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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.

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Editorial

The Future Prospects For Lung Cancer Treated With Systemic Therapy

Cancer remains a major public health problem in Indonesia, requiring substantial treatment costs. The three most common types are breast cancer, cervical cancer, and lung cancer. Screening and early detection programs are essential to achieving better outcomes. Screening initiatives are expected to reduce cancer incidence, though their effectiveness can only be confirmed through long-term evidence. Meanwhile, early detection programs aim to improve patient prognosis. The success of these programs depends not only on adequate facilities and infrastructure but also on increasing public awareness and understanding of cancer, especially considering that many patients are still diagnosed at an advanced stage. Consequently, it is not surprising that a significant portion of healthcare funding is allocated to cancer treatment.

The main goals of cancer management are to cure the disease, prolong survival, and relieve symptoms when a cure is not possible. For early-stage cancers, the primary objective is often to completely eliminate the malignancy through treatments such as surgery or chemotherapy. In contrast, for advanced-stage cancers, the focus shifts toward slowing disease progression, managing complications, and improving the patient's quality of life. Lung cancer, in particular, has a poor prognosis and is associated with a shorter average life expectancy. It remains the leading cause of cancer-related death worldwide, largely because most cases are diagnosed at an advanced stage when systemic therapy becomes the mainstay of treatment. Systemic therapy for lung cancer includes chemotherapy, targeted therapy, and immune checkpoint inhibitors (ICIs). Platinum-based doublet chemotherapy given in three-week cycles remains a cornerstone, while targeted therapy may be used when appropriate molecular markers are identified.

Currently, tyrosine kinase inhibitors (TKIs) targeting EGFR mutations are available for patients with EGFR gene alterations, while ALK inhibitors are indicated for those with positive ALK IHC results. Similarly, ICIs can be administered to patients with positive PD-L1 expression on immunohistochemistry. Evidence-based studies demonstrate that properly selected and administered systemic therapies result in significantly better outcomes. Overall survival among patients receiving targeted therapy or ICIs shows a remarkable improvement compared with conventional chemotherapy, particularly when considering reduced therapeutic toxicity and better quality of life.

Furthermore, several studies have shown that combining chemotherapy with targeted therapy or ICIs can yield promising results. Despite the challenges posed by small sample sizes and incomplete mortality records, studies in Indonesia also reveal a positive trend: appropriately administered targeted therapies or ICIs in suitable patients demonstrate superior efficacy compared with conventional chemotherapy.

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Original Article

Overall survival of non-small cell lung cancer treated with systemic therapy: The experience at a regional hospital, Bandar Lampung

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Abstract

Background: The benchmark for the success of cancer treatment is the survival rate. Although the hope for survival is increasing, there are still concerns regarding the cost of treating lung cancer with targeted therapy which is very expensive and has not yet been included in the national formulary for third-generation EGFR-TKI targeted therapy (osemertinib).
Method: Analytic descriptive with retrospective cohort design processed with SPSS 25 with log-rank test and shown with Kaplan Meier product limit curve. Data was taken at Dr. H. Abdul Moeloek Hospital from January 2020 to December 2022.
Results: We analyzed 92 Lung adenocarcinoma who have treated with systemic therapy. Thirty-nine (42.9%) subjects were treated with EGFR-TKI therapy, and 53 (47.1%) subjects were treated with chemotherapy that used paclitaxel-carboplatin regimen. The median survival time of the group treated with EGFR-TKI was 7 months (95% CI: 3.805-10.195) while the chemotherapy group was 5 months (95% CI: 3.788- 6.212) while the overall median survival was 6 months (95% CI: 4.836-7.164). There was no significant difference with the p-value: 0.209.
Conclusion: The median survival rate of two groups was not significantly different.

Keyword: EGFR-TKI, carboplatin-paclitaxel, lung adenocarsinoma, survival rate

Abstrak

Latar Belakang: Tolok ukur keberhasilan pengobatan kanker adalah angka kesintasan hidup. Meskipun harapan untuk bertahan hidup semakin meningkat, masih terdapat kekhawatiran mengenai biaya pengobatan kanker paru dengan terapi target yang sangat mahal. Terapi ini juga belum masuk dalam formularium nasional untuk terapi target generasi ketiga EGFR-TKI (osemertinib)
Metode: Deskriptif analitik dengan desain kohort retrospektif yang diolah dengan SPSS 25 dengan uji log-rank dan disajikan dengan kurva Kaplan Meier. Pengambilan data dilakukan di RSUD Dr. Hj. Abdul Moeloek dari bulan Januari 2020 hingga Desember 2022.
Hasil: Telah dianalisis 92 adenokarsinoma paru yang telah diobati dengan terapi sistemik. Tiga puluh sembilan (42,9%) subjek diterapi dengan EGFR-TKI dan 53 (47,1%) subjek dengan kemoterapi yang menggunakan regimen paclitaxel-carboplatin. Kesintasan hidup rata-rata waktu kelompok yang diobati dengan EGFR-TKI adalah 7 bulan (95% CI: 3.805-10.195) sedangkan kelompok kemoterapi adalah 5 bulan (95% CI: 3.788- 6,212). Median kesintasan hidup keseluruhan adalah 6 bulan (95% CI: 4.836- 7.164). Tidak ada perbedaan yang signifikan dengan nilai-p 0,209.
Kesimpulan: Rerata median kesintasan hidup dari dua kelompok tidak berbeda secara signifikan

***Kata Kunci**: adenokarsinoma paru, angka kesintasan hidup, EGFR-TKI, carboplatin-paclitaxel.*

Background

Regional General Hospital Dr. H. Abdul Moeloek (RSUDAM) is a Type A Referral and Education Hospital in Lampung Province, Sumatra. Data on lung cancer cases at RSUDAM from Fransiska's research results in 2018-2021 found 244 cases with a number of cases man:women around 3:1. Based on the age category, most cases of lung cancer were between 35-65 years old, 173 people (70.9%), and based on the stage of lung cancer, most cases of lung cancer came in stage IV B with a total of 92 people (37.7%), stage IV A 91 people (37.3%), stage III B 38 (15.6%) and stage III A as many as 23 people (9.4%).[1]

Treatment of lung cancer uses multimodality therapy. The choice of therapy is based on histological/ cytological type, stage, condition of the patient, availability of drugs in the hospital and the economic capacity of the patient. Surgery and radiotherapy are local treatments while chemotherapy and targeted therapy are systemic treatments. The management of lung cancer non-small cell carcinoma subtype adenocarcinoma (non-squamous) which has mutations in the epidermal growth factor receptor (EGFR) in exons 19 and 21 can be given treatment with the first generation of EGFR-tyrosine kinase inhibitors (TKI) (gefitinib, erlotinib) or second generation of TKI (afatinib), whereas those with mutations in exon 18, 20, L861Q) will respond well to second and third generation EGFR-TKI (osemertinib). Currently, the era of national health insurance (JKN) is managed by the Social Security Administration Agency(BPJS), the requirement to get EGFR-TKI chemotherapy drugs is to have EGFR examination results which not all patients can carry out.[2]

The benchmark for the success of cancer treatment is the survival rate. Survival in cancers with high malignancy such as lung cancer is 1-year survival, 2-year survival and 3-year survival.[3] Although survival expectations are increasing there are still concerns regarding the cost of treating lung cancer with targeted therapy which is very expensive and has not yet been included in the national formulary for third-generation EGFR-TKI target therapy (osemertinib).

Supriadi Kasum's research at the RSUP Persahabatan for lung cancer cases between 2010 - 2013 concluded that the survival time of non-small cell lung cancer patients of the adenocarcinoma type (non-squamous) treated with EGFR-TKI was slightly longer than first-line chemotherapy (263 days vs. 260 days).[4] Hasan Nyambe's retrospective study at Wahidin Sudirohusodo Hospital Makassar in 2017-2019 survival in non-small cell lung cancer (KPKBSK) patients who received EGFR-TKI had a significantly higher survival rate than those who received first-line chemotherapy (conventional chemotherapy).[5]

Research on survival rates of lung cancer patients at RSUD Dr. Hi. Abdul Moeloek has never done this. This study aims to determine the characteristics and survival rates of lung cancer patients with subtype adenocarcinoma who received EGFR-TKI therapy and who received conventional chemotherapy with carboplatin and paclitaxel. Survival analysis provides great benefits not only for predicting survival chances, but also for better management of lung cancer patients.

Methods

This research is a descriptive-analytic study using a retrospective cohort design. The research sample was obtained from medical record data of patients diagnosed with lung cancer of non-small cell carcinoma of the adenocarcinoma type who received conventional chemotherapy (Carboplatin and paclitaxel) and EGFR-TKI therapy from January 2020 to December 2022 at Dr. H. Abdul Moeloek Bandar Lampung, using the total sampling method (consecutive sampling). The data were processed using the SPSS 25.0 program, then survival analysis was carried out using the Kaplan-Meier product limit method. The log-rank test is used to get the difference between the sub-variables. Significance was determined with a p-value <0.05.

Results

Research subject data from the age variable were grouped into 4 categories, namely age < 45 years, 46 – 60 years, 61 – 75 years and > 75 years. In the group of subjects with EGFR-TKI therapy, the highest number of subjects was in the age range between 46-60 years, with 20 subjects (51.28%), as well as in the group of subjects with carboplatin-paclitaxel therapy with 31 subjects (58.49%). This data is shown in Figure 1.

Table 1. Data on the characteristics of the two groups of research subjects

Variable	Category	EGFR-TKI (N=39)		P-Value*	Chemotherapy with carboplatin-paclitaxel		P-Value**
		n	%		n	%	
Age	Mean	58.08 ± 12.3		0.980	54.11 ± 10.13		0.140
	Median	53.33			56.25		
	(min-max)	(32-84)			(31 – 77)		
Gender	Male	12	30.8	0.581	35	66	0.420
	Female	27	69.2		18	34	
Smoking status	Non- Smokers	26	66.67	0.497	15	28.3	0.450
	Smokers	13	33.33		38	71.7	
Staging	3B	5	12.8	0.577	8	15.1	0.412
	4A	32	82.1		34	64.2	
	4B	2	5.1		11	20.7	
	No data	20	51.3		34	64.2	
EGFR Mutation	Ex 18	1	2.6	0.748	0	0	0.518
	Ex 19 Del	13	33.3		0	0	
	Ex 21	5	12.8		0	0	
	WT	0	0		19	35.8	

Note:
*P-value from Shapiro-wilk
** P-value from Kolmogorof-Smirnof

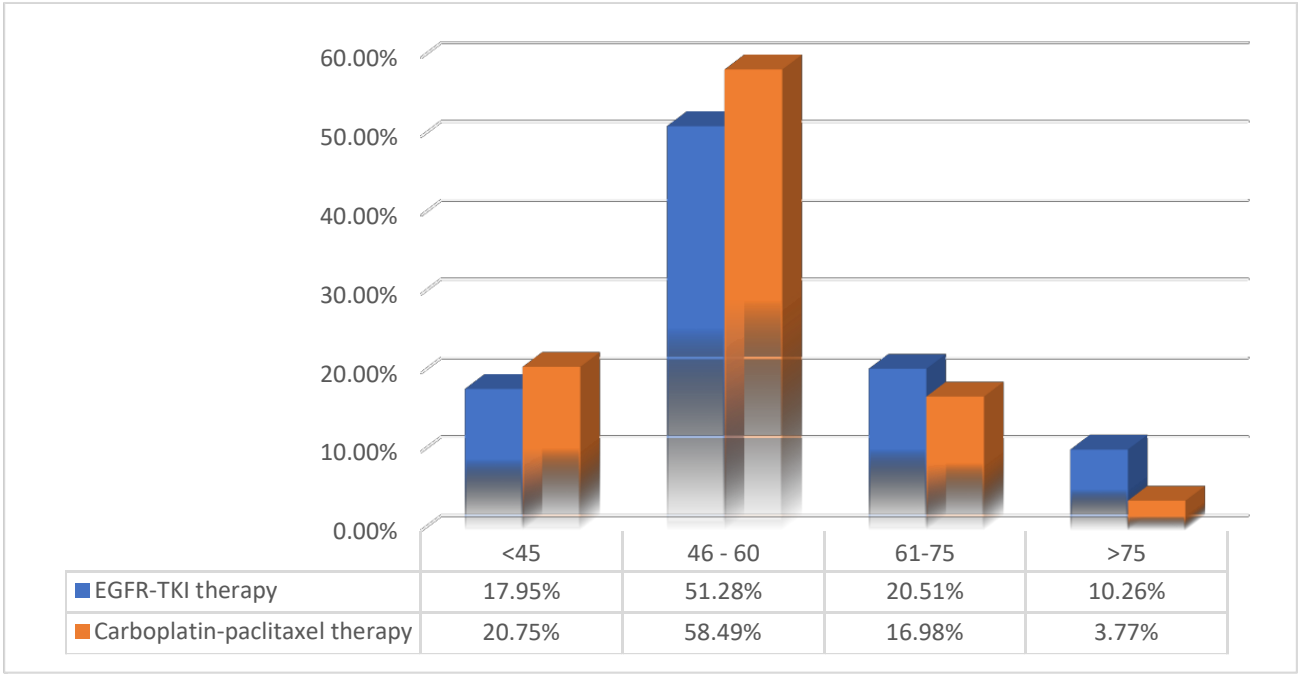

Figure 1. Description of the basic data on the characteristics of research subjects by age group

Survival Rate in The Adenocarcinoma Lung Cancer Group Receiving Systemic Therapy

In the Kaplan Meier chart in Figure 2. it is shown that 50% survival rate in the EGFR-TKI groups 7 months. Whereas in the paclitaxel carboplatin therapy group 50% survival rate was 5 months. Overall, 50% survival rate is 6 months.

The average survival rate in the EGFR-TKI group was 10.50 months with a 95% confidence interval between 7.28 and 13.72. The mean survival rate for the carboplatin-paclitaxel group was 7.81 months with a 95% confidence interval between 5.80 and 9.81. The mean survival rate for the two groups was 8.90 months with a 95% confidence interval between 7.10 and 10.66 and was not significantly different with a p-value > 0.05 (p = 0.209). Data analysis results are shown in Table 2.

Survival Rate in The Adenocarcinoma Lung Cancer Group Receiving Systemic and Influencing Factors

In the table of statistical analysis results with SPSS 25 (table 3) in the EGFR-TKI treatment group with Kaplan Meier the mean survival rate (mean) in women was 11.53 months with a 95% confidence interval between 7.29 to 15.78 (95% CI: 7.29-15.78). The mean survival rate for males was 8.13 months with a 95% confidence interval between 4.66 months and 11.60 (95% CI: 4.66-11.60). Statistically, there is no significant difference in the average survival rate with a value of p = 0.370 for men and women.

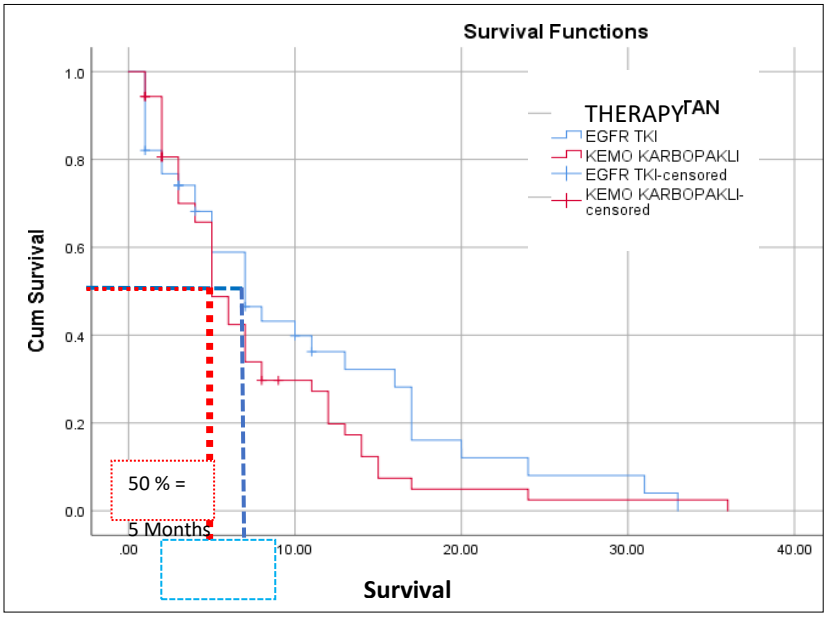

Figure 2. Kaplan Meier curve comparison survival rate EGFR-TKI Group with carboplatin-paclitaxel group of subjects with lung adenocarcinoma

Table 2. Analysis of differences in survival rates between the EGFR-TKI group and the paclitaxel-carboplatin group for subjects with lung adenocarcinoma

Therapy	Mean			Median			P-Value
	Estimate	95% CI		Estimate	95% CI		
		Lower bound	Upper bound		Lower bound	Upper bound	
EGFR-TKI	10.498	7.280	13.715	7.000	3.805	10.195	0.209
Chemotherapy	7.807	5.799	9.814	5.000	3.788	6.212	
Overall	8.875	7.094	10.656	6.000	4.836	7.164	

Table 3. The survival rate of the EGFR-TKI treatment group is based on independent variables

Variable	Catagory	Mean			Median			P-value
		Estimate	95% CI		Estimate	95% CI		
			Lower bound	Upper bound		Lower bound	Upper bound	
Age	<45	14.518	8.011	21.025	17.000	8.530	25.470	0.195
	46-60	12.049	6.215	17.883	7.000	4.389	9.611	
	61-75	6.375	2.545	10.205	7.000	2.199	11.801	
	> 75	5.750	0.000	13.715	1.000	-	-	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
Gender	Male	8.130	4.656	11.604	7.000	.386	13.614	0.370
	Female	11.533	7.285	15.782	7.000	3.532	10.468	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
Smoking status	Non smokers	12.419	7.980	16.858	7.000	3.664	10.336	0.088
	Smokers	7.000	3.764	10.236	7.000	000	14.105	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
Staging	3B	16.000	6.066	25.934	11.000	0.000	23.413	0.614
	4A	9.803	6.279	13.326	7.000	4.545	9.455	
	4B	10.000	10.000	10.000	10.000			
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	
Mutation status	No Data	9.022	5.154	12.889	7.000	4.951	9.049	0.046
	Wild Type	-	-	-	-	-	-	
	Exon 18	1.000	1.000	1.000	1.000	-	-	
	Exon 19 Del	15.194	7.938	22.450	13.000	8.221	17.779	
	Exon 21	7.133	.223	14.044	5.000	1.681	8.319	
	Overall	10.498	7.280	13.715	7.000	3.805	10.195	

The survival rate in the EGFR-TKI group based on the age group was 14.52 months at the longest in the age group <45 years with a 95% confidence interval between 8.01 and 21.03 (95% CI = 8.01-21.03). The mean longer survival rate in this therapy group was also found in the non-smoking group, the 3B stage group and the exon 19 Del mutation status group. There was a significant difference in mutation status with p = 0.046.

The results of the analysis in Table 4.3 show that the Exon 19 Del mutation status has an average survival rate of 15.20 months (95% CI 7.938 – 22.450). However, the average survival rate based on age, sex, smoking status, staging and mutation status in the EGFR-TKI treatment group was not significantly different with an average of 10.50 months with a 95% confidence interval between 7.28 and 13.72.

Survival Rate in The Adenocarcinoma Lung Cancer Group Receiving Carboplatin-Paclitaxel Therapy

In the carboplatin – paclitaxel therapy group, the results of survival rate analysis using the Kaplan Meier test mean survival rate was 11.21 months with a 95% confidence interval between 7.03 and 15.39 (95% CI 7.029 – 15.388) based on independent variable factors, age group < 45 years. There was no significant difference in the mean survival rate in this group based on age, sex, smoking status, staging or mutation status with an average of 7.84 months, with a 95% confidence interval between 5.84 and 9.84 (95% CI 5.840 – 9.836). The results of the analysis of survival rates in the carboplatin – paclitaxel group are presented in Table 4.

