer. Lung cancer stem cell is the factory that produce lung cancer cells, and it provides answer to the suboptimal results of current treatment modalities. The cure to lung cancer can be realized if one day we can discover the location of the factory (stem cell) and destroy it completely. So please help us realize that dream.

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All manuscripts should be prepared in accordance with "Uniform Requirements for Manuscript Submission to Biomedical Journals" (also known as "Vancouver Style"), as agreed by the International Committee for Medical Journal Editors. The entire manuscript must be typewritten in two columns with Arial font size 10, single spaced, left and right aligned, on one sided page with white bond paper, 216 x 279 mm (8 ½ x 11 in.) or ISO A4 (212 x 297 mm), with margins of at least 25 mm (1 in.), including the

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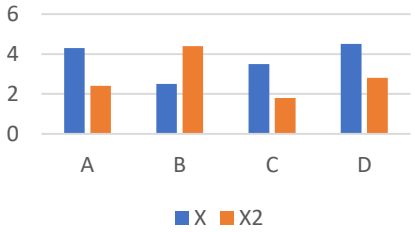

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