Table 4. Survival rate in the carboplatin-paclitaxel group based on independent variables

Variable	Catagory	Mean			Median			P-value
		Estimate	95% CI		Estimate	95% CI		
			Lower bound	Upper bound		Lower bound	Upper bound	
Age	<45	11.208	7.029	15.388	14.000	0.000	31.344	0.084
	46-60	6.661	4.722	8.599	5.000	3.270	6.730	
	61-75	9.111	2.248	15.975	5.000	4.026	5.974	
	> 75	3.500	2.520	4.480	3.000	-	-	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
Gender	Male	7.981	5.276	10.686	5.000	.3.788	6.212	0.978
	Female	7.500	4.971	10.029	7.000	3.245	10.755	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
Smoking status	Non smokers	8.000	5.375	10.625	7.000	4.273	9.727	0.738
	Smokers	7.888	5.188	10.588	5.000	3.577	6.423	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
Staging	3B	9.375	3.894	14.856	6.000	.3.228	8.772	0.245
	4A	6.818	4.147	9.490	5.000	4.136	5.864	
	4B	9.515	6.151	12.880	12.000	6.477	17.523	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	
Mutation Status	No Data	7.805	5.310	10.301	6.000	4.180	7.820	0.668
	Wild Type	7.820	4.964	10.676	5.000	2.720	7.280	
	Overall	7.838	5.840	9.836	5.000	3.786	6.214	

Discussion

Data on the characteristics of study subjects in the EGFR-TKI therapy group found that subjects with lung adenocarcinoma cancer were more common in women, and non-smokers, mean age of 58.08 ± 12.3. The age group between 45-65 years has the most lung cancer in both groups. The most common EGFR status mutations occurred in Exon 19 Del 13 (33.3%). In this study, 20 subjects received EGFR-TKI therapy but their mutation status was not recorded in the subjects' medical records. This result is different from the results of Novita's research at Adam Malik Hospital, data from 1 January 2014 - 31 December 2016 that the highestnumber of cases of EGFR mutations were exon 21.[6] The results of the same data as this study were obtained from Hendra Taufik's research on tissue biopsies and plasma ctDNA in several hospitals in Medan from April 2018 – February 2019 the highest number of Exon 19 Del mutationsfrom the two examinations.[7]

Based on gender, the smoking status of the results of this study differed from Novita's research from data on the characteristics of subjects with EGFR mutation lung adenocarcinoma at Adam Malik Hospital, males and more smokers. Based on the age group, the youngest subject was 32 years old and the oldest was 84 years old, in contrast to the results of Novita's study, there were no data obtained at ages <40 years.[6]

Lung adenocarcinoma subjects in the carboplatin – paclitaxel therapy group were mostly male and smoked according to the results of a study by MAW Wicaksono et al at Dr. Kariadi General Hospital Semarang 2014-2016.[8] The same study by Ungky AS et al at dr. Saiful Anwar Hospital Malang 2018-2019 in cases of wild-type lung adenocarcinoma were more common in men and smokers with a survival rate of 5.01 months (153 days).[9]

The mean survival rate for the EGFR-TKI treatment group for women (11.53 months) was longer than that for men (8.13 months) but was not statistically significantly different. Overall, the survival rate for men and women was 10.50 months longer than the paclitaxel carboplatin chemotherapy group, which was 7.81 months, but was not statistically significantly different. These results are different from the studies of Tomasini et al. in 2017 (8.38 months vs. 4.99 months) and Kawaguchi et al. in 2014 in Japan which stated that the survival rate (survival rate) of chemotherapy in adenocarcinoma Wild type was 10.1 months compared to 9 months in EGFR-TKI (erlotinib).[10,11]

This research was conducted during the Covid 19 pandemic where activity restrictions were imposed so that several research subjects were constrained in visiting the hospital.Comorbid factors in research subjects were not documented.

Conclusion

1. Gender, age, smoking status and staging showed no significant difference in the results of the survival rate analysis of the two groups. The status of the Exon 19 Del mutation had the longest survival rate and was statistically significantly different with p=0.046.
2. Overall, the average survival rate in the EGFR-TKI group was 10.50 months.
3. Overall, the average survival rate in the carboplatin – paclitaxel group was 7.84 months.
4. The median survival rate in the EGFR-TKI group for 7 months with a 95% confidence interval was between 3.81 and 10.20, while in the carboplatin-paclitaxel group for 5 months with a 95% confidence interval between 3.79 and 6,21. The overall median survival rate of the two groups was 6 months, with a p = 0.209 indicating that there was no significant difference between the two groups.

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Original Article

The influence of GCB and Non-GCB subtypes based on the Hans algorithm on 2 Year event-free survival in diffuse large B-cell lymphoma patients who received RCHOP therapy

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Abstract

Background: Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma. Based on the Hans algorithm, DLBCL is divided into two main subtypes, namely Germinal Center B-Cell-like (GCB) and non-GCB. GCB has a better prognosis than non-GCB subtypes.
Aim: To compare the effect of these subtypes on the 2-year event-free survival (EFS) of DLBCL patients who received RCHOP therapy.
Methods: This research is a retrospective cohort study sourced from patient medical record data from Dr. Cipto Mangunkusumo (RSCM) who was registered from January 2014-March 2021. We collected demographic data, clinical examination results, complete hematology laboratories, lactate dehydrogenase (LDH), radiological examinations and events for 2 years. Survival analysis was performed using the Kaplan-Meier curve, cox-regression test was performed to assess the hazard ratio. Nominal variables will be compared using the Chi-Square test or Fisher's Exact test, while numerical variables will be subjected to an independent T-Test or Kruskal-Walls test.
Results: Our study found 108 DLBCL patients with 33 GCB subtype patients (30.6%), median age 53 years (range 18—88 years), 60 (55.6%) were at stage I or II, and 89 (82%) patients had extranodal lesions 0-1. Event-free survival in the GCB subtype was 54.5% and in the non-GCB subtype group was 42.7%. The mean EFS for the GCB subtype was 19.6 months (95% CI, 17.38-21.82) and for the non-GCB subtype 18.6 months (95% CI, 17.21-20.01). The hazard ratio for GCB subtype was 0.749 (95% CI: 0.416-1.349, p = 0.336).
Conclusion: DLBCL patients with the GCB subtype have better 2-year EFS and a longer mean EFS time compared to non-GCB. The GCB subtype was protective against the event, although it was not statistically significant.
Keywords: *DLBCL, GCB, non-GCB, RCHOP, survival*

Abstrak

Latar Belakang:*Diffuse large B-cell lymphoma* (DLBCL) merupakan subtipe tersering dari *non-Hodgkin's lymphoma*. Berdasarkan algoritma Hans, DLBCL dibagi menjadi dua subtipe utama, yaitu *Germinal Center B-Cell-like* (GCB) dan non-GCB. Subtipe GCB memiliki prognosis yang lebih baik dibandingkan dengan subtipe non-GCB.
Tujuan: Membandingkan pengaruh kedua subtipe tersebut terhadap *event-free survival* (EFS) 2 tahun pada pasien DLBCL yang mendapatkan terapi RCHOP.
Metode: Penelitian ini merupakan studi kohort retrospektif yang bersumber dari data rekam medis pasien di RSUPN Dr. Cipto Mangunkusumo (RSCM) yang terdaftar pada periode Januari 2014 hingga Maret 2021. Data yang dikumpulkan meliputi data demografis, hasil pemeriksaan klinis, laboratorium hematologi lengkap, LDH, pemeriksaan radiologis, dan kejadian selama 2 tahun. Analisis kesintasan hidup dilakukan menggunakan kurva Kaplan-Meier, dan uji regresi Cox digunakan untuk menilai *hazard ratio*. Variabel nominal dibandingkan menggunakan uji Chi-Square atau uji Fisher's Exact, sementara variabel numerik dianalisis dengan uji T independen atau uji Kruskal-Wallis.
Hasil: Penelitian ini melibatkan 108 pasien DLBCL, dengan 33 pasien (30,6%) memiliki subtipe GCB. Median usia adalah 53 tahun (rentang 18—88 tahun), sebanyak 60 pasien (55,6%) berada pada stadium I atau II, dan 89 pasien (82%) memiliki lesi ekstranodal 0–1. *Event-free survival* 2 tahun pada subtipe GCB adalah 54,5%, sedangkan pada kelompok non-GCB adalah 42,7%. Rerata EFS pada subtipe GCB adalah 19,6 bulan (CI 95%: 17,38–21,82), sedangkan pada subtipe non-GCB adalah 18,6 bulan (CI 95%: 17,21–20,01). *Hazard ratio* untuk subtipe GCB adalah 0,749 (CI 95%: 0,416–1,349; p = 0,336).
Kesimpulan: Pasien DLBCL dengan subtipe GCB memiliki EFS 2 tahun yang lebih baik dan rerata waktu EFS yang lebih panjang dibandingkan dengan subtipe non-GCB. Subtipe GCB bersifat protektif terhadap kejadian, meskipun secara statistik tidak bermakna.

Kata kunci: *DLBCL, GCB, kesintasan hidup, non-GCB, RCHOP*

Background

Diffuse Large B-Cell Lymphoma is the most common subtype of non-Hodgkin's lymphoma (LNH) accounting for 30-40% of all LNH cases. In 2020, there were 77,240 new DLBCL cases in the United States and it is projected to increase 11% in 5 years.[1–3] DLBCL has two main subtypes, namely Germinal Center B-Cell-like (GCB) and Activated B-Cell-like (ABC), where the GCB subtype has a better prognosis than ABC (3-year survival without progression 75% vs 40-50%).[2] The division of subtypes is basically done by making gene expression profiles, but the high cost means that this method cannot carried out in daily clinical care. Classification of DLBCL subtypes in daily practice is carried out using the Hans algorithm, namely the use of immunohistochemistry, such as CD10, BCL6 and MUM1. Classification using the Hans algorithm has accuracy in terms of prognostic and therapeutic response that is equivalent to gene expression profiling methods.[4]

The main therapy for DLBCL is the RCHOP immuno-chemotherapy regiment (rituximab, cyclophospha-mide, doxorubicin, vincristine, and prednisone) with a cure rate of 60-70%. However, in 30-40% of cases DLBCL does not respond to this regimen and makes the prognosis worse.[5] In this study, we wanted to assess how the GCB and non-GCB subtypes based on the Hans algorithm influence 2-year EFS of DLBCL patients who received RCHOP therapy.

Methods

This study used a retrospective cohort design and was conducted at the Cipto Mangunkusumo National Central General Hospital (RSUPN Cipto Mangunkusumo). This study received ethical clearance from Ethical Committee FKUI-RSUPN dr. Cipto Mangunkusumo with reference number KET-133/UN2.F1/ETIK/PPM.00.02/ 2023.

Data retrieved from medical records of patients who received treatment at the RSCM Hematology Oncology Medical Policlinic from January 2014 to March 2021. Data taken includes patient identity, age, gender, DLBCL stage, extranodal involvement, tumor size (bulky or not), performance status (ECOG), complete hematology laboratory examination results, LDH, date and cycle of RCHOP chemotherapy. Event recorded inculdes disease-related death, relapse (recurrence) and refractory (progression of the disease, and failure in treatment in the form of partial response or stable disease) requiring second-line therapy is carried out when evaluating the response to treatment. Response evaluation was conducted after 3-4 R-CHOP cycle using imaging, after 6-8 times R-CHOP with or without radiotherapy using imaging, and surveillance evaluation of patients who have completed RCHOP for 2 years.

Statistical analysis was carried out using SPSS 20 software (IBM). Analysis is used to see the relationship between dependent and independent variables, and comparison of group outcomes. The level of significance used is $\alpha = 0.05$. Comparison of numerical variables that are normally distributed, hypothesis testing is carried out using the independent T test, while comparison of numerical variables that are not normally distributed, hypothesis testing is carried out using the Mann-Whitney test. Hypothesis testing of nominal variables is carried out using the Chi-Square test. Variables are said to be statistically significantly related if a p value <0.05 is found. The statistical test used to determine EFS is the Kaplan Meier Curve and Cox-regression analysis to obtain the Hazard Ratio (HR) value with a 95% confidence interval.

Result

Medical records and histopathology data from the FKUI/RSCM Anatomical Pathology Laboratory found 156 patients who met the inclusion criteria. 48 patients were excluded, with details of 7 patients having primary DLBCL of the central nervous system, 3 patients having a history of HIV, and 38 patients not having paraffin blocks. Based on Hans' algorithm, 33 research subjects (30.6%) had the GCB subtype. 56 research subjects (52%) were men with a median age of 53 years (range 18—88 years). 89 subjects (82%) of the study had 0-1 extranodal lesions and 60 (55.6%) subjects according to Ann Arbor were classified as stage I-II. 58 subjects (53.7%) experienced an event. Data regarding patient demographics, laboratory parameters, and immunohistochemical examination results are presented in table 1.

Table 1. Clinical and Molecular Characteristics of Research Subjects

Variable	GCB (n = 33)	Non-GCB (n = 75)
Hb, mean ± SD	11.19 ± 2.1	11.55 ± 2.16
Leukocyte, mean ± SD	6.5524 ± 1.25	6.854 ± 1.789
Thrombocyte, mean ± SD	386.36 ± 74.7	354.92 ± 128.71
Neutrophil, mean ± SD	65.74 ± 16.37	66.98 ± 13.187
Lymphocyte, median ± IQR	18.2 ± 12.45	17.4 ± 10.90
Monocyte, median ± IQR	10.00 ± 6.00	11.00 ± 5.00
IPI Score (n=99)		
Low IPI	21 (72.4%)	4 (77.15%)
High IPI	8 (27.6%)	16 (22.85%)
Ann Arbor Stadium		
Ann Arbor I and II	15 (54.55 %)	45 (60%)
Ann Arbor III and IV	18 (45.45%)	30 (40%)
Ekstranodal Involvement		
0-1	23 (69.67%)	56 (74.66%)
>1	10 (30.33%)	19 (25.34%)
LDH (n=99)		
LDH ≤1x Upper Normal Limit	6 (20.68%)	12 (15%)
LDH >1x Upper Normal Limit	23 (79.32%)	58 (85%)
Event		
No Event	18 (54.5%)	32 (42.7%)
Event/Mortality	15 (45.5%)	43 (57.3%)
Sex		
Man	19 (57.57%)	37 (49.33%)
Woman	14 (42.43%)	38 (50.67%)
Age		
≥ 60 Years	12 (36.36%)	28 (37.33%)
Usia <60 Years	21 (63.64%)	47 (63.67%)

In the EFS analysis, it was found that 18 subjects with GCB subtype DLBCL (54.5%) did not experience an event, while 32 subjects with non-GCB subtype DLBCL (42.7%) did not experience an event. Analysis using cox regression (table 2) found a hazard ratio of 0.749 (95% CI: 0.416-1.349, p = 0.336). In the EFS analysis using the Kaplan-Meier method (figure 1), the average EFS of subjects with the GCB subtype reached 19.6 months (95% CI, 17.38-21.82) and the non-GCB subtype 18.6 months (95% CI, 17.21-20.01).

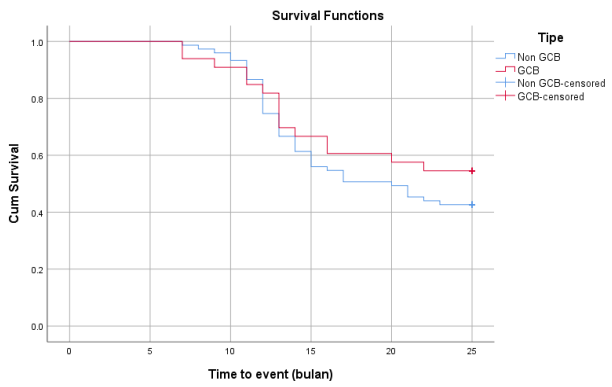

Figure 1. Kaplan-Meier EFS curve for GCB and non-GCB subtypes

Discussion

In this study, it was found that 52% of DLBCL patients were male. This is in accordance with similar studies in Indonesia and abroad which show that the majority of DLBCL patients are male.[6–8] The median age of the subjects in this study was 53 years, in line with the research of Reksodiputro et al and the observational research of Huang et al from Fujian.[8,9] However, the median age is younger than the median age of patients from Western countries and other Asian countries, such as Japan and Korea, which show a higher median age, namely 64 years.[10] This difference occurs because the incidence of Non-Hodgkin's Lymphoma is influenced by race and genetics, lifestyle, Epstein-Barr virus (EBV) infection, and occupational history.[11] Meta-analysis showed that a higher proportion of EBV-positive DLBCL was found in the East Asian and Southeast Asian populations (7.2%) compared to the world population (4%).[12] This study found that only 27% of subjects had extranodal manifestations which is in accordance with the research of Blansky et al where extranodal DLBCL was found in 22.2-28.7% of cases.[6] The majority of DLBCL cases found (55.6%) were at stages I-II. These findings are in accordance with Castillo's study where DLBCL patients of Asian descent were more commonly found in stages I and II (51%). This is not in accordance with data showing that only 30% of DLBCL cases are found at stages I and II. The high rate of finding DLBCL cases in this study can be associated with the use of positron emission tomography (PET) in DLBCL detection.[2,10]

In this study, it was found that low IPI scores were found more frequently in non-GCB types than GCB (77.15% vs 72.4%), although it was not statistically significant (p=0.617). This is different from the study conducted by Patrascu et al where IPI was found low was found to be significantly higher in the GCB group.[13] Differences in inclusion and exclusion criteria in each study can explain the differences that occurred. The non-GCB group was found to be more common during Ann-Arbor stages I and II than the GCB group, although it was not significant (60% vs 54.55%, p=0.161). This is different from the research of Istiadi et al which showed that the Ann-Arbor type I and II groups were more frequently found at the time of diagnosis of the GCB type. This difference can be explained by the difference in location, where this research was carried out at RSUPN Cipto Mangunkusumo which is the national reference for Indonesia, indicating that DLBCL patients who were referred were in an advanced stage.[14] GCB patients were diagnosed extranodally >1 in 30.33% of cases, which was higher than in the non -GCB 25.34%. These data were not statistically significant and similar results were found in previous studies where DLBCL lineages had no effect on nodal or extranodal phenotypes.[15]

During the 2-year follow-up period, 58 patients experienced events (53.7%) in the form of disease-related death, relapse (recurrence) and refractory (progression of the disease, and failure in treatment in the form of partial response or stable disease) requiring second-line therapy. These data are similar to the results of other studies which state that recurrence or treatment failure occurs in 40-50% of patients.[16,17] The event free survival rate in the GCB subtype according to the Hans algorithm is higher than in the non-GCB subtype (54.5% vs 42.7%). Other studies have shown similarly that GCB is superior in EFS, whether determined by CD10 (GCB vs Non-GCB, 51% vs 47%, p=0.89), Bcl-6 (GCB vs Non-GCB, 57% vs 35%, p=0.013), or MUM1 (GCB vs Non-GCB, 62% vs 31%, p=0.003).[18] This is also supported by the low hazard ratio (0.749, IK95% 0.416-1.349), although it is not statistically significant. The use of the Hans algorithm in determining prognosis was also found to be similar in other studies where the GCB subtype group had overall survival (54.9% vs 42.3%, p<0.001) and EFS (67.3% vs 43.3%, p<0.001) better than the non-GCB subtype group.[19] The overall EFS in this study (46.3%) was similar to the EFS studied in the systematic review, namely ranging from 38.7% - 97.3%. When compared with several other studies, this study found a lower EFS. The differences that occur between previous studies and this study can be explained by differences in the frequency of administration of immunochemotherapy regimens. The inclusion and exclusion criteria used in each study are also different, for example some studies only included patients aged 18-60 years. Other studies only examined elderly patients aged ≥65 years. Several other studies also only examined patients with tumor sizes <7.5 cm.[20]

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Conflict of Interests

No conflict of interest arises during this study conception and implementation. This research was funded privately by corresponding author (FS).

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Case Report

Recurrent buccal Kimura's disease with contralateral parotid gland, lymph nodes, and subcutaneous involvement: A rare case

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Abstract

Background: Kimura's disease (KD) is a rare chronic inflammatory condition predilected in the head-neck region as a painless lump that may mimic malignancy. No previously recurrent KD has been reported in Indonesian males, especially with contralateral involvement.
Case Illustration: We report a 30-year-old male who had a progressive buccal lump with a history of biopsy-proven KD. Neck US and MRI imaging and histopathology confirmed a recurrence of buccal KD with involvement of the contralateral right parotid gland, bilateral lymph nodes, and subcutaneous buccal region. After superficial right parotidectomy, steroid, and further chemoradiotherapy, postoperative residuals were shown in follow-up CT. Combined neck US and MRI/CT can demonstrate mass extension. Follow-up imaging is important to evaluate mass extensions and residuals.
Discussion: Kimura's disease is rare in Indonesia. Diagnosis relies on chronic disease history, imaging findings, and histopathological confirmation. Imaging features are non-specific and may mimic neoplasms, making MRI the modality of choice, though biopsy is essential to exclude malignancy. Management includes surgery and prolonged low-dose steroids, with radiotherapy considered for recurrences or steroid-resistant cases.
Conclusion: Diagnosis of recurrent Kimura's disease requires clinical evaluation supported by imaging and histopathology, with ultrasound and MRI/CT useful in assessing lesion extent and residual involvement.

***Keywords**: buccal swelling, Kimura's disease, lymphadenopathy, recurrent, parotid*

Abstrak

Latar Belakang: Penyakit Kimura (Kimura's disease/KD) merupakan kondisi inflamasi kronik yang langka, dengan predileksi di daerah kepala dan leher, ditandai oleh benjolan tidak nyeri yang dapat menyerupai keganasan. Belum pernah dilaporkan kasus KD rekuren sebelumnya pada pria Indonesia, khususnya dengan keterlibatan sisi kontralateral.
Ilustrasi Kasus: Kami melaporkan laki-laki berusia 30 tahun dengan benjolan bukal progresif dan riwayat KD yang telah dikonfirmasi melalui biopsi. Pemeriksaan ultrasonografi (US) leher, MRI, dan histopatologi mengonfirmasi rekurensi KD bukal dengan keterlibatan kelenjar parotis kanan kontralateral, kelenjar getah bening bilateral, dan jaringan subkutan bukal. Setelah menjalani parotidektomi superfisial kanan, terapi steroid, dan kemoradioterapi lanjutan, ditemukan adanya residu pascaoperasi pada CT scan tindak lanjut. Kombinasi US leher dengan pencitraan MRI/CT dapat menunjukkan perluasan massa. Pencitraan tindak lanjut penting dilakukan untuk mengevaluasi perluasan massa dan sisa lesi.
Diskusi: Penyakit Kimura jarang ditemukan di Indonesia. Diagnosis bergantung pada riwayat penyakit kronis, temuan pencitraan, dan konfirmasi histopatologi. Karakteristik pencitraan bersifat tidak spesifik dan dapat menyerupai neoplasma, sehingga MRI menjadi modalitas pilihan, meskipun biopsi tetap penting untuk menyingkirkan keganasan. Penatalaksanaan meliputi pembedahan dan pemberian steroid dosis rendah jangka panjang, dengan radioterapi sebagai pertimbangan pada kasus rekuren atau yang tidak responsif terhadap steroid.
Kesimpulan: Diagnosis penyakit Kimura rekuren memerlukan evaluasi klinis yang didukung oleh pencitraan dan histopatologi. Pemeriksaan USG dan MRI/CT bermanfaat untuk menilai luasnya lesi dan residu penyakit.

***Kata kunci**: limfadenopati, parotis, pembengkakan bukal, penyakit Kimura, rekuren*

Introduction

Kimura's disease (KD) is a chronic inflammatory granulomatous disease predilected in Asian males.[1] The typical manifestation is a progressive, painless lump in the head-neck that may resemble malignancy, potentially resulting in excessive or delayed treatment.[1–4] Only 200 cases have been histopathologically reported worldwide. There are no reported cases of recurrent KD in Indonesian males, especially in the contralateral subcutaneous tissue.[5–7]

Case Illustration

A 30-year-old Indonesian male presented with a painless lump on the right cheek for about seven years. Laboratory showed increased eosinophils and total IgE. At age fourteen, he had a biopsy-proven left-sided KD managed with parotidectomy, steroids, and radiotherapy. On physical examination, there was a skin-coloured rubbery mass with palpable neck lymph nodes. Imaging showed involvement of the right parotid gland, buccal subcutaneous tissue, and bilateral lymph nodes **[Figure 1].** Histopathology confirmed a recurrent KD. He underwent a right parotidectomy, mass excision-regional flap, steroids, and further chemoradiotherapy for postoperative residuals after a follow-up CT.

Imaging Findings

Neck ultrasonography revealed an ill-defined heterogeneous solid mass with intralesional vascularisation in the right buccal involving the right parotid gland. The right submandibular gland was enlarged with heterogeneous parenchyma. The right neck lymph nodes were also enlarged **[Figure 2]**. No abnormalities were found in the chest radiograph and abdominal ultrasonography. Neck MRI revealed a T1-T2WI iso-hyperintense lobulated solid mass, heterogeneously contrast-enhanced with diffusion restriction in the right buccal involving the parotid gland. The lesion extended to the right zygomatic-buccal-mandibular subcutaneous tissue, bordering the submandibular gland and nearby musculatures, without signs of bone infiltration. A lesion with similar characteristics and smaller size was also found in the left zygomatic-buccal subcutaneous tissue **[Figure 3]**.

Histopathology

Histopathology consistent with Kimura's disease. No malignant signs were seen **[Figure 4]**.

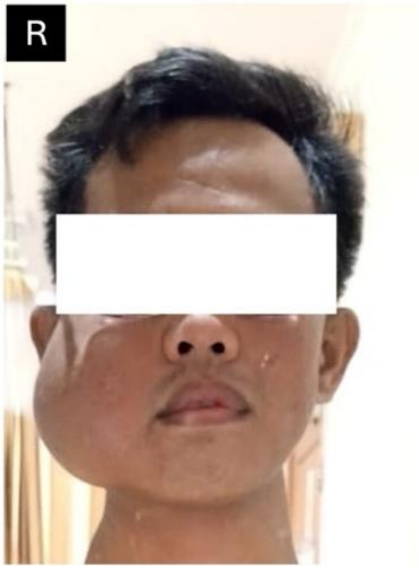

Figure 1

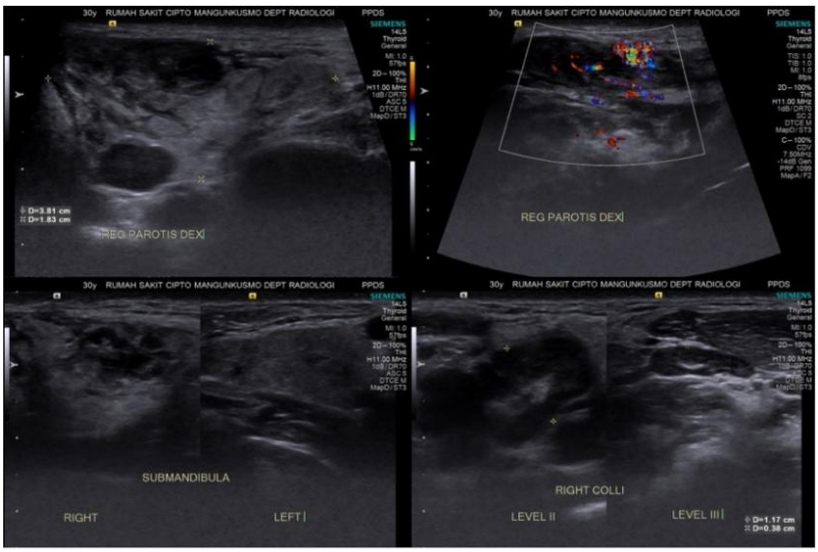

Figure 2

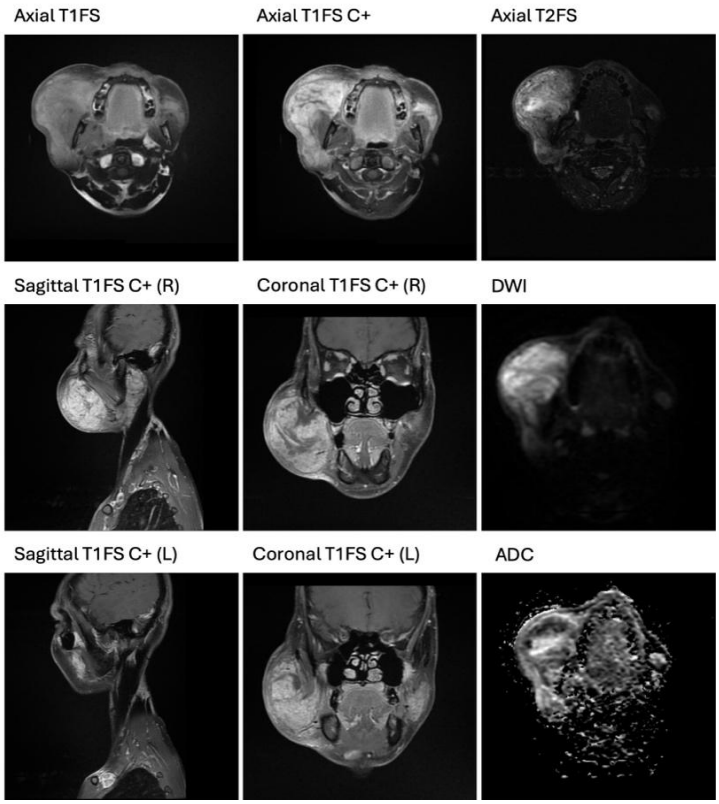

Figure 3

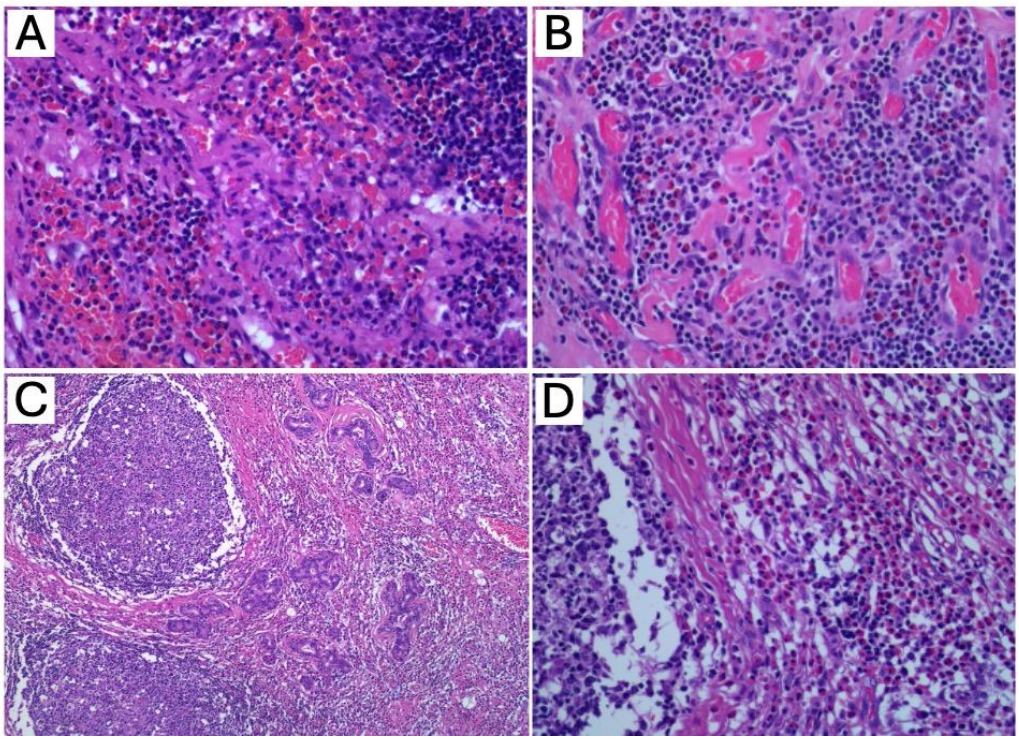

Figure 4.

Management and Follow-Up Imaging

After mass excision and tapering off methylprednisolone, our patient underwent a one-month follow-up CT. An irregular, ill-defined, non-contrast-enhanced solid lesion in the right buccal subcutis involving masticator space and parotid bed. A similar lesion in the left buccal subcutis slightly involved the left masticator space **[Figure 5, Figure 6]**. Our patient underwent further chemoradiotherapy for these postoperative residuals.

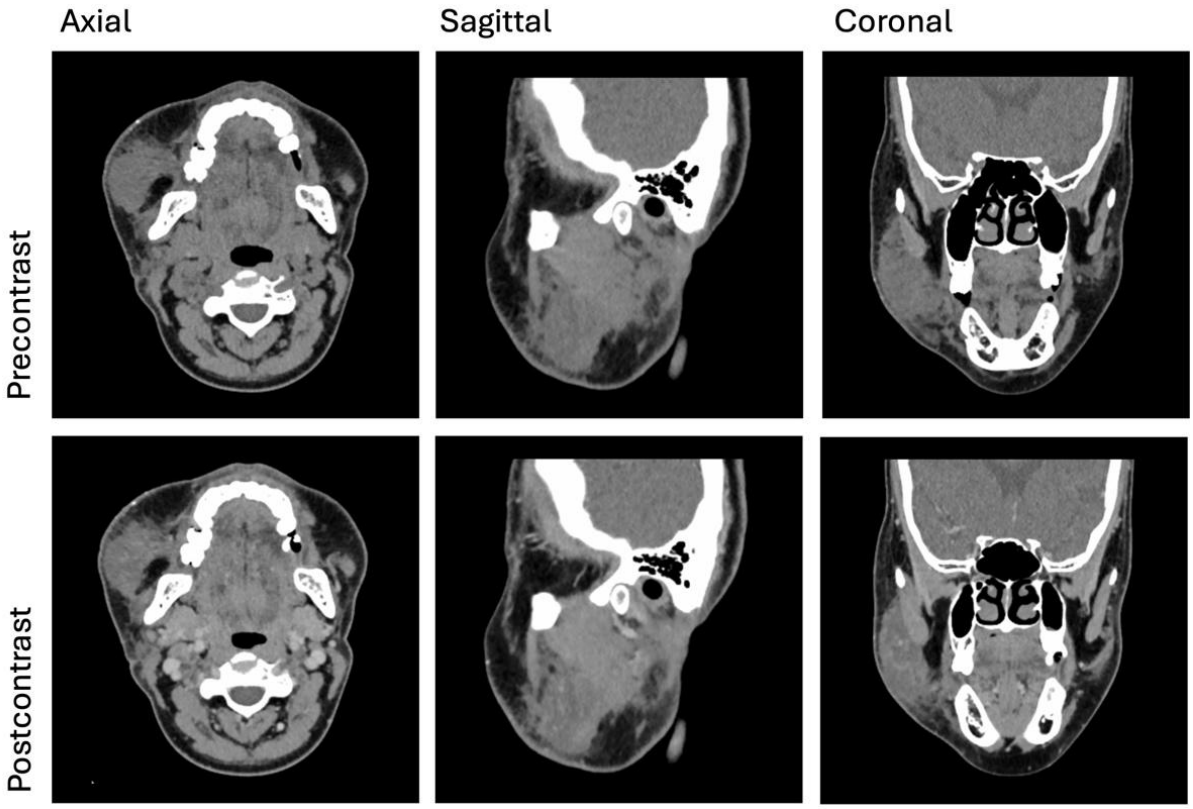

Figure 5.

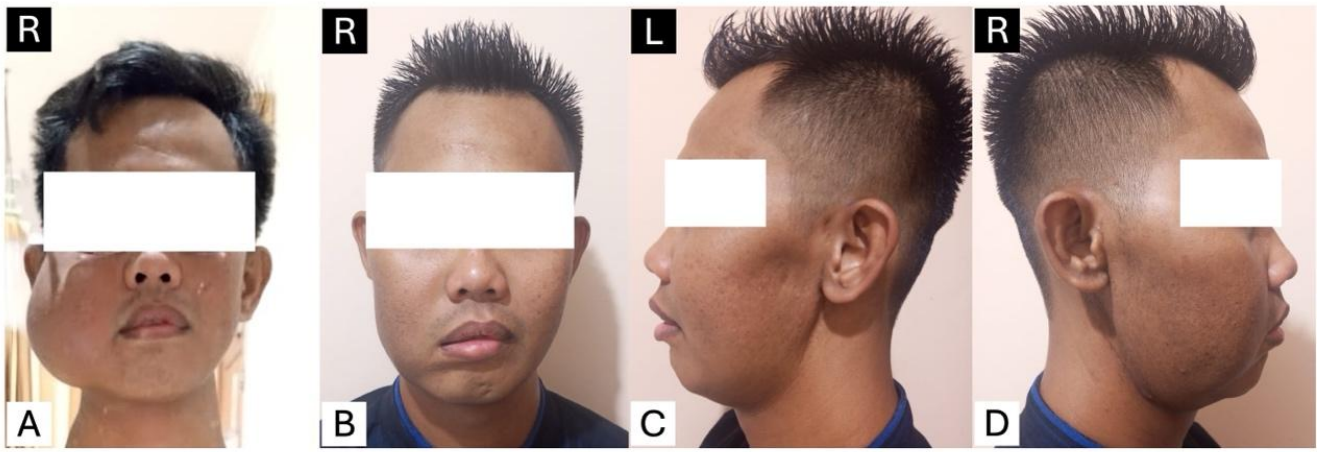

Figure 6.

Discussion

Kimura's disease in Indonesia is rare. Our patient demographics are consistent with the majority of reported cases as a progressive, painless lump in head-neck subcutaneous tissue in Asian males aged 10-40 years (peak in the third decade).[2,8] Our patient had the disease recurrent over 16 years, as some cases of recurrence have been reported over three decades.[9] This history of disease helped lead to the diagnosis.

Imaging characteristics are non-specific. In ultrasonography, salivary glands may appear enlarged and heterogeneous, resembling neoplasm, especially lymphoma. Involved lymph nodes also enlarged with hilar vascularization.[10] On CT, enlarged salivary glands appear hypodense and heterogenously contrast-enhanced. Enlarged lymph nodes show hypodense post-contrast.[11] Our patient had no involvement in other body regions. Some literature reports that KD may involve the axilla, inguinal, extremities, and abdomen.[12] MRI becomes the modality of choice. Lesions may appear well-circumscribed/infiltrative, iso-/hyperintense on T1-T2WI, and homo-/heterogeneous postcontrast. Lymph nodes show homogenous invasion without necrosis.[13,14] Despite similar characteristics, diagnosis should not be based on imaging alone. Histopathology remains necessary to exclude malignancy.[15]

The main management is surgery and conservative constant low-dose steroids to reduce the size of enlarged lymph nodes. Lesions usually re-expand after the steroid is stopped.[16] Radiotherapy is useful for lesions unresponsive to steroids or recurrences after surgery.[15]

Conclusion

Clinical examination with supporting radiology and histopathology is required for KD recurrence diagnosis. A combination of ultrasound and MRI/CT may show mass expansion in the salivary gland, lymph nodes, subcutaneous tissue, and possible residuals.

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Case Report

Multidisciplinary approach in prostate cancer management: Harmonizing the role of surgery, radiation, and systemic Therapy

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Abstract

Background: Prostate cancer management necessitates a comprehensive multidisciplinary approach, involving specialists such as medical oncologists, urologists, pathologists, radiologist, and radiation oncologists.
Case Illustration: A 68-year-old male underwent interventions for metastatic prostate cancer. Initially diagnosed with localized disease, he received a radical prostatectomy (RP) and subsequently underwent radiation therapy (RT) along with androgen deprivation therapy (ADT). His initial diagnosis categorized him as high-risk localized prostate cancer (stage cT2cN0M0), guided by screening recommendations, leading to a histopathological diagnosis of pT2N0M0. Prognostic factors like Gleason score and PSA level informed treatment decisions. Although PSA levels initially decreased post-prostatectomy, subsequent rises necessitated further intervention.
Discussion: Early postoperative radiotherapy and adjuvant ADT demonstrated efficacy in improving patient outcomes. Metastatic screening and subsequent therapy were guided by evidence-based protocols. Despite the patient's response to treatment, bone metastasis occurred, prompting palliative external radiation and zoledronic acid therapy. After RP, RT, ADT, palliative external RT, and bisphosphonate therapy, imaging revealed no residual lesions or signs of metastasis, with a significantly decreased PSA level.
Conclusion: This case serves as a compelling example of a multidisciplinary team's involvement in maximizing patient care and treatment effectiveness for metastatic prostate cancer.

Keywords: *multidisciplinary approach, prostate cancer, radiotherapy, surgery, systemic therapy*

Abstrak

Latar belakang:
Latar Belakang: Penatalaksanaan kanker prostat memerlukan pendekatan multidisipliner yang komprehensif, melibatkan berbagai spesialis seperti onkologi medik, urologi, patologi, radiologi, dan onkologi radiasi.
Ilustrasi Kasus: Seorang laki-laki berusia 68 tahun menjalani berbagai intervensi untuk kanker prostat metastatik. Awalnya didiagnosis dengan kanker prostat lokalisata, dan pasien menjalani prostatektomi radikal (RP), kemudian dilanjutkan dengan terapi radiasi (RT) dan terapi deprivasi androgen (ADT). Diagnosis awal menunjukkan kanker prostat lokal risiko tinggi (stadium cT2cN0M0), dan berdasarkan rekomendasi skrining, terkonfirmasi secara histopatologi sebagai pT2N0M0. Faktor prognostik seperti skor Gleason dan kadar PSA menjadi dasar pengambilan keputusan terapi. Meskipun kadar PSA awalnya menurun setelah prostatektomi, namun bila terjadi peningkatan maka memerlukan intervensi tambahan.
Diskusi: Radioterapi pascaoperasi dini dan ADT adjuvan menunjukkan efikasi dalam meningkatkan keberhasilan tata laksana pasien. Skrining metastasis dan terapi selanjutnya dilakukan berdasarkan protokol berbasis bukti. Meskipun pasien menunjukkan respons terhadap terapi, akan tetapi terjadi metastasis tulang, sehingga diberikan radioterapi eksternal paliatif dan terapi asam zoledronat. Setelah diberikan RP, RT, ADT, radioterapi eksternal paliatif, dan terapi bifosfonat, tidak tampak adanya lesi residu atau tanda metastasis pada pencitraan, dengan kadar PSA yang menurun signifikan.
Kesimpulan: Kasus ini merupakan contoh nyata peran tim multidisiplin dalam mengoptimalkan tata laksana dan efektivitas terapi pada kanker prostat metastasis.

Kata kunci: *kanker prostat, pembedahan, pendekatan multidisipliner, radioterapi, terapi sistemik*

Background

Prostate cancer is a leading malignancy among men worldwide, holding the position as the second most common cancer globally and consistently ranking in the top five in many areas such as Indonesia.[1-3] The disease progresses from prostatic intraepithelial neoplasia (PIN) to invasive adenocarcinoma, influenced by proto-oncogene activation and tumor suppressor gene inhibition.[4] Common symptoms include lower urinary tract issues, erectile dysfunction, and hematuria, though some cases are identified through PSA screening, which can yield both false positives and negatives.[5]

Digital rectal examination (DRE) aids in distinguishing benign from malignant conditions[6], while histopathological testing and imaging are essential for accurate diagnosis and staging.[7] Management approaches range from active surveillance in low-risk disease[8] to aggressive treatments for advanced-stage treatments.[9,10] Bone metastasis remains a significant challenge, affecting prognosis and quality of life.[11] Multimodal treatments, combining surgery, radiation, and systemic therapies, have shown promise in controlling disease progression and improving outcomes.[12] However, identifying predictive factors and tailoring treatments to individual patients remain critical research areas.[13]

A multidisciplinary approach is crucial for the successful management of prostate cancer, encompassing every stage from detection to treatment. This collaborative strategy involves specialists from various fields, including medical oncology, urology, pathology, radiology, and radiation oncology, working together to provide comprehensive care.[14] Early detection and accurate staging are vital, requiring coordinated imaging and biopsy interpretation efforts. Risk stratification and evaluation are enhanced by the diverse expertise within the team, ensuring personalized treatment plans.

This report details a case of advanced metastatic prostate cancer treated with a multidisciplinary approach that included various intervention modalities, demonstrating the complexity and collaborative efforts required for effective management.

Case Illustration

A 68-year-old male visited the hospital for a follow-up appointment regarding his prostate cancer therapy. Thirteen years before admission, he sought help for urinary difficulty, leading to benign prostate hyperplasia (BPH) diagnosis with elevated prostate-specific antigen (PSA) levels, remaining below 10 ng/ml. Despite regular follow-ups, his symptoms worsened over eight years, prompting a prostate biopsy confirming cancer. He experienced radical prostatectomy and pelvic lymph node dissection, resulting in a decrease in PSA levels from 37.2 to 0.54 ng/mL. However, his PSA levels gradually rose again by 2020, necessitating radiation therapy (SIB IMRT) for 25 sessions, Goserelin injections every three months, and Bicalutamide, which lowered PSA levels below the detection threshold.

He is a controlled diabetic with no smoking history. His family has no cancer history, except for his sibling's breast cancer. His Eastern Cooperative Oncology Group (ECOG) performance status is 0, with a Karnofsky performance status of 100, and a body mass index (BMI) of 22.5 kg/m². The digital rectal examination reveals a palpable, mobile tumor confined within the prostate gland, involving both lobes. No tenderness or induration is appreciated in the surrounding tissue. No palpable masses or nodules elsewhere, as well as lymphadenopathies.

The histological analysis of the prostate biopsy initially revealed adenocarcinoma on both sides with a Gleason score of 4+3 (7). Pathology, imaging, and biochemical studies established the diagnosis of pT2N0M0, PSA >20 ng/mL, grade group 3 (stage IIIA) prostate cancer. After radical prostatectomy, there was a notable decrease in the PSA level, which fell significantly to 0.54 ng/mL. One year later, the PSA level gradually increased to 1.51 ng/mL until radiotherapy. A post-treatment MRI of the prostate, after RP+SIB-IMRT+ADT, showed no pathological masses or enhancements within the prostate, with no evidence of lymphadeno-pathy. PSA post-radiotherapy decreased to 1.07 ng/mL.

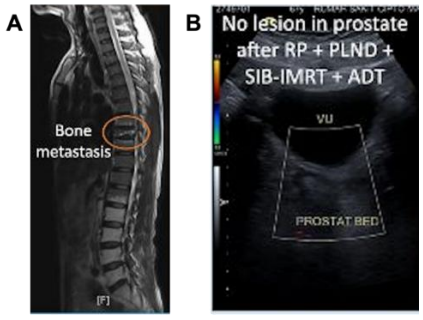

Figure 1. Imaging evaluation. Metastasis in the T9 vertebral body is shown in a contrast-enhanced MRI (A). Abdominal ultrasound examinations conducted after radical prostatectomy (RP), pelvic lymph node dissection (PLND), simultaneous-integrated boost intensity-modulated radiation therapy (SIB-IMRT), and androgen deprivation therapy (ADT) showed no focal pathological lesions in the prostate bed.

Following the patient's complaint of bone pain two months later, an anomaly was observed in a bone scan, suggesting pathological activity on the T9 vertebra's right aspect. Additionally, a thoracolumbar X-ray displayed deterioration of the T9 vertebral body on the right side, encompassing the right pedicle. A contrast-enhanced MRI confirmed metastasis in the T9 vertebral body (Figure 1A). Patient received palliative external radiation and bisphosphonate therapy while continuing ADT.

Abdominal ultrasound examinations conducted post-treatment and six months later showed no focal pathological lesions in the prostate bed or evidence of metastasis in the intra-abdominal organs (Figure 1B). Furthermore, a CT scan conducted four years after radical prostatectomy and three years into hormonal therapy and radiotherapy showed no residual lesions in the prostatic bed or signs of metastasis in the intrathoracic and intra-abdominal organs, nor any lymphadenopathy. Finally, a bone scan performed after palliative external radiotherapy, continuous monthly bisphosphonate treatment, and intermittent ADT showed no active pathological processes in the T9 vertebra, coupled with a significantly decreased PSA level of <0.008 ng/mL. PSA response to interventions is shown in Figure 2.

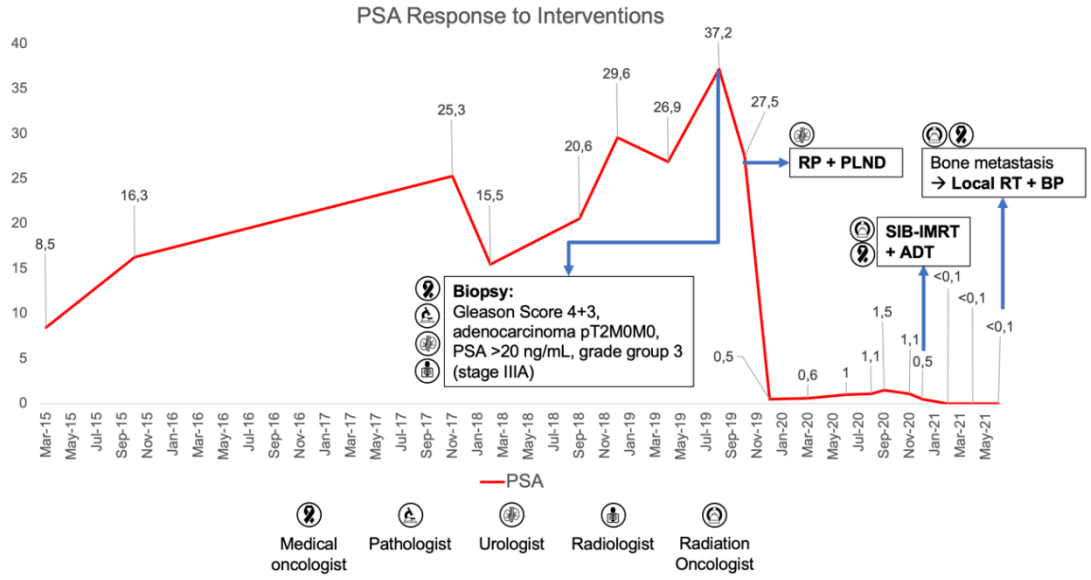

Figure 2. PSA response to interventions, highlighting the multidisciplinary approach of prostate cancer treatment. RP, radical prostatectomy; PLND, pelvic lymph node dissection; RT, radiotherapy; BP, bisphosphonate therapy; SIB-IMRT, simultaneous-integrated boost intensity-modulated radiation therapy; ADT, androgen deprivation therapy

Discussion

Prostate cancer ranks second among male cancers globally and is among the top five cancers affecting males in Indonesia.[2,3] Its sporadic occurrence accounts for about 85%, while familial cases make up 10 to 15%, and hereditary cases constitute 3-5%.[15] A family history of breast cancer is evident, which, coupled with age and a history of malignancies, poses significant risks for this patient. Prostate cancer typically manifests between the ages of 65 to 68 years.[16] The chances surge as age progresses, with a lifetime likelihood of 12.5%, escalating to 9.0% in males aged 70 years and beyond. Autopsy findings indicate that 40% of men over 60 who have not undergone screening are found to have prostate cancer, surging to 60% in those over 80.[2] Additionally, individuals with familial breast cancer exhibit a 21% elevated risk of prostate cancer and a 34% elevated chance of developing a lethal disease.[17]

During diagnosis, the patient's PSA level stood at 27.54 ng/mL, and a physical examination revealed a tumor confined within the prostate without evidence of lymphadenopathy or metastasis (stage cT2cN0M0)[18], thereby categorizing it as high-risk localized prostate cancer.[19]

The 2024 EAU Guidelines for Prostate Cancer strongly advocate for metastatic screening via PSMA-PET/CT and cross-sectional abdominopelvic imaging,

along with a bone scan, in cases of high-risk localized disease.[20] The patient underwent metastatic screening with CT abdominopelvic scan, which showed no abnormalities in the seminal vesicles, perirectal fat, or intraabdominal and pelvic organs. A bone scan was not performed due to facility limitations. Combined with histopathological studies, the initial pathological diagnosis of the patient is pT2N0M0.

Prognostic factors for this patient include Gleason score, age >60 years, tumor stage, and PSA level. A Gleason score of 4+3 is linked with a heightened risk of mortality in overall survival and cancer-specific survival when compared to a score of 3+4.[21] Using the life expectancy estimation tool recommended by the NCCN guidelines, this patient has a 77% chance of survival in 10 years and a 57% chance in 15 years if untreated.[22]

Radical prostatectomy (RP) with pelvic lymph node dissection (PLND) was selected given the patient's symptomatic presentation and favorable life expectancy.[10,23] According to the NCCN guidelines, radical prostatectomy is advised for localized disease in individuals with a projected lifespan of at least 10 years, provided that their tumor can be fully removed surgically and they do not have significant comorbidities that would make surgery inappropriate.[10] The limited PLND involved dissection of the obturator lymph nodes (left and right) and the external iliac (right) nodes. Limited PLND is preferred over extended PLND because, despite the higher detection rate of positive lymph nodes with extended PLND, it does not enhance the rate of biochemical recurrence-free survival and is linked to a greater likelihood of complications, notably lymphocele.[24,25]

The patient's likelihood of progression-free status following radical prostatectomy stands at 18% over 5 years and 10% over 10 years. The probability of remaining recurrence-free after surgery is 74% in 2 years, 52% in 5 years, 43% in 7 years, and 35% in 10 years. The 15-year prostate cancer-specific survival is 92%.[26]

Although RP+PLND reduced PSA levels from 37.2 to 0.54 ng/mL, PSA remained detectable and gradually rose again months later, which is considered a post-RP adverse feature. In principle, radical prostatectomy should result in a PSA level that cannot be detected within 21-30 days after surgery, given the 3.15-day half-life of PSA.[27] If PSA levels fail to drop to undetectable levels after RP, it's termed PSA persistence, which significantly raises the risks of cancer-related death, biochemical recurrence, and disease recurrence.[28] Given the patient's short PSA doubling time of 5.7 months and extended life expectancy, adjuvant therapy was initiated, comprising EBRT + intermittent ADT. Intermittent ADT was preferred over continuous ADT due to its potential for comparable survival outcomes with superior quality-of-life benefits.[29-31] The patient concurrently received Goserelin (a luteinizing hormone-releasing hormone [LHRH] agonist) injections every three months for one year and Bicalutamide (a first-generation antiandrogen), alongside SIB-IMRT for 25 sessions.

Adjuvant radiation therapy following RP extends the duration of biochemical progression-free survival, metastasis-free survival, and overall survival compared to simply observing the patient's condition, as demonstrated in several key randomized clinical trials (RCTs).[32] However, early postoperative radiotherapy is preferred over ART post-RP to reduce overtreatment and risk of toxicity, as there was no notable disparity in results between the two approaches in a meta-analysis.[33] In this patient, early postoperative radiotherapy was chosen over ART, with radiotherapy initiated only after one year of observation confirming a continuous increase in PSA following RP, rather than administering radiotherapy immediately after RP as in ART.

Adding ADT to radiotherapy after radical prostatectomy significantly improves patient outcomes. Two RCTs demonstrated that adding 4-6 months of ADT, either comprising LHRH agonist alone or combined with an antiandrogen, to radiotherapy after radical prostatectomy significantly improves 5-year biochemical or clinical progression rates and freedom from progression.[34,35] Comparison between RP alone versus RP combined with adjuvant ADT reveals a statistically significant improvement in 10-year cancer-specific survival (CSS) rates in the RP + ADT group (94% vs 87%), highlighting the potential benefits of adjuvant hormonal therapy in enhancing long-term outcomes.[36] Additionally, ADT and radiation therapy (RT) combination demonstrates superior metastases-free survival compared to ADT monotherapy.[37] Notably, the integration of RP, RT, and ADT yields favorable outcomes across multiple prognostic indicators observed within the initial five years post-treatment, including biochemical relapse-free survival (90.5%), metastases-free survival (95.5%), disease-specific survival (100%), and overall survival (90.6%) rates.[38]

After radiation therapy, four rounds of goserelin injections, and bicalutamide treatment, the patient's PSA level dropped below the detection threshold (<0.008 ng/mL). A decrease in PSA levels following ADT indicates a response to endocrine therapy and suggests continued sensitivity to androgens. However, two months later, the patient reported experiencing mild pain in the lower right back region. Subsequent imaging studies, including a bone scan, thoracolumbar X-ray, and contrast-enhanced MRI, confirmed the presence of metastasis in the T9 vertebral body. Approximately 85% of prostate cancer cases are initially localized, yet nearly 40% advance to metastatic disease, with over 90% of advanced cases involving bone metastases.[39]

Therapy for M1 prostate cancer is divided into treatment for M1 castration-sensitive and castration-resistant prostate cancer.[10] Following ADT, the patient's testosterone level was assessed, revealing a measurement of 16.1 nmol/L, indicating the recovery of testicular function. Combined with the patient's PSA response to previous ADT treatment, this categorizes prostate cancer as castration-sensitive (CSPC). The next step involves determining whether the cancer is of high or low volume. According to CHAARTED criteria, this patient has low-volume disease. Standard treatment for low-volume metachronous metastases typically involves ADT combined with one of the preferred regimens: Abiraterone, apalutamide, or enzalutamide.[10] However, these three medications were not listed in the national health insurance formulary at treatment time.[40] Additionally, the patient underwent EBRT, which has demonstrated efficacy in increasing overall survival, especially in patients with a low metastasis burden.[41] EBRT may be applied to bone metastases, particularly in weight-bearing bones or when a patient exhibits symptoms, both of which apply to this patient's case. If EBRT is administered with ADT, one option for ADT includes LHRH agonist either alone or given concurrently with abiraterone or docetaxel.[10] The patient received intermittent ADT (goserelin), with reintroduction of ADT if PSA levels rose above 20 ng/mL or exceeded 10 ng/mL with accompanying symptoms.[42] Bicalutamide was administered concurrently with goserelin to prevent initial testosterone flare in weight-bearing bone metastases.[43] Adding bicalutamide to LHRH agonist therapy also leads to a 22% decrease in the risk of death (P=0.0498), significantly improves overall survival rates (75.3% vs 63.4%), and markedly increases the proportion of patients accomplishing PSA nadir concentrations ≤1 ng/mL (81.4% vs 33.7%; P<0.001), while also prolonging PSA progression-free survival compared to LHRH agonist monotherapy.[44,45] Docetaxel was not prescribed due to insufficient evidence supporting its efficacy in patients with metachronous, low-volume disease.[46]

ADT poses a risk of bone loss[47,48], particularly concerning in bone metastatic prostate cancer due to elevated fracture risk. While bone antiresorptive therapy isn't indicated for reducing symptomatic skeletal-related events (SREs) and does not signifycantly increase survival in CSPC[49,50], it's recommended for managing heightened fracture risk.[10] According to the Fracture Risk Assessment Tool (FRAX; https://www.fraxplus.org/calculation-tool/), this patient has a 3.0% probability of experiencing major osteoporotic events and a 1.5% probability of hip fracture over the next ten years. Considering the fracture risk alongside the patient's bone metastasis, continuous monthly zoledronic acid was administered. In castration-resistant prostate cancer (CRPC), denosumab demonstrates superior efficacy in halting SREs compared to zoledronic acid. However, it is associated with a higher incidence of hypocalcemia and osteonecrosis of the jaw.[51] There are no direct comparative studies of bone antiresorptive drugs in metastatic castration-sensitive prostate cancer (CSPC).

Zoledronic acid is associated with hypocalcemia[52] and may worsen kidney function in patients with mild to moderate kidney disease (defined as baseline CrCl 30-60 mL/min).[53] Calcium ion and blood as well as kidney function were checked before each zoledronic acid administration for dose adjustment. The patient underwent follow-up every 1-2 months, including PSA and testosterone level checks, assessment of ADT side effects, and laboratory tests including complete peripheral blood count, serum urea and creatinine, lipid profile, blood glucose, and calcium levels. Thrombosis risk assessment was also conducted. Routine thromboprophylaxis for outpatients receiving systemic therapy for cancer is not recommended.[54]

Conclusion

This case exemplifies the efficacy of a multidisciplinary team approach in managing metastatic prostate cancer, highlighting the critical roles of urologists, pathologists, radiologists, radiation oncologists, and medical oncologists from diagnosis through ongoing treatment. The collaborative efforts of these specialists were pivotal to the successful management and

improved outcomes of the patient. Additionally, this case underscores the significance of timely identification of prostate cancer, particularly during the follow-up of BPH, to enhance early intervention and treatment effectiveness.

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None.

Conflict of Interests

The authors declare no conflicts of interest.

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Review Article

Microbial allies and enemies: How the skin microbiome influences skin cancer

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Abstract

The microbiota is a population of bacteria that inhabit the human body, whereas the microbiome is the set of genes encoded by these microorganisms. While the microbiota refers to the organisms living in various parts of the human body, microbiome is regarded as their genetic information. The microbiota can affect skin cancer risk and treatment response through influencing immune processes, production of certain metabolites and toxins, and their interactions. Cancer is defined as uncontrolled or abnormal cell proliferation. The pathogenesis of skin cancer is multifactorial which includes disruption of the skin barrier, the immune system, metabolites and toxins from microbes, and ultraviolet radiation. The microbiome is an important component of the tumor microenvironments, both in the skin and gut. Microbial dysbiosis is associated with chronic inflammation which may further mediate carcinogenesis. The polymorphic microbiome is consider one of the enabling characteristics of the hallmarks of cancer. Abnormal skin microbiota will produce cytokines and chemokines that contribute to tumor growth. Various microbiota has tumorigenesis effects such as *Staphylococcus aureus*, beta-HPV, *Corynebacterium*, and *Fusobacterium*, but there are also protective microbiota namely *Cutibacterium, Malassezia,* and *Staphylococcus epidermidis*. Studies showed that the presence of microbiome polymorphic variability between individuals has a profound impact on cancer phenotypes.

Keywords: *carcinogenesis, dysbiosis, microbiome, skin cancer*

Abstrak

Mikrobiota adalah populasi bakteri yang menghuni tubuh manusia, sedangkan mikrobiom ialah kumpulan gen yang dikodekan oleh mikroorganisme tersebut. Mikrobiota mengacu pada organisme-organisme yang hidup di berbagai bagian tubuh manusia, sedangkan mikrobiom adalah informasi genetik yang dibawa mereka. Mikrobiota dapat mempengaruhi risiko kanker kulit dan respon pengobatan dengan memengaruhi proses imun yang terjadi, produksi dari metabolit dan toksin tertentu, serta interaksi antar mereka. Kanker didefinisikan sebagai proliferasi sel yang tidak terkendali atau abnormal. Patogenesis kanker kulit bersifat multifaktorial yang meliputi gangguan pada *barrier* kulit, sistem imun, metabolit dan racun dari mikroba, serta radiasi ultraviolet. Mikrobiom adalah komponen penting dari *tumor microenvironments*, baik pada kulit maupun usus. Disbiosis mikroba berhubungan dengan peradangan kronis yang selanjutnya dapat memediasi karsinogenesis. Mikrobiom polimorfik dianggap sebagai salah satu karakteristik *the hallmarks of cancer*. Mikrobiota kulit yang abnormal akan menghasilkan sitokin dan kemokin yang berkontribusi terhadap pertumbuhan tumor. Berbagai mikrobiota memiliki efek tumorigenesis seperti *Staphylococcus aureus, beta-HPV*, *Corynebacterium, dan Fusobacterium*, namun ada juga mikrobiota yang bersifat protektif yaitu *Cutibacterium, Malassezia,* dan *Staphylococcus epidermidis.* Studi menunjukkan bahwa adanya variabilitas polimorfik mikrobiom antar individu memiliki dampak besar pada fenotipe kanker.

Kata kunci: *disbiosis, kanker kulit, karsinogenesis, mikrobiom*

Background

The human body's largest organ is the skin, which functions as a physical barrier against invading microorganisms. Millions of bacteria, fungi, and viruses, both pathogenic and commensal microbiota, inhabit the skin. When the barrier is damaged, or the equilibrium between pathogenic and commensal microbiota is altered, skin disease or systemic disease may develop.[1] Microbial dysbiosis is associated with the ability of eluding immune responses, carcinogenesis processes stimulated by inflammation, and chronic inflammation, where chronic inflammation is attributed to cancer progression.[2]

Cancer is an uncontrollable or abnormal proliferation of cells caused by genetic abnormalities or environmental factors.[2] Incidence rates of skin cancer have increased worldwide during the past decade. In the United States, skin cancer affects around 3,3 million people. Among the various types of skin cancer, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), collectively known as non-melanoma skin cancer, and malignant melanoma (MM) are the most prevalent. For instance, in 2017, the National Central General Hospital Dr. Cipto Mangunkusumo (RSCM) recorded 263 cases of skin cancer, with BCC accounting for 66.9%, followed by SCC at 27.4%, and MM at 5.7%.[3]

The pathogenesis of skin cancer is complex, with ultraviolet light, chemicals, bacteria, fungi, and viruses playing crucial roles in cancer formation.[4] The microbiota is a population of bacteria that inhabit the human body, whereas the microbiome is the set of genes they encode.[5] While the microbiota refers to the organisms living in various parts of the human body, microbiome is regarded as their genetic information. The microbiota can affect skin cancer risk and treatment response. Skin microbiota, together with damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and microbial toxins can prompt chronic inflammation and cellular damage to the skin.[2] Chronic inflammation and microbial dysbiosis are interrelated, which may mediate the carcinogenic process.[2] The microbiota, DAMPs, PAMPs, toxins, immune cells, cytokines, and chemokines contribute in immunosuppression, cellular proliferation, and inflammation, thus modifying the tumor microenvironment and promoting skin cancer.[2] Research indicates that the microbiome could be used to treat various diseases, including cancer.[4] This leads to microbiome studies to determine the development of cancer.[2]

The characteristics and role of normal microbiomes on the skin

The human body contains various types of commensal and pathogenic bacteria. Distinct organisms, including bacteria, fungi, and viruses, have different distributions on the skin. Compared to the digestive system, the weight of skin microbes is relatively low, but the amount of bacterial diversity in the skin is comparable to that of the large intestine. Intrinsic (age, nutrition, sex, immunological status, and genetic susceptibility) and extrinsic (environment and behavior) factors determine microbial diversity.[6]

Microbiota distribution depends on local skin's physiological characteristics, such as moist, dry, and sebaceous (oily) areas. The sebaceous area is dominated by lipophilic *Propionibacterium* species, whereas *Staphylococcus* and *Corynebacterium* are prevalent in moist areas such as skin folds.[1] Commensal *Streptococcus* regulates skin inflammation by producing lipoteichoic acid, which activates the skin's innate immune response. *Staphylococcus* species have been identified in different skin diseases, such as atopic dermatitis, with abundant *Staphylococcus aureus* (*S. aureus)* colonization in lesional and non-lesional skin in adults.[7]

A study found that Proteobacteria are the most prevalent bacteria in all skin swabs, scrapings, and biopsies samples.[8] Bacteria were discovered not only on the skin surface but also in previously considered sterile layers such as the dermis and adipose tissue.[9] This colonization is influenced by the varying oxygen levels between the skin surface and deeper layers. Proteobacterial interaction with dendritic cells can induce the production of IL-1, IL-17, and IFN-γ by T cells migrating to the epidermis, activate natural killer cells, and stimulate keratinocytes to secrete antimicrobial peptides (AMP). Furthermore, microbiota colonization is also affected by the difference in oxygen pressure between the skin surface and the deeper layers.[8,9]

While bacteria are the most prevalent species in the skin microbiome, fungi are also observed. On healthy skin, the fungal microbiota, also known as mycobiota comprises *Malassezia* species primarily, along with *Candida, Aspergillus, Cryptococcus, Rhodotorula,* and *Epicoccum* species. The fungal distribution throughout the body is determined by the characteristics of the microbe, the area of the body affected, age, and gender.[7] The trunk and arms are dominated by fungi of the genus *Malassezia*, while the feet are colonized

by *Malassezia spp., Aspergillus spp., Cryptococcus spp., Rhodotorula spp.,* and *Epicoccum spp*.[10] Due to the absence of fatty acid synthesis genes in the genus *Malassezia*, which mainly requires human long-chain fatty acids for growth, this species is found in areas of oily skin. *Malassezia globosa's* protease 1 can hydrolyze protein A from *S. aureus*, allowing it to prevent bacterial biofilm formation, and immune evasion strategies, and maintain healthy skin.[11]

Candida albicans is also a component of the skin's mycobiota; the skin's pH affects its growth. An increase in pH, which is common in moist environments, promotes overgrowth. *C. albicans* and *S. aureus* overgrowth play a crucial role in the etiology and pathogenesis of skin cancer.[11]

In contrast to bacteria and fungi, the anatomical location of the body does not affect the colonization of eukaryotic DNA viruses. There are no unique gene markers for distinguishing viruses; nonetheless, viral diversity can be observed by sequencing viral-like particles or through shotgun metagenomics. Eukaryotic viruses play a role in skin diseases, including oncoviruses that cause Merkel cell polyomavirus, which is a rare but aggressive skin cancer.[11]

Metagenomic studies on 103 healthy individuals revealed a significant prevalence of human papillomavirus (HPV) in the skin (61.3%), followed by other ecosystems such as the vagina, mouth, and intestines. This virus is known to cause multiple forms of tumors in humans. It is found to increase the risk of SCC of the skin. Shotgun sequencing analysis demonstrated that the HPV population of healthy skin is more complicated. In addition, it is crucial to understand the genotypes of non-oncogenic viruses, as these genotypes can either drive or inhibit HPV infection.[12]

Invasion of pathogens including HPV on the skin will trigger the main components of innate immunity such as keratinocytes to increase AMP production. AMPs such as cathelicidin LL-37 and human β-defensins (i.e., hBD-1, 2, 3, and the antimicrobial protein RNase 7) induce innate and adaptive immunity mediators to prevent pathogenic skin invasion. Therefore, the regulation of the interaction between keratinocytes, immune cells, and microbes by AMP, cytokines, and chemokines is essential for skin integrity.[7,13]

Survival of the skin microbiota is regulated by the desquamation of the stratum corneum epithelium and the skin's pH, inhibiting the growth of pathogens that compete for nutrition. Other variables, such as the use of skin care products or smoking, can further influence the variety of microbiota.

The relationship between skin microbiomes and gut microbiomes

Human commensal microbiota resides primarily in the intestine, although there is an interaction between the skin and gut microbiota.[2] The microbiome is symbiotically associated with the barrier tissue of the body that is exposed to the external environment, primarily the skin and the internal environment, particularly the gut mucosa. There is growing evidence that microbiome variation between individuals within a population can significantly affect cancer phenotype.[14] The skin microbiota is dominated by *Actinobacteria*, whereas the gut microbiota primarily consists of *Firmicute*s and *Bacteroidetes*. Both possess substantial intra-individual variation. The relationship between skin and gut microbiomes is a complex and dynamic interplay that extends beyond their local environments. This relationship, often referred to as the gut-skin axis, involves bidirectional communication between these two microbiomes and the immune system. Understanding how changes in one microbiome impact the other can provide valuable insights into maintaining skin and gut health.[7]

The modulating effect of the gut microbiome

The modulating effect of the gut microbiome on immune function plays a crucial role in maintaining overall health. For instance, certain gut bacteria can influence the development and function of immune cells, impacting the body's ability to respond to infections and regulate inflammation. The ability of the gut microbiota to express chemokines and immunomodulatory cytokines which ultimately enter the systemic circulation provides evidence of the association between colon cancer and melanoma. This can affect the development and therapeutic response of cancer in other organs.[14] For example, patients with melanoma who responded to anti-programmed cell death (PD) 1 treatment had more "good bacteria" in their intestines than those who did not respond. These data imply that the gut microbiome is essential for skin cancer immunity regulation.[2]

The mechanism by which the microbiome modulates this immune response remains unknown. However, the tumor-inducing microbiome has two known impacts. The first effect is colonic epithelial mutagenesis, caused by the production of bacterial toxins and other substances that directly damage DNA, affecting

systems that preserve genome integrity or indirectly inhibit DNA replication and repair. The second mechanism is the presence of particular bacterial species that stimulate carcinogenesis, specifically butyrate-producing bacteria, whose populations are increased in colorectal cancer patients. The complex physiological consequences of butyrate metabolite products include the production of senescent epithelial cells and fibroblasts.[14]

The role of skin microbiome in the development and progression of skin cancer

The interaction between a compromised skin barrier, ultraviolet (UV) exposure, and commensal bacteria on the skin can impact the composition of the skin microbiome. A combination of altered skin microbiota, DAMPs, PAMPs, and microbial toxins can induce persistent inflammation and cellular damage, which can result in the beginning and progression of skin cancer. Microbiota, DAMPs, PAMPs, microbial toxins, CD8+ T cells, regulatory T cells, tumor macrophages, cytokines, and chemokines are the most influential variables in the tumor microenvironment (TME) in skin cancer. By inducing immunosuppression, cell proliferation, and inflammation, it contributes to the development of skin cancer (Figure 1,2). In addition, gut microbial metabolites, cytokines, and chemokines may indirectly affect cutaneous TME via systemic circulation.[2]

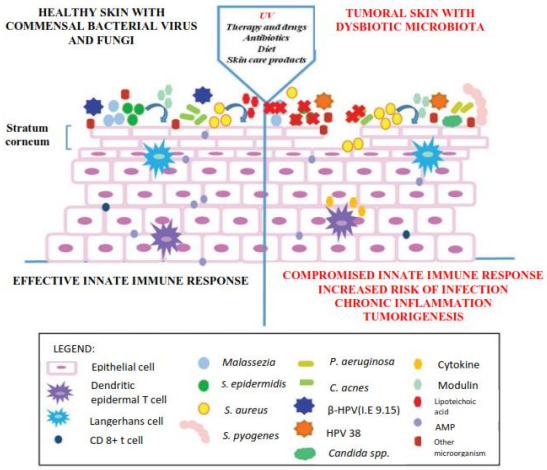

Figure 1. Changes in the microbiome in the pathogenesis of skin cancer.[7]

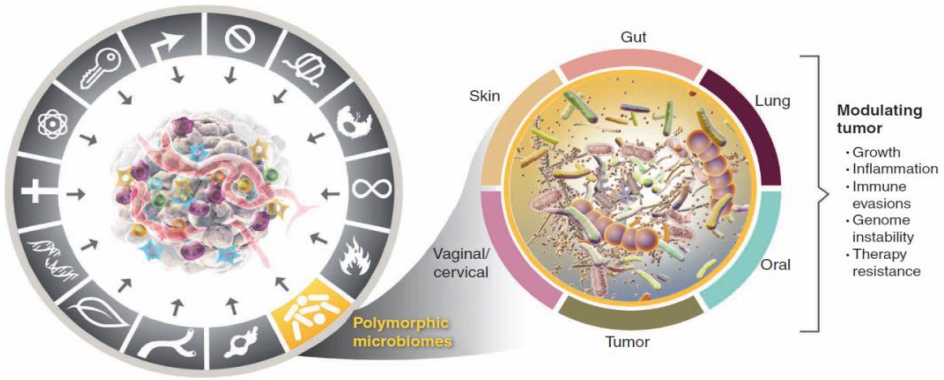

Figure 2. Polymorphic microbiomes. Left, polymorphic microbiomes in one individual can diversely influenced by either inducing or inhibiting many of the hallmark capabilities. Right, multiple tissue microbiomes are implicated in modulating tumor phenotypes and modulating the acquisition both positively and negatively of the hallmark capabilities in certain tumor types.[14]

Skin barrier disruption on skin cancer

A damaged skin barrier may result in microbial dysbiosis. Multiple studies have demonstrated that disruption of the skin barrier can lead to microbial dysbiosis, altering the skin's homeostasis and commensal microbiome.[15] This dysbiosis can be exacerbated by proteases produced by the skin microbiota, which can damage the epidermal barrier. In a mouse model of non-melanoma skin cancer, studies have shown that excessive colonization of S. aureus can promote the expression of human defensins and tumor cell proliferation.[16] Additionally, chronic inflammation of damaged or chronically diseased skin is known to potentially contribute to the development of SCC. However, further research is needed to understand the specific microbiota associated with barrier alteration in skin cancer.[17]

Skin immune system and skin cancer

The interaction between the immune system and microbiota has a role in the development of tumors. The microbiome can stimulate cancer by causing chronic inflammation, disrupting the balance between cell growth and death, and stimulating the immune system. The immune system of the skin is comprised of both the innate and adaptive immune systems. The dysbiosis of this antibacterial defense system allows the movement of cellular and microbial components across the barrier, resulting in an inflammatory innate immune response.[5] Keratinocytes, endothelial cells, fibroblasts, neutrophils, macrophages, dendritic cells, and mast cells are the primary components of innate immunity, while T and B cells are categorized as adaptive immune cells.

Keratinocytes produce various cytokines, chemokines, antimicrobial lipids, and AMP. Under the stimulation of microbial PAMPs or DAMPs, AMPs, specifically cathelicidin LL-37 and human β-defensin, are continually generated and regulated.[18] Macrophages are also significantly involved in the development of melanoma. M1 macrophages target the tumors to induce phagocytosis and immune responses aimed at inhibiting advancement and metastasis of cancer. However, cancer cells express CD47 to evade macrophages. Hydrolysate 3-(trihydroxygermyl) propanoic acid (THGP) displays the ability to enhance antitumor immunity by stimulating polarization of M1 macrophages and decrease presentation of signal-regulatory protein alpha (SIRP-α) in macrophages as well as CD47 in cancer cells.[19]

Pattern recognition receptors (PRR) produced from macrophages, dendritic cells, and epithelial cells also play an important role. PRR can distinguish the distinct molecular properties of PAMPs and DAMPs and elicit an appropriate immune response. Various PRR types correlate to the pathogen's distinctive pattern, intracellular location, expression, and signaling pathway. The majority are classified into cytoplasmic receptors and toll-like receptors (TLRs). Approximately ten TLRs have been found in humans.[18]

Toll-like receptors (TLRs) play a crucial role in the skin's immune response. They can be expressed by various cell types in the skin, including keratinocytes, melanocytes, and antigen-presenting cells. Activation of TLRs initiates the innate immune response by recognizing PAMPs or DAMPs. However, chronic TLR activation can lead to chronic inflammation, which is implicated in various skin disorders and diseases, including skin cancer. Understanding the specific TLRs involved in skin inflammation and their role in disease development is an active area of research. TLR 4 is the only type of TLR recognized to significantly impact skin inflammation and malignancy. Activation of TLR 4 and subsequent internal signaling pathways might result in the activation of transcription factors such as NFκ-B, interferon regulatory factors 3 (IRF-3), and activator proftein-1 (AP-1), which regulate the expression of genes involved in inflammation, cellular apoptosis, survival, and differentiation.[2] Increased TLR expression has been found in skin cancer. Compared to the control, the expression of TLR 4 was higher in SCC. In UV-induced animal models, topical administration of the TLR 4 inhibitor resatorvid has diminished tumor size and number. This suggests that TLR suppression is beneficial for UV-induced non-melanoma skin cancer. Overexpression of TLR 4 in both radial and vertical melanoma growth phases was related to recurrence in malignant melanoma (MM). Imiquimod, a TLR 7 agonist, is an effective treatment for various skin malignancies, including SSC, BCC, CTCL, and lentigo maligna melanoma.[2]

Adaptive immunity, especially elevated T-cell infiltration, has displayed an enhanced overall survival in patients with advanced melanoma.[20] Researchers have performed various trials to induce T-cell inflamed tumors from its condition of T-cell deficit.[20] An oncolytic virus with simultaneous expression of granulocytes-macrophage colony-stimulating factor (GM-CSF) and programmed death ligand (PDL-1) stimulates T-cell infiltration into TME.[20] In comparison to various cancers, melanoma and non-melanoma skin cancers

respond better to immunotherapy.[19] Imiquimod, an immune-modulating agent, can fight against primary and metastatic skin cancer.[19] Immune checkpoint inhibitor (ICI) therapies, including PDL-1 and cytotoxic T-lymphocyte-associated protein (CTLA-4), have also been developed and proved to be an effective on immunotherapy for both types of skin cancers.[19] These ICIs activate exhausted CD8+ T lymphocytes found in tumors.[20] Stromal cells found in TME, such as the tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs), may function as targets for some immunotherapies.[19] Regardless on how immunotherapy has displayed remarkable effectivity towards skin cancer, it may not be well responded by every case, highlighting the need for further research.[19]

During immunosuppressed states, for instance, post receiving organ transplant individuals and patients suffering rheumatic diseases, the risk of skin infections by opportunistic fungus and yeast overgrowth increases.[7] Radiotherapy and chemotherapy can cause epithelium damage through the disturbance of epithelial cells regeneration, thus enabling the penetration of fungi and yeasts due to the impaired barriers.[7] Opportunistic infections should not be underestimated as they contribute to increased morbidity and mortality, diminished quality of life, and impose patients with significant healthcare costs. It is of the best interest to identify, prevent, and treat infections accordingly, especially for immunosuppressed patients, as they are at higher risks and may suffer adverse consequences. Hence, understanding how chemotherapy and radiotherapy recipients are more prone to infections can aid in improving skin cancer treatment strategies.

Microbial metabolites and toxins in skin cancer

TME in skin cancer consists of various cell types, including immunocytes, fibroblasts, vascular and lymphatic endothelial cells, pericytes, adipocytes, and numerous chemicals, released by tumor and non-tumor cells. The microbiome, including its metabolites, is an integral part of TME.[5] Metabolites produced by microorganisms can interact directly with cancer cells or promote carcinogenesis through modulating TME components, such as immune cells and stromal cells. Immune cells like the TLRs and NOD-like receptors (NLRs) are classified as PRRs to identify microbial components. For example, certain microbial metabolites that are found in different cell organelles have been shown to promote inflammation or alter the local immune environment, contributing to tumor growth and progression. By regulating the availability of metabolites, initiating DNA damage, and regulating the system, the mechanism of action of microbial metabolites might influence the development of cancer.[18] Microbial metabolites produced toxins that change DNA and cause oncogenic mutations. Several studies have associated exotoxins from *S. argenteus* and *Staphylococcus enterotoxin A* with CTCL. Currently, most research indicates that microbial metabolites and toxins are expressed by the gut microbiome; however, it is believed that the skin microbiome can also produce them.[18]

Ultraviolet radiation and the skin microbiome in skin cancer

UV rradiation is a significant carcinogen in skin cancer development. UV light promotes DNA damage and mutations, leading to the clonal proliferation of cancer cells. Additionally, UV exposure induces the production of reactive oxygen species (ROS) and inhibits the immune system, contributing to photocarcinogenesis.[21] Recent research has also highlighted the role of the skin microbiome in UV-induced skin damage. The microbiome's composition and function can be altered by UV exposure, influencing the skin's response to UV radiation and potentially affecting the development of skin cancer. The altered skin microbiome may generate changes in gene expressions that associate with immune processes. A study discovered that exposure to UVB can alter the skin and gut microbiome.[22] In the presence of a microbiome, UV exposure reduces systemic immunosuppression, according to the findings of other researchers. In addition, the degree of epidermal hyperplasia and neutrophil infiltration increased in the presence of the microbiome, whereas the infiltration of mast cells, monocytes, and macrophages increased regardless of the microbiome. There are also significant changes in genomic expression based on the skin microbiome's existence. Based on these data, it is possible to conclude that the skin microbiome can reduce UV-induced immunosuppression via modifying cytokine expression genes and skin cellular infiltration.[21] Further studies are needed to elucidate the complex interplay between UV radiation, the skin microbiome, and skin cancer.

Intratumoral microbiota and skin cancer

Intratumoral microbiota found in TME is found to be capable of entering tumor cells. Some of its peptides can be expressed by antigen-presenting cells (APCs) of the immune system and may trigger immune responses from the host. In certain malignancies, regulatory T cells are known to inhibit anti-tumor

immune responses and create immunosuppressive TME. Regulatory T cell infiltration is frequently detected in SSC, BCC, and MM skin samples, decreasing T cell activity and establishing an immunosuppressive TME for skin cancer.[2]

Depending on the species, intratumoral bacteria have positive and negative correlations with tumor growth. *Lachnoclostridium* bacteria demonstrated the strongest positive correlation with CD8+ T cell infiltration, followed by *Gelidibacter, Flammeovirga*, and *Acinetobacter*, whereas *Algibacter* and *Epilithnimonas* demonstrated a negative correlation. A positive correlation exists because these bacteria enhance the infiltration of CD8+ T lymphocytes, which increases the expression of the chemokines CXCL9, CXCL10, and CCL5. *Lachnoclostridium* was significantly related to a reduced risk of mortality, suggesting that enhanced infiltration of CD8+ T cells and an increased number of *Lachnoclostridium* may provide a favorable prognosis in melanoma patients.[20]

Mechanism of the relationship between skin microbiomes and skin cancer

Non-melanoma skin cancer

The relationship between the skin microbiome and non-melanoma skin cancer, particularly squamous cell carcinoma (SCC), involves several key mechanisms. The skin microbiome can influence the development of SCC through its effects on the immune system, the production of metabolites, and the modulation of inflammatory pathways. For example, certain bacteria in the skin microbiome can produce metabolites that promote inflammation and cell proliferation, contributing to the development of SCC. Additionally, the skin microbiome can interact with immune cells in the skin, leading to an imbalance in the immune response that favors tumor growth. Understanding these mechanisms is crucial in developing targeted therapies that can modulate the skin microbiome for SCC prevention and treatment.

Non-melanoma skin cancer is the most prevalent skin cancer worldwide, and its frequency is increasing. Non-melanoma skin cancer, including SCC and BCC, is a malignant skin tumor not associated with melanocytes.[2] BCC metastasizes less frequently than SCC but has a significant morbidity rate. Actinic keratosis is a non-melanoma skin cancer that frequently affects white individuals with extensive sun exposure.[7] Due to a lack of references, this literature review focuses solely on the microbiome of SCC.

In one study, biopsies and swabs of tumors revealed an association between *S. aureus* and SCC. *S. aureus* is found to be significantly increased in the skin microbiome of patients suffering from skin diseases. Colonization with *S. aureus* was higher in SCC biopsies (29.3%) than in healthy skin biopsies (5.7%), and the prevalence of *S. aureus* in SCC swab samples (31.7%) was higher than in healthy skin swab samples (15,0%). As actinic keratosis are precancerous lesion of SCC, an increase in *S. aureus* colonization is related to the progression of actinic keratosis to SCC.[16] A recent study on the 16S ribosomal RNA sequencing gene in skin biopsies revealed that *S. aureus* levels were high in actinic keratosis and SCC.[17] Increased *S. aureus* numbers were also associated with elevated hBD-2 expression in SCC. The SCC cells with hBD-2 directly accelerated tumor cell proliferation. A study revealed that a high number of *S. aureus* could affect the expression of hBD-2, which can promote the proliferation of SCC.[16,17]

S. aureus stimulates the secretion of IL-1a and IL-36a by keratinocytes via the peptide modulin. This cytokine-mediated signaling pathway is required for T cell IL-17 secretion. Along with IL-22 and tumor necrosis factor-alpha (TNF-α), these pro-inflammatory cytokines regulate *S. aureus* colonization of the skin by activating inflammatory pathways. All these substances significantly initiate tumor growth by promoting the proliferation and migration of skin cancer cells with metastatic disease.[7]

Microbial profiling analysis revealed that S. *aureus* was more prevalent in SCC and actinic keratosis samples than in BCC. When the skin barrier is intact, *S.aureus* can not infect immunocompromised individuals; nevertheless, some circumstances, such as burns or atopic dermatitis, might lead to *S. aureus* infection.[2]

Due to chronic inflammation, *S. aureus* strains contribute to skin carcinogenesis and function as risk markers for developing SCC. Consequently, lesions with a persistent infection should be monitored and treated. As the reason for SCC development, the existence of bacteria such as *S. aureus, S. pyogenes*, and *P. aeruginosa*, which are responsible for chronic and suppurative inflammation, is still debatable.[7]

Cutibacterium and Malassezia play significant roles in inflammation that promotes tumorigenesis. They are, respectively, the most abundant bacterium and yeast that thrive in healthy, sebaceous skin. Their dysbiosis in the skin microbiome can be a biomarker for certain

diseases. The number of *Cutibacterium* and *Malassezia* in the skin of patients with actinic keratosis and SCC was lower than that of healthy, non-lesional skin, based on an Australian cohort study. The decreased number of *Malassezia* in SCC increases the likelihood of the yeast's protective feature.[7,23,24]

Cutibacterium is a genus of skin bacteria predominantly found in lipophilic regions, specifically the sebaceous area. The decrease in the number of *Cutibacterium* in actinic keratosis and SCC can be attributed to a dry and scaly surface of actinic keratosis accompanied by a decrease in sebum, which represents a decrease in skin hydration and an increase in skin pH. In addition, since *Cutibacterium acnes* (C. acnes) can create AMP, reducing the number of *Cutibacterium* can also promote the growth of *S. aureus*.[2]

Staphylococcus epidermidis (*S. epidermidis*) can inhibit the growth of skin cancers. Commonly present on healthy human skin, *S. epidermidis* is a coagulase-negative bacteria whose presence inhibits the growth of *S. aureus*.[22] *S. epidermidis*'s secretome can inhibit skin inflammation by activating regulatory T cells. Recent research indicates that the 6-N-hydroxy-aminopurine (6-HAP) generated by *S. epidermidis* can inhibit DNA synthesis and the proliferation of tumor cells. Colonization of a 6-HAP-releasing *S. epidermidis* strain reduced UV-induced tumor growth in a mouse model compared to the colonization of a 6-HAP-free control strain.[2]

The current study indicates a relationship between SCC and HPV. Compared to healthy individuals, patients with non-melanoma skin cancer had a higher likelihood of HPV infection.[25] In addition, a meta-analysis revealed an elevated risk of HPV infection in SCC compared to normal skin. In addition, immuno-compromised patients were shown to have a higher HPV prevalence than immunocompetent patients.[26] Approximately 50 beta HPV varieties associated with SCC have been identified to date. The synergistic effect between beta strains of cutaneous HPV and UV radiation is crucial to developing SCC. Beta HPVs, including HPV 5 and HPV 8, have been isolated from the skin of patients with epidermodysplasia verruciformis, which typically progresses to SCC. Several investigations have demonstrated that beta-cutaneous HPVs function as a carcinogen to initiate cell damage in response to UV exposure but are not required to preserve SCC as HPV is not transcribed in SCC's maintenance phase.[25] The mechanism of beta HPV in skin carcinogenesis is known as the hit-and-run mechanism. However, this is still debatable and warrants additional study.[27]

Candida is the most prevalent fungal pathogen. According to a nationwide population-based epidemiological study, *Candida* infection is related to an elevated risk of numerous malignancies, including hematological, head and neck, pancreatic, skin, and thyroid. The role of yeast in cancer development is via pro-inflammatory mechanisms in the TME. However, experimental studies directly identifying the association between the fungal microbiome and skin cancer are scarce.[2] In patients with non-melanoma skin cancer, another study on the response of *Malassezia* to photodynamic therapy (PDT) revealed that PDT decreases *Malassezia* in the peritumoral skin (Figure 3).[7]

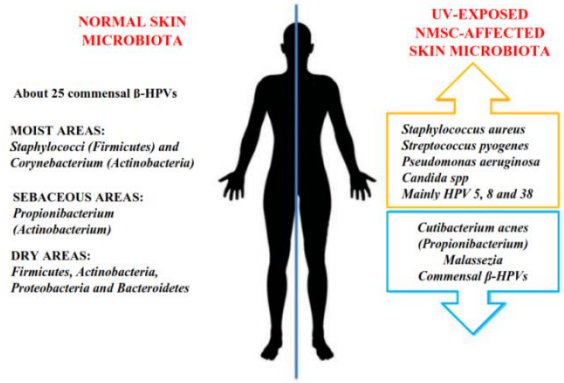

Figure 3. Non-pathogenic microbiota and their changes in normal skin and non-melanoma skin cancer due to UV exposure.[7]

Malignant Melanoma

Seventy-five percent of all skin cancer-related deaths are caused by MM, making it the most devastating type of skin cancer. It is not easily susceptible to treatment and can lead to fatal outcomes. Incidence and mortality of MM have increased substantially during the past four decades in western regions, rising to 10-50 new cases for every 100 000 people in a year (approximately 3-8% increase). Malignant melanoma is a heterogeneous illness with distinct subtypes based on anatomical distribution, somatic mutation patterns, and histological characteristics.[28] Microbiota such as bacteria and viruses can generate various immune pathways that lead to beneficial or detrimental effects on MM. Culture-based microbial study on 27 acral melanoma patients revealed that the genus *Corynebacterium* was more closely related to stage III/IV MM patients than stage I/II MM patients. Interleukin (IL)-17 levels were higher in patients with positive *Corynebacterium* than in those with negative

Corynebacterium.[29] By upregulating IL-6, signal transducers, and activating transcription 3, IL-17 can promote melanoma growth. As established in mouse model research, *Corynebacterium* species can affect the development of MM via an IL-17-dependent pathway. In another study using a mouse model, intratumor injection of *C. acnes* significantly reduced tumor size. Melanoma cell growth was suppressed by the production of Th1 cytokines, including IL-12, TNF-α, and interferon-gamma (IFN-γ), following intratumor injection of *C. acnes*.[30] It was also reported that *C. acnes* can suppress the survival of UVB-irradiated melanocytes by increasing apoptosis, coproporphyrin secretion, and TNF-α regulation.[31]

Studies have shown that bacteria residing on the skin vary between healthy individuals and cancer patients. The multifaceted impact of certain microbiota and metabolites of the skin microbiome on MM, combined with specific interactions and environmental influence, can lead to proliferation or inhibition of the tumor. A study found that intravenous injection of 6-HAP produced from *S. epidermidis* could decrease the proliferation of melanoma cells and strengthen *S. epidermidis*' protective effect against MM.[32] In contrast, some researchers reported that *S. epidermidis* and lipoteichoic acid from *S. epidermidis* could improve melanocyte survival by upregulating TRAF1, CASP14, CASP5, and TP73 in response to UVB irradiation. The skin microbiota plays a role in melanocytic illnesses such as melanoma and melanocytic nevi. Control samples were obtained from the same patients' normal skin on the contralateral side.[33] After getting the skin swabbed, the samples obtained were analysed through partial sequencing of the 16S ribosomal RNA gene using the 454 GS-FLX Titanium platform, followed by bioinformatic and statistical processes. 16S ribosomal RNA sequencing demonstrated a modest decrease in microbial diversity between melanoma and melanocytic nevi skin samples. A study of the skin microbiome on pig models with melanoma revealed significant differences between cancer and normal skin samples in the variety of bacterial and microbial compositions.[32] Numbers of *Fusobacterium* and *Trueperella* were higher in melanoma skin samples than in control samples.[34] Previous studies have indicated a correlation between elevated *Fusobacterium* levels and several types of cancer, including pancreatic, colorectal, and oral malignancies.[35] *Fusobacterium nucleatum* can enhance tumor proliferation by suppressing natural killer cell cytotoxic via the interaction of its Fap2 protein with T cells.[2]

Besides bacteria, viruses are also components of the microbiota implicated in the progression of MM. However, the function of viruses in cutaneous melanoma is somewhat ambiguous. Multiple epidemiological studies have demonstrated an association between HPV and melanoma. A population-based cohort analysis revealed an association between HPV infection and an elevated risk of melanoma.[25] High-risk mucosal HPV viruses were detected in 27% of MM samples from skin biopsies using PCR-ELISA. HPV 16 and HPV 33 were the most frequently detected viruses.[36] A study on ocular melanoma indicated that down-regulation of HPV 18 E6/E7 could decrease tumor growth and cell cycle progression by activating the p53 and Rb pathways. HPV 22 was discovered more frequently in melanoma than in the normal skin of the same individual as a control. However, neither MM's clinical nor histological features were related to HPV prevalence. Further research is required to identify whether cutaneous HPV is a cofactor in the development of MM.[37]

Human endogenous retroviruses (HERVs) can serve as cellular reservoirs for retroviral genes with pathogenic characteristics. ERV sequence activation is related to melanocyte transformation and melanoma cells' ability to avoid immune surveillance. UVB-induced melanoma cells exhibited increased expression of retroviral envelope protein and activation of the retroviral pol gene, suggesting that UV radiation is involved in the pathogenesis of melanoma..[38]

Conclusions

Particular bacterial species can directly stimulate the hallmark of proliferative signaling and modulate growth suppression; whereas direct effects on other hallmarks capabilities, such as avoiding cell death; inducing angiogenesis; and stimulating invasion and metastasis; remain obscure. Polymorphic variation in microbiomes constitutes a distinctive enabling characteristic for the acquisition of hallmark capabilities, albeit intersecting with and complementing those of genome instability and mutation, and tumor-promoting inflammation via immunomodulation, toxin production, as well as cell disruption.[14]

Various skin microbiomes related to skin cancer and their corresponding mechanisms could be either preventive or carcinogenic (table 1). The interaction between a damaged skin barrier, UV exposure, and skin commensal bacteria affects the composition of the skin microbiome.[2] Abnormal skin microbiota, accompanied by microbial metabolites and toxins,

can generate persistent skin inflammation and cellular damage, resulting in skin cancer development. Numerous cytokines and chemokines are the most influential factors in the TME of skin cancers.[18] Cytokines and chemokines contribute to tumor growth by promoting inflammation, immunosuppression, and cell proliferation. In addition, it is known that microbial metabolites, cytokines, and chemokines from the gut can enter the systemic circulation and indirectly influence the malignant microenvironment of the skin. Additional study is required to establish the varied roles of the microbiome in skin cancer in terms of carcinogenesis and protective effects against cancer development that may be beneficial to the prevention and treatment of skin cancer.[18]

Table 1. Various skin microbiomes associated with skin cancer and their mechanisms.

Skin microbiome	Data collection	Mechanism
Non-melanoma skin cancer[5]		
An increased number of or associated with a tumor-forming action		
Staphylococcus aureus	Humans, skin biopsies, and swabs	Causes chronic inflammation Associated with increased hBD-2 expression causing tumor cell proliferation Produced by disruption of the skin barrier
Beta type HPV	Mouse model, skin biopsy Human, skin biopsy	Acts as co-carcinogenesis, causing cellular damage under UV radiation but was not required for SCC maintenance
Reduced number or associated with antitumor activity		
Cutibacterium spp.	Human, skin swab	Metabolic changes in SCC can inhibit the growth of *Cutibacterium* and induce the growth of *Staphylococcus aureus*
Malassezia spp.	Human, skin swab	Resulting from disruption of the skin barrier and decreased sebum availability in SCC Inhibits the growth of *S. aureus* 6-HAP biofilm formation
Staphylococcus epidermidis		*S. epidermidis* derived 6 HAP suppresses DNA synthesis and provides an antiproliferative effect on tumor cells
Melanoma maligna[5]		
An increased number of or associated with a tumor-forming action		
Corynebacterium spp.	Human, skin swab	Increases dependent-IL-17
Staphylococcus epidermidis *Fusobacterium nucleatum*	Pig, skin scraping Human, skin biopsy	Increases melanocyte survival through upregulation of TRAF1, CASP14, CASP5, and TP73 during UVB radiation Inhibits NK cell cytotoxicity through interaction with Fap2
High-risk mucosal HPVs		May serve as a cofactor in MM development
Reduced number or associated with antitumor activity		
Cutibacterium acnes		Induces Th1 cytokines such as IL-12, TNF-α, and IFN-γ Promote apoptosis, increase secretion of coproporphyrins, and upregulate TNF-α
Staphylococcus epidermidis		*S. epidermidis*-derived 6-HAP inhibits melanoma cell growth

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Conflict of Interests

The authors have no financial conflicts of interest.

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The comprehensive cancer management as an effort to improve the quality of cancer care in Indonesia towards a Golden Indonesia 2045

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Abstract

Cancer remains a major public health challenge in Indonesia, with increasing incidence and mortality rates. GLOBOCAN 2020 data highlights a growing cancer burden, particularly in developing countries, where late-stage diagnoses and treatment delays contribute to poor outcomes. Breast cancer is the most prevalent cancer in Indonesia, followed by cervical cancer, leukemia, and colorectal cancer. Despite national efforts, a high proportion of patients present at advanced stages, leading to decreased survival rates and increased healthcare costs. This study examines the factors influencing cancer diagnosis and treatment delays in Indonesia. A comprehensive literature review was conducted, analyzing hospital-based cancer registry data, epidemiological trends, and healthcare system challenges. Key barriers include limited screening coverage, inadequate public awareness, reliance on alternative therapies, and systemic delays in referrals, diagnostics, and treatment initiation. Additionally, disparities in access to advanced cancer care exacerbate the issue. Findings emphasize the need for a comprehensive cancer management approach, integrating early detection programs, precision medicine, and multidisciplinary care. Strengthening primary healthcare services, enhancing oncology education for healthcare professionals, and developing comprehensive cancer centers are crucial steps. National cancer control policies must align with global strategies to improve patient outcomes. As Indonesia approaches its "Golden Indonesia 2045" vision, it is essential to prioritize cancer prevention and treatment. Addressing healthcare system inefficiencies, fostering collaborations between government, academia, and private sectors, and ensuring equitable access to quality cancer care will be pivotal in reducing the cancer burden and improving survival rates.

Keywords: *comprehensive cancer management, early detection, Golden Indonesia 2045, multidisciplinary, precision medicine*

Abstrak

Kanker tetap menjadi tantangan utama dalam kesehatan masyarakat di Indonesia, dengan angka kejadian dan mortalitas yang terus meningkat. Data GLOBOCAN 2020 menunjukkan peningkatan beban kanker, terutama di negara berkembang, di mana diagnosis pada stadium lanjut dan keterlambatan pengobatan berkontribusi terhadap luaran yang buruk. Kanker payudara merupakan jenis kanker paling umum di Indonesia, diikuti oleh kanker serviks, leukemia, dan kanker kolorektal. Meskipun berbagai upaya nasional telah dilakukan, proporsi pasien yang terdiagnosis pada stadium lanjut masih tinggi, yang berdampak pada penurunan angka ketahanan hidup dan peningkatan biaya pelayanan kesehatan. Studi ini menganalisis faktor-faktor yang mempengaruhi keterlambatan diagnosis dan pengobatan kanker di Indonesia melalui kajian literatur yang komprehensif, mencakup data registri kanker berbasis rumah sakit, tren epidemiologi, serta tantangan dalam sistem layanan kesehatan. Hambatan utama yang diidentifikasi meliputi keterbatasan cakupan skrining, rendahnya kesadaran masyarakat, ketergantungan pada terapi alternatif, serta keterlambatan sistemik dalam proses rujukan, diagnostik, dan inisiasi pengobatan. Selain itu, ketimpangan akses terhadap layanan kanker tingkat lanjut memperburuk permasalahan yang ada. Hasil studi ini menekankan pentingnya pendekatan manajemen kanker yang komprehensif melalui integrasi program deteksi dini, pengobatan berbasis presisi, dan perawatan multidisiplin. Penguatan layanan kesehatan primer, peningkatan pendidikan onkologi bagi tenaga medis, serta pengembangan pusat kanker terpadu merupakan langkah strategis yang perlu diimplementasikan. Kebijakan pengendalian kanker nasional harus selaras dengan strategi global guna meningkatkan luaran klinis pasien. Seiring dengan visi "Indonesia Emas 2045", pencegahan dan pengobatan kanker harus menjadi prioritas utama. Upaya perbaikan efisiensi sistem kesehatan, penguatan kolaborasi antara pemerintah, akademisi, dan sektor swasta, serta penyediaan akses yang merata terhadap layanan kanker berkualitas menjadi langkah krusial dalam menurunkan beban kanker dan meningkatkan angka ketahanan hidup pasien di Indonesia.

Kata kunci: *deteksi dini, Indonesia Emas 2045, manajemen kanker komprehensif, multidisiplin, pengobatan berbasis presisi*

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GLOBOCAN 2020 data estimates there were 19.3 million new cancer cases and nearly 10 million cancer deaths in 2020. Female breast cancer ranks first as the most common cancer, with an estimated 2.3 million new cases (11.7%), followed by lung cancer (11.4%), colorectal cancer (10%), prostate cancer (7.3%), and stomach cancer (5.6%). Lung cancer remains the leading cause of cancer death, with an estimated 1.8 million deaths (18%), followed by colorectal cancer (9.4%), liver cancer (8.3%), stomach cancer (7.8%), and female breast cancer (6.9%). The mortality rate of female breast cancer and cervical cancer is higher in developing countries (approximately 15 deaths per 100,000 population) compared to developed countries (12.8 deaths per 100,000 population, respectively). The global cancer burden is projected to reach 28.4 million cases by 2040, marking a 47% increase from 2020, with a larger increase in developing countries (64%-95%) compared to developed countries (32%-56%). This is attributed to demographic changes and may be further exacerbated by an increase in risk factors associated with globalization and economic growth.[1]

Research on the incidence, mortality, burden, and trends of early-onset cancer (cancer occurring in individuals under 50 years old) globally shows that the incidence of early-onset cancer increased by 79.1% from 1990 to 2019. During the same period, there was also a 27.7% increase in deaths from early-onset cancer. In 2019, breast cancer in individuals under 50 resulted in a loss of 348.1 years per 100,000 people in terms of healthy life expectancy, while trachea, bronchus, and lung cancers in individuals under 50 caused a loss of 167.6 years per 100,000 people. The greater the loss of time, the heavier the disease burden. Breast cancer poses a higher disease burden than cancers of the trachea, bronchus, and lungs.[2]

Another study indicates that by 2030, there will be a 31% increase in the incidence of early-onset cancer, accompanied by a 21% rise in deaths from early-onset cancer. The increase in early-onset cancer morbidity is associated with higher Sociodemographic Index (SDI) levels, while mortality rates significantly decline as SDI increases from 0.7 to 1. The SDI reflects economic conditions, assessed through per capita income; educational conditions, measured by the proportion of the population completing secondary and higher education; and the birth rate of countries worldwide. This index is expressed on a scale from 0 to 1, with higher SDI values indicating better socioeconomic development, which has a strong impact on the health conditions of a country's population.[2]

Asia is a densely populated and diverse region, housing 60% of the global population. Due to continuous socioeconomic development and improvements in healthcare services, life expectancy in Asia has significantly increased. It is projected that the proportion of individuals aged 60 and above could reach 25% by 2050. This demographic shift is anticipated to substantially increase the cancer burden in Asian countries. Furthermore, lifestyle transitions such as smoking, alcohol consumption, dietary patterns, diabetes, and lipid disorders—driven by urbanization, Westernization, and globalization—may have contributed to the evolving cancer burden in Asia.[3]

In 2020, the cancer incidence in Asia was recorded at 169.1 cases per 100,000 individuals, accounting for 49.3% of the global cancer incidence burden. The most prevalent cancers were lung cancer (13.8%), breast cancer (10.8%), and colorectal cancer (10.6%). Cancer mortality in Asia was 101.6 deaths per 100,000 individuals, representing 58.3% of global cancer-related deaths, with lung cancer (19.2%), liver cancer (10.5%), and stomach cancer (9.9%) being the leading causes of cancer death. The incidence of cancer has notably risen in the female population, particularly in South Korea, with an average annual percentage change of 5.73%. Additionally, cancer incidence has increased in populations under 40 years of age, with the highest rise observed in South Korea, where the average annual percentage change was 8.42% in women and 5.28% in men. Nevertheless, overall cancer mortality has declined. This study concludes that there is a substantial burden of cancer incidence and mortality in Asia. Although mortality rates have decreased, the incidence has increased, especially among women and younger populations. The study suggests further investigation to examine the potential causes behind these epidemiological trends.[3]

Indonesia also conducts hospital-based cancer registry studies. A study at a hospital in Makassar, published in 2022, documented cancer registry data from January 2002 to December 2019. The most frequent cancer types were breast cancer (1008 cases, 12.9%), leukemia (683 cases, 8.7%), and cervical cancer (631 cases, 8.1%), followed by colorectal cancer (551 cases, 7%) and ovarian cancer (496 cases, 6.3%). Leukemia was the leading cause of cancer death (219 cases, 12.7%), followed

by breast cancer (198 cases, 11.4%) and colorectal cancer (147 cases, 8.5%). Cancer was more frequently diagnosed in women (4485 cases, 57.3%) compared to men (3339 cases, 42.7%). The youngest cancer patient was 6 months old, and the oldest was 93 years old. Most patients were aged 40-49 years (2035 cases, 26%), followed by 50-59 years (1962 cases, 25.1%), 60 years and above (1653 cases, 21.1%), 30-39 years (935 cases, 12%), under 20 years (633 cases, 8.1%), and 20-29 years (606 cases, 7.7%).[4]

Similarly, a study at a hospital in Jakarta using 2013 patient data found that, out of 4915 cancer cases, women (2963 cases, 60.26%) outnumbered men (1952 cases, 39.74%). The most common cancers were breast cancer (13.33%), cervical cancer (12.55%), and cancers of the hematopoietic and reticuloendothelial systems (8.97%). Among women, cancer was most frequent between ages 44-54 (889 cases, 30%) and least frequent under age 24 (9.79%). Among men, cancer was most common between ages 55-64 (422 cases, 21.64%) and least common under age 24 (18.85%).[5] Another study using 2008-2012 data from a hospital in Jakarta showed that the most common cancers were cervical cancer (2878 cases, 15.8%), breast cancer (2459 cases, 13.5%), hematopoietic and reticuloendothelial system cancers (1422 cases, 7.8%), nasopharyngeal cancer (1338 cases, 7.4%), and lymphatic cancer (1104 cases, 6.1%). The majority of patients were over 39 years old (12,483 cases, 68.3%), while the rest were aged 20-39 (3971 cases, 21.8%) and 0-19 (1807 cases, 9.9%).[6]

Research in Indonesia produces conclusions similar to the global GLOBOCAN 2020 data and studies in Asia, indicating that breast cancer is the most common cancer. Women are more frequently affected than men, and there is a trend of cancer occurring at younger ages, particularly under 50 years. However, there are some differences from Asian and global data, notably that lung cancer does not appear as the most frequent cancer or the leading cause of death in Indonesia, at least in the hospitals studied in Makassar and Jakarta. In Indonesia, the most common cancers are breast cancer, cervical cancer, leukemia, and colorectal cancer, while the leading causes of cancer death are leukemia, breast cancer, and colorectal cancer.

In addition to the increasing incidence of cancer in younger age groups, a study from a hospital in Jakarta revealed that most breast cancer patients presented at the hospital in advanced stages, with 19.9% in stage IV and 13.13% in stage IIIB. Although staging information for 283 patients was unavailable, researchers concluded that a majority of breast cancer cases presented at the hospital in late stages. A similar trend was observed in cervical cancer patients, where most cases presented in locally advanced stages (36.63%). A meta-analysis also showed that cervical cancer is more frequently diagnosed at advanced stages. Data from 25 studies across three global regions, involving 53,233 participants, indicated that the estimated pooled global prevalence of advanced-stage cervical cancer was 60.66%. Subgroup analysis revealed that the prevalence of advanced-stage cervical cancer was 62.6% in Africa, 46.51% in Asia, and 50.16% in North America.[7]

This situation inevitably affects the survival rates of cancer patients. One-year survival rates differ significantly between patients diagnosed at early versus advanced stages. For example, colorectal cancer has a one-year survival rate of 97.7% when detected early, but this drops to 43.9% when detected at an advanced stage. Similarly, lung cancer patients have a one-year survival rate of 87.3% at early stages, which decreases to 18.7% at advanced stages. In the U.S., Caucasians are generally diagnosed at stage I-II, whereas African-Americans are often diagnosed at stage IIB or later. Socioeconomic factors play a critical role, as patients often seek medical treatment only after the disease has progressed significantly. A meta-analysis found that education level and residence location are significant factors influencing the occurrence of advanced-stage cervical cancer. Other reasons for delayed cancer diagnosis and treatment include misinformation about cancer, the lack of screening capabilities in all healthcare facilities, and a reliance on alternative medicine.[8,9]

Another issue in Indonesia is delayed cancer treatment. A study conducted at a hospital in Jakarta from May to August 2015 on 294 outpatient cancer patients in the radiation oncology department revealed significant treatment delays. Among the patients, 86% experienced delays in receiving treatment. Delayed treatment was observed in 153 patients, 43% of whom had a history of using alternative therapies. Advanced age, low education levels, and a history of alternative medicine use were statistically significant factors associated with delayed treatment, with p-values of 0.047, 0.047, and <0.001, respectively. Additionally, 214 patients experienced delays caused by service providers, with

proportions of 9%, 36%, and 80% for physician-related delays, diagnostic system delays, and treatment system delays, respectively. All types of service provider delays were statistically significant in relation to treatment delays. [10]

Service provider delays are classified into physician delays and system delays. Physician delays are defined as a referral delay of more than 30 days from the first medical consultation to a specialist or healthcare provider at a referral hospital capable of performing diagnostic procedures. System delays are further divided into diagnostic system delays (more than 30 days from the first visit to a specialist or referral hospital to cancer diagnosis) and treatment system delays (more than 30 days from diagnosis to the initiation of definitive treatment). It is estimated that 47% of cervical cancer patients experience treatment delays, with stage IIIB being the most common stage. Treatment delays occurred in 48.3% of breast cancer patients diagnosed with stage IIIB, and in nasopharyngeal cancer patients, delays were most common in stage IVB, followed by stage III.[10] Thus, most treatment delays occur in patients with advanced-stage cancer. Research indicates that a 12-week treatment delay negatively affects prognosis,[11] while another study in Asia found that treatment delays of more than six months lead to worse disease-free survival.[12]

Delayed breast cancer screening (when patients seek diagnosis after the recommended time, often when the cancer is already in stage III) and the factors contributing to such delays have been studied in a hospital in Riau in 2016. This research found that 60.6% of women (123 patients) delayed their breast cancer screenings. Women with insufficient knowledge were 3.11 times more likely to experience delays compared to those with adequate knowledge. Other factors included low income, which increased the likelihood of delays by 2.852 times, and the distance to healthcare facilities, where patients living farther from healthcare services were 2.466 times more likely to delay screenings compared to those living closer. Additionally, the absence of symptoms increased the likelihood of delay by 2.324 times compared to patients who experienced specific symptoms.[13]

The delay in cancer treatment in Indonesia is also attributed to the use of complementary and alternative therapies, which are common among the population. A qualitative study conducted in two hospitals in North Sumatra on 15 advanced-stage cancer patients from July to December 2013 revealed that patients often preferred complementary and alternative therapies over medical treatment, viewed medical treatment as a last resort, or integrated complementary therapies as supportive care alongside medical treatment. External influences, religious beliefs, and limited involvement of primary healthcare services were also factors in these decisions. [14]

Advanced-stage cancer not only worsens patient prognosis and survival rates but also significantly increases healthcare costs. A study involving an insurance institution found that from 2016-2020, 20,422 members were diagnosed with cancers such as breast cancer, cervical cancer, colorectal cancer, lung cancer, ovarian cancer, or prostate cancer. Average healthcare costs increased annually and cumulatively up to four years post-diagnosis, with the most dramatic cost increases occurring in stage IV cancers. For most cancer types, such as cervical and lung cancer, costs remained relatively stable or fluctuated only slightly across different stages, while for ovarian cancer, costs in stages III and IV rose sharply compared to stages I and II. Annual and cumulative healthcare costs up to four years after diagnosis were significantly higher for members diagnosed in later stages than for those diagnosed in earlier stages. This highlights the importance of early cancer detection to reduce both annual and cumulative healthcare costs. [15]

Higher costs in later cancer stages are closely tied to advancements in cancer treatment. In recent years, newer drugs have emerged as treatment options, especially for advanced-stage cancers. These newer treatments fall under the categories of targeted therapies and immunotherapies, which are chosen based on specific diagnostic tests that predict the success of the treatment. Advanced-stage adenocarcinoma of the lung requires testing for PDL-1, EGFR mutations, and ALK mutations to determine the appropriate therapy. PDL-1 positivity greater than 50% indicates eligibility for immunotherapy, such as pembrolizumab. Positive EGFR mutations in exon 19 and 21 make patients eligible for anti-EGFR drugs such as osimertinib, gefitinib, erlotinib, and afatinib. Positive ALK mutations indicate eligibility for anti-ALK drugs such as brigatinib, alectinib, entrectinib, and ceritinib. If all these markers are negative, chemotherapy remains the treatment of choice.[16]

In advanced breast cancer with triple-negative receptor status (negative estrogen receptor, negative progesterone receptor, and negative HER-2 receptor), the BRCA-1 and BRCA-2 genes, as well as PDL-1, have been introduced as determinants for treatment options. For patients who test positive for BRCA-1 and BRCA-2 mutations, treatment options include anti-BRCA therapies, such as Olaparib (a PARP-1 inhibitor). For patients with PDL-1 scores greater than 1%, immunotherapy can be administered in conjunction with chemotherapy, such as atezolizumab with nab-paclitaxel or pembrolizumab with any chemotherapy regimen. If both markers are negative, the treatment choice is chemotherapy. These treatment guidelines are supported by various cancer treatment protocols worldwide based on reliable scientific evidence. Immunotherapy works by activating the patient's immune cells to attack cancer cells, while targeted therapy involves drugs that inhibit specific pathways involved in cancer development. For example, in lung cancer driven by EGFR mutations, targeted therapy aims to block these mutations effectively.[17-20]

Immunotherapy and targeted therapy require specific testing to determine the presence of biomarkers, ensuring appropriate drug administration. The accuracy of treatment and testing has given rise to the term Precision Medicine. Precision medicine is a therapeutic and disease prevention approach that takes into account the variability in genes, environment, and lifestyle of each individual. Although relatively new, the concept of precision medicine has existed since the classification and matching of blood donors with patients in need of transfusions. This concept has reduced the risk of complications and improved outcomes.[21]

In the era of precision medicine, molecular testing plays a crucial role. A literature review I conducted on Chronic Myeloid Leukemia (CML) highlighted the necessity of testing for BCR-ABL1 mutations in CML patients, as these mutations are the most common cause of resistance to tyrosine kinase inhibitors. Tyrosine kinase inhibitors represent the first-line therapy for CML patients, except during pregnancy. Patients resistant to tyrosine kinase inhibitors are offered alternative medications that remain effective for their specific mutations. For example, patients with the T315I mutation are recommended to receive ponatinib alone, as they are resistant to other tyrosine kinase inhibitors. Patients with mutations Y253H, E255V/K, and F359V/I/C can be treated with dasatinib, bosutinib, or ponatinib. [22]

Molecular testing also plays a role in determining treatment outcomes for patients. I previously researched the relationship between FLT3-ITD mutations and one-year survival rates in acute myeloid leukemia (AML) patients in Indonesia. In that study, 11 out of 51 patients had FLT3-ITD mutations. No correlation was found between FLT3-ITD mutations and one-year survival, indicating that the one-year survival of AML patients is not influenced by FLT3-ITD mutations. These findings align with another study conducted on 320 patients in China and 100 patients in Italy, which also found that one-year survival in AML patients was unaffected by FLT3-ITD mutations. Prior to this research, systematic reviews and meta-analyses I conducted with my team suggested that FLT3-ITD mutations adversely impact the survival of AML patients.[23] The differing results between these two studies may be due to racial influences on the prognosis of AML patients. Homogeneous cytogenetic cohort studies have indicated that race does indeed affect prognosis; Caucasian patients generally have better survival outcomes compared to African and Hispanic patients.[24]

It is undeniable that precision medicine comes at a high cost. Testing for genetic and protein alterations can be expensive, especially when numerous changes are assessed, and insurance may not cover all tests. Genetic mutation testing can increase the overall costs of cancer management. In other words, early detection is often less expensive than conducting precision testing. For patients needing the best treatment options, specific targeted therapies or immunotherapies based on genetic or protein alterations can be costly to obtain. [21]

Based on data from BPJS Kesehatan from 2019 to 2021, cancer is one of the eight diseases with the largest funding burden in Indonesia, ranking second. The number of cancer cases peaked in 2019, with a total of 2,743,858 cases and funding reaching Rp 4.12 trillion. In 2020, the number of cancer cases decreased to 2,553,033, with total funding of Rp 3.58 trillion. However, the number of cases rose again in 2021 to 2,595,520, with funding amounting to Rp 3.5 trillion. The total funding for cancer during this period reached Rp 11.21 trillion, which constitutes 18.26% of the total BPJS Kesehatan funds.[25]

A study attempted to compare the relationship between health expenditure and cancer outcomes in various countries. Health expenditure is measured by health expenditure per capita (HEpc), which is the

total expenditure of a country on health, both from the public and private sectors, divided by the population. Cancer outcomes are assessed using site-standardized proxy relative survival (SS-RS), which reflects the age-standardized cancer mortality/incidence ratio. The higher the SS-RS value, the lower the mortality rate due to cancer. The three countries with the highest SS-RS values are Korea, Australia, and Norway, all of which have high HEpc. The study estimated that to achieve SS-RS values of 0.35, 0.45, and 0.55, health budgets of US$328, US$1260, and US$4840, respectively, would be needed, or approximately 5 million, 19.5 million, and 75 million rupiah.[26,27] Indonesia, with an HEpc of US$132.96 in 2020 (around 2 million rupiah), still faces significant challenges. To achieve an SS-RS value of 0.55, each individual in Indonesia would need to increase their health budget by 73 million rupiah.[28] The research concluded that countries with lower-middle incomes, including Indonesia, need to consider increasing health budgets to improve cancer survival rates.[29]

The high proportion of advanced-stage cancer patients coming to hospitals may be related to the low coverage of early detection, particularly for breast and cervical cancer. The coverage of early detection for cervical cancer (Visual Inspection with Acetic Acid/IVA) and breast cancer (Clinical Breast Examination/SADANIS) in 2017 was only 3,038,296, or about 8.1%.[30] This figure is significantly lower than that in the United States, which achieved 57.1% for breast cancer, 39% for cervical cancer, and 36.3% for prostate cancer.[31] Early detection plays a crucial role in reducing the cancer burden. A study in the UK showed that routine early detection of cervical cancer can reduce the incidence of stage 1A cervical cancer by 67% and advanced cervical cancer by 95%. In 2013, it was estimated that early detection of cervical cancer in the UK could prevent 70% of cervical cancer deaths across all ages. If everyone underwent regular early detection, up to 83% of cervical cancer deaths could be prevented.[32]

Another study on national cancer screening programs in Asia indicates that South Korea is one of the countries that has successfully reduced the incidence of cervical cancer through the implementation of a national cancer screening program. The national cervical cancer screening program in South Korea has been in place since 1999. By 2015, the incidence of cervical cancer decreased from 16.3 cases per 100,000 population to 9.1 cases per 100,000 population. This national cancer screening program is accessible to recipients of Medical Aid and participants in the National Health Insurance scheme. South Korea has a single public health insurance system with universal coverage, operated by the National Health Insurance Service (NHIS). The Medical Aid program is designed for individuals with low income who are unable to afford healthcare services. Currently, South Korea's national cancer screening program provides screening for gastric, liver, colorectal, breast, cervical, and lung cancers. The national cervical cancer screening program offers free cytology screening every two years. The target population for cervical cancer screening was women aged 30 and above until 2015; however, in 2016, it was expanded to include women aged 20 and above.[33]

The increasing trend of cancer occurrence in individuals under 50 years of age, particularly among females, along with the high proportion of cancer diagnosed at advanced stages, poses a significant threat to the world, especially Indonesia, which is projected to reach its demographic bonus peak by 2045. The demographic bonus refers to the rise in the population of productive age (16-65 years) in a country, accompanied by a decline in birth and death rates. As of June 2022, Indonesia's population reached 275.36 million, of which 190.83 million (69.3%) are classified as productive age, 67.16 million (24.39%) as non-productive age, and 17.38 million (6.31%) as elderly. From 2020 to 2030, Indonesia will experience a demographic bonus, with the peak of the productive age population expected to coincide with Indonesia's 100th anniversary in 2045. This condition is referred to as "Indonesia Gold 2045." Consequently, preparations must be made to prevent potential disasters, which include enhancing the quality of the population through health and education interventions.[34,35]

The projected peak of the demographic bonus in 2045 (Indonesia Gold 2045) may increase the cancer burden, given the global trend of rising early-onset cancer. Efforts are needed to prevent such possibilities. In fact, approximately one-third to one-half of cancer cases have the potential to be prevented. This proportion is expected to continue rising with a better understanding of cancer risk factors and the development of cancer prevention interventions.[36]

The first crucial step in cancer prevention efforts is education. Education serves as an independent protective factor that supports health. Education

delivered in comfortable settings for the community (e.g., community centers or schools) and in easily understandable language plays a vital role in cancer prevention. The primary goal of education is to help the community understand cancer, particularly regarding cancer prevention closely related to cancer risk factors.[37]

Primary Health Care Facilities (PHCF) serve as the frontline in cancer prevention through promotional and preventive efforts. Healthcare providers working in PHCF need to be equipped with adequate knowledge regarding oncology to provide effective education to the community. However, a study in the UK analyzing the learning experiences of medical students in oncology indicated that medical students' satisfaction with the quality and quantity of oncology teaching during their medical education remains low.[38] A survey conducted among final-year medical students in Australia and New Zealand revealed that less than half of the students felt confident in conducting anamnesis or physical examinations of cancer patients.[39] Other research in Canada showed that oncology ranked as the least well-taught specialty during medical education according to both medical students and faculty members.[40] No similar studies have been conducted in Indonesia, presenting an opportunity for Indonesian medical education researchers to explore this area. Nonetheless, we must anticipate such conditions arising in Indonesia.

One study indicated that medical students who frequently have clinical exposure to cancer cases show improved competence in cancer prevention counseling.[41] Another study demonstrated that medical students' confidence in conducting cancer prevention counseling can be enhanced by watching counseling recordings and participating in role-playing exercises related to cancer prevention, accompanied by peer feedback.[42] Research conducted on medical students in Australia and other countries indicated that those who adopted healthy lifestyle behaviors during their medical education found it easier to counsel patients on similar preventive measures.[43-45] From these studies, it is evident that frequent clinical exposure and various oncology learning methods can enhance medical students' understanding of cancer. The adoption of healthy lifestyle behaviors during medical education plays a critical role in efforts to educate the community about cancer prevention.

Another important point regarding cancer that healthcare professionals need to understand relates to early detection. As previously mentioned, early detection plays a crucial role in cancer control efforts in many countries. Mammography, breast ultrasound, and self-breast examination, commonly known as SADARI, are some of the screening modalities for breast cancer. Self-breast examination is very easy to perform and can be taught by healthcare professionals in Primary Health Care Facilities (PHCF) to the community. Early detection of cervical cancer can be conducted through IVA (Visual Inspection with Acetic Acid) or Pap Smear examinations at PHCF.[46] However, for certain types of cancer, such as lung cancer that requires low-dose lung computed tomography (LDCT) for early detection, or colorectal cancer that necessitates fecal occult blood tests (FOBT) for early detection, these examinations cannot be performed at PHCF. Nevertheless, healthcare professionals play a vital role in explaining these modalities before ultimately referring patients to Advanced Health Care Facilities (AHCF). Therefore, understanding early detection methods is essential for healthcare professionals, particularly those working in PHCF.

Studies indicate that patients who understand their disease and the treatments they will receive are more compliant with therapy, ultimately leading to better treatment outcomes.[47] Therefore, doctors have an important role in providing education related to cancer, especially regarding treatment options that patients can accept. Doctors who can explain cancer treatment methods to patients will enhance their understanding of cancer therapies. Although cancer treatments are carried out in AHCF, healthcare professionals in PHCF should be able to explain evidence-based treatments so that cancer patients are aware of therapies whose efficacy and safety have been tested. Thus, strengthening oncology education becomes crucial.

Enhancements in oncology education also need to be made at the residency stage. A survey conducted in Canada indicated that 63% of internal medicine residents felt that oncology education was insufficient. They reported feeling unprepared to handle diseases related to oncology after completing their oncology rotation. Additionally, 82% of oncologists in Canada believe that oncology education during the internal medicine residency is still lacking. They also mentioned that diseases related to oncology are taught less frequently than those unrelated to

oncology. These oncologists suggested that clear learning objectives and education through books or the internet could be beneficial for learners.[48]

Another study showed that about one-third of internal medicine residents who completed a hematology-oncology rotation at comprehensive cancer centers reported an increase in oncology knowledge. The study also stated that most internal medicine residents developed an interest in the field of hematology-oncology after their clinical rotation.[49] However, the opposite was found in another study, which indicated that internal medicine residents experienced a decline in interest in hematology-oncology after their rotation in inpatient hematology-oncology services.[50] It seems that residents' perceptions of the oncology learning experience are influenced by the learning environment.[51]

Strengthening oncology education at the level of general practitioners and residents can be achieved by ensuring that learners possess sufficient competencies to practice clinically after graduation. To ensure that learners have adequate competencies, adequate assessment instruments are needed. Entrustable Professional Activities (EPA) are one of the instruments that can be used to evaluate learners' competencies in clinical work environments. EPA can be defined as professional practices that can be entrusted to learners once they are considered capable of performing entrusted professional practices without supervision. EPA encompasses a combination of various competencies, such as patient care, interpersonal communication, medical knowledge, systems-based practice, practice-based learning and improvement, and professionalism. According to this concept, there needs to be 'inherent' supervision over students or residents in achieving a trustworthy professional activity in the clinical learning environment. An EPA is something that can be performed, observed, and measured independently in both process and outcomes. Through EPA, competency assessments of learners can be conducted. Activities or professional practices that can be categorized as EPA can be determined through review and discussion with experts in the relevant field. Established EPAs will still need to be validated for application.[52]

A study found that Entrustable Professional Activities (EPA) can be effectively applied in the clinical education of medical students. EPAs are said to have the potential to optimize the assessment of medical students' competencies.[53] Education on cancer prevention, early detection, and treatment for patients could be included as one of the EPAs in medical education. In the field of oncology education at the residency stage, the EPAs could involve planning patient management, monitoring patients undergoing cancer treatment, prescribing systemic therapy, discussing health issues with patients, preparing for potential oncology emergencies, coordinating healthcare services for patients, and documenting various cancer services provided to patients in medical records. Each of these EPAs includes milestones that can serve as guidance for learners.[54] My colleagues and I from the Department of Internal Medicine, the Internal Medicine College, and the Faculty of Medicine at Universitas Indonesia conducted a study to determine EPAs for internal medicine residents. This study identified 28 EPAs.[55]

Cancer is caused by various risk factors, which can be categorized into non-modifiable and modifiable risk factors. Non-modifiable risk factors include genetics, age, sex, and race.[56,57] A study revealed that the primary modifiable risk factors contributing to the significant years of healthy life lost per 100,000 population for patients under 50 years old with various cancers are modifiable risk factors. For breast cancer, alcohol consumption can increase the risk by 4.5%, smoking can increase the risk by 4.4%, high red meat consumption can increase the risk by 2.9%, physical inactivity can increase the risk by 0.6%, and high fasting blood sugar can increase the risk by 2.6%. Conversely, for tracheal, bronchial, and lung cancers in patients under 50 years old, smoking can increase the risk by 41.4%, infrequent fruit consumption can increase the risk by 4.4%, and high fasting blood sugar can increase the risk by 3.2%.[2] A meta-analysis indicated that the risk factors influencing colorectal cancer occurring in those under 50 years old include inflammatory bowel disease, which increases the risk by 4.43 times, obesity increasing the risk by 1.52 times, metabolic syndrome increasing the risk by 1.29 times, smoking increasing the risk by 1.44 times, alcohol consumption increasing the risk by 1.41 times, a sedentary lifestyle increasing the risk by 1.24 times, processed meat consumption increasing the risk by 1.53 times, and sugary beverage consumption increasing the risk by 1.55 times.[58]

The World Health Organization (WHO) recommends measures to reduce risk factors through policy-making and prevention programs. Cost-effective policies should be implemented to reduce the burden of cancer, such as raising taxes on tobacco and alcohol;

eliminating exposure to tobacco smoke or implementing tobacco marketing strategies; restricting unhealthy food and beverage marketing to children; ensuring quality public open spaces with adequate infrastructure for physical activity; reducing air pollution; and providing human papillomavirus (HPV) vaccines. Research on the causes of cancer in humans and carcinogenesis should also be pursued.[36]

The WHO also recommends that each country develop policies and plans for the prevention and control of non-communicable diseases, including national cancer control plans that focus on equity and access.[36] Many countries around the world already have national cancer control programs. These programs are derivatives of national cancer control plans aimed at addressing the cancer burden in a country. As of 2000, based on WHO estimates, 48% of countries had national plans for the control of non-communicable diseases, including cancer, or national cancer control plans. This estimate increased to 87% by 2015. According to data from the International Cancer Control Partnership (ICCP), in 2013, there were 91 national cancer control plans from 42 countries available on the ICCP website. This number increased to 115 from 50 countries in 2015 and 224 from 93 countries in 2018.[59]

A study analyzing national cancer control plans worldwide found that countries with national cancer control plans have more comprehensive, coherent, and consistent national plans compared to countries that only have national non-communicable disease control plans. Countries with national cancer control plans focus on more comprehensive cancer control components than those that only address non-communicable disease control. Generally, countries with only non-communicable disease control plans focus on managing risk factors related to non-communicable diseases and cancer, without encompassing all aspects of comprehensive cancer management. National cancer control plans can play a crucial role in determining necessary policies to enhance the capacity and coverage of cancer management, palliative care, and research compared to non-communicable disease control plans. The implementation of national cancer control plans is more effective in addressing the national cancer burden than the cancer control measures included in non-communicable disease control plans. This is suspected to be due to a greater commitment from the government in countries with national cancer control plans compared to those with only non-communicable disease control plans.[59]

National cancer control plans are an integral part of comprehensive cancer centers. The World Health Organization (WHO) recommends that every country have a national cancer control plan that includes prevention, screening, diagnosis, treatment, survivorship, and palliative care. Comprehensive cancer centers have the potential to serve as focal points in national cancer control and influence the development of health systems and cancer management.[60]

Figure 1. Components of the Cancer Control Plan[60]

(Adapted and modified from Gospodarowicz M, Trypuc J, D'Cruz A, Khader J, Omar S, Knaul F. Cancer Services and the Comprehensive Cancer Center. Disease Control Priorities, Third Edition (Volume 3))

A comprehensive cancer center serves as a central force for the national cancer control plan and is tasked with developing innovative approaches to cancer prevention, diagnosis, and treatment. This can be achieved through basic and clinical research, patient care, training new clinicians and scientists, and community engagement, as well as enhancing education and training. The excellence of a cancer center is often correlated with the strength of its educational and training programs. Cancer management in this era requires a multidisciplinary approach, necessitating that the education and training offered encompass various fields. Improving the quality of education and training, especially in oncology as a significant support for comprehensive cancer centers, is expected to enhance the quality of cancer prevention and management for patients.[61]

In implementing education and training, most comprehensive cancer centers are affiliated with university medical schools. In this affiliation, the executives of the comprehensive cancer center must establish strong collaboration with colleagues in hospitals, clinical practices, medical faculties, and other health science experts. This cooperation can maximize funding from various sources, including national and local grants, institutional funds, private donations, and industry contributions.[62]

Cancer patient care and related research are closely linked to the academic support of the faculty and career advancements that result in ongoing research in the field of cancer specialization. Major lecture programs featuring internal or external speakers can educate staff and students about new scientific discoveries. Comprehensive cancer centers also form partnerships with communities, governments, and industries to develop community outreach programs aimed at improving health literacy, establishing early detection programs, and raising funds for cancer research.[62] Thus, comprehensive cancer centers are inseparable from universities. Both hospitals and universities play crucial roles in education, so the loss of one component can impact educational outcomes. As previously mentioned, residents in internal medicine reported a better learning experience in oncology when they studied at comprehensive cancer centers compared to solely at inpatient cancer services.[49,50] The Faculty of Medicine at Universitas Indonesia (FKUI), Dharmais Cancer Hospital, and Dr. Cipto Mangunkusumo Hospital (RSCM) hold significant potential to serve as comprehensive cancer centers as described above. The Faculty of Medicine, through its programs involved in cancer control from preventive to palliative care, needs to collaborate with hospitals to enhance competencies in oncology through education and training within the hospitals. Referring to the recommended comprehensive cancer center model, it seems that education and training in oncology cannot be separated from the academic role of a medical faculty.

The structure of a comprehensive cancer center is derived from its mission and the framework necessary to support that mission. The primary mission of a comprehensive cancer center is to reduce cancer incidence and improve the quality of life and survival rates of patients with malignant diseases. There are three main areas in cancer care: research, clinical care, and education, which collaborate to achieve these goals. Several interconnected departments are required to meet the objectives of the cancer center. Department heads may be filled by physicians, scientists, or administrators, depending on the focus of the department. Department leaders report to the director of the comprehensive cancer center, who is assisted by a deputy director and a hospital advisory board. The director of the comprehensive cancer center is typically a distinguished individual trained in a specific area of cancer research but possesses a vision for the broad research and clinical foundation required by the center. The responsibilities of the cancer center director include setting departmental goals, coordinating efforts between departments, recruiting and retaining scientific staff, securing national, state, and philanthropic funding, creating new programs, and monitoring the financial aspects of the center.[62]

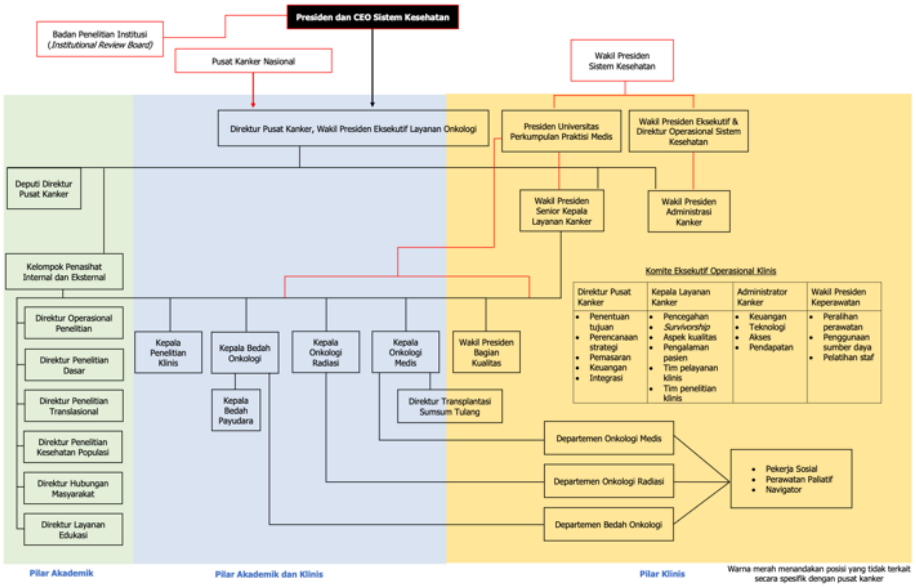

Figure 2. Framework of the Comprehensive Cancer Center[62]

(Adapted and modified from Aljurf M, Majhail NS, Koh MBC, Kharfan-Dabaja MA, Chao NJ. The Comprehensive Cancer Center)

Cancer patients require multidisciplinary care to achieve optimal outcomes. Therefore, clinicians involved in the oncology multidisciplinary team participate in direct patient care by establishing oncology diagnoses and providing appropriate management. The oncology multidisciplinary team may consist of medical hematology-oncology, radiation oncology, radiology, hematology, pathology, nuclear medicine, surgery, and nursing. This team will hold regular meetings, referred to as tumor board meetings, to discuss patients concerning key radiographic and pathological findings, diagnostic and/or therapeutic options, and the best management for each patient.[63]

Tumor board meetings typically begin with a presentation regarding the patient's history, including comorbid conditions, clinical, and psychological status, as well as clinical findings obtained prior to the meeting. Clinical staging will then be determined by each specialty, such as pathologists or radiologists, before agreeing on an optimal treatment plan. The average duration of these meetings is 76 minutes.[64]

A systematic review of colorectal multidisciplinary team meetings found that in the United States, these meetings significantly influence preoperative decision-making, such as staging methods and neoadjuvant treatment selection. Since the implementation of multidisciplinary meetings or tumor board meetings, there has been an improvement in postoperative mortality in Denmark. The systematic review concluded that multidisciplinary team meetings play a crucial role in enhancing patient care measures and should produce clear recommendations for each patient.[64]

A systematic review of 16 studies on the benefits of tumor board meetings for gastrointestinal cancer patients showed that tumor board meetings could alter diagnoses formulated by individual doctors in 18.4% to 26.9% of evaluated cases, with this finding noted in four studies. Two studies reported that tumor board meetings could accurately formulate diagnoses in 89% and 93.5% of evaluated cases; nine studies indicated that treatment plans changed in 23.0% to 41.7% of evaluated cases; and four studies found that the outcomes of discussions in tumor board meetings were implemented in 90% to 100% of evaluated cases.[65]

A study conducted in the UK aimed to assess the benefits of multidisciplinary oncology teams for colorectal cancer patient care. In this study, there were 310 patients, of which 176 were not treated by a multidisciplinary oncology team (as the team had not yet been established), and 134 were treated by the multidisciplinary oncology team. The results showed that the group treated by the multidisciplinary oncology team had a three-year survival rate of 66%, whereas the group not treated by the multidisciplinary oncology team had a three-year survival rate of 58%. This difference was statistically significant. The disparity may have arisen because, after the establishment of the multidisciplinary oncology team, there was an increase in the administration of adjuvant chemotherapy, which in turn improved the three-year survival rate of patients.[66]

The presence of a multidisciplinary oncology team also positively impacts patient safety. Studies have reported that the rate of medication errors in outpatient chemotherapy patients ranges from 3% to 19%, varying across different clinical practice sites.[67] Another study analyzing the impact of multidisciplinary teams indicated improvements in cancer diagnosis and treatment, leading to increased patient survival rates of over 50% in many developed countries, with figures now approaching 60% for long-term survival.[68]

The establishment of a well-functioning multidisciplinary oncology team is closely linked to interprofessional education at both undergraduate and postgraduate (specialist) levels. This education shapes healthcare professionals with expertise in their respective fields and the ability to collaborate with specialists from other disciplines. The benefits of interprofessional education have been systematically reviewed in Best Medical Education (BEME). Overall, learners responded positively to interprofessional education, their attitudes toward collaborative learning improved, and they gained the knowledge and skills necessary for collaborative practice. The review found that faculty development, facilitator preparation, reflection on learners' practices, and pedagogy play crucial roles in interprofessional learning. Additionally, relationships with the healthcare system, cost-effectiveness of services, and collaboration between institutions should also be considered when implementing interprofessional education.[69]

As previously mentioned, research in Asia indicates that while cancer mortality has decreased, its incidence has increased, suggesting a rise in the number of cancer survivors. In the United States, the number of cancer survivors rose from about 3 million in 1971 to 13.7 million in 2012, with projections estimating nearly 18 million survivors by 2022. The Institute of Medicine

(IOM) emphasizes the importance of policies that ensure access and coverage of health insurance for all aspects of cancer survivor care, including psychosocial services.[70]

A study in the Netherlands found an increase in consultations with primary care services among cancer patients diagnosed for 2 to 5 years compared to a control group of the same age and sex without cancer. The proportions for each type of cancer were 15% for colorectal cancer, 24% for breast cancer, and 33% for prostate cancer. Although a study in the U.S. showed a smaller increase in primary care utilization among breast cancer survivors (a 10% increase in the fourth year post-diagnosis; $P<0.05$), these results highlight the critical role of primary care in the management of cancer survivors.[70]

In addition to their role in cancer survivor care, primary care services are also vital in palliative care for cancer patients. It is estimated that there are 40 million individuals with terminal illnesses who require palliative care, yet 86% do not receive it, including 98% of children in low- to middle-income countries. Access to such care is often challenging because most patients prefer to remain in their homes and communities. Primary health services, being the closest to the community, are ideally positioned to deliver this care. Consequently, WHO recommends integrating palliative care into primary care services to enhance accessibility for the population.[71]

There is a need to reassess whether general practitioners, as frontline providers in primary care, are adequately prepared to deliver quality palliative and cancer survivor care. A study in the UK revealed that general practitioners recognized the importance of their roles in providing palliative care; however, they also felt a lack of experience and training, which hindered their ability to offer optimal service.[72] A systematic review also indicated that primary care physicians lacked sufficient skills and confidence to provide cancer survivor care.[73] This issue is tied to the limited education on palliative and survivor care that medical students receive. A study of final-year medical students in the Netherlands found that nearly 60% felt unprepared to deliver palliative care and lacked adequate knowledge in this area. One reason cited for this was the limitations within the medical education curriculum, with only 5.6% of respondents feeling they had received sufficient training in palliative care. This educational gap is particularly evident in the psychosocial and spiritual aspects of care.[74] Additionally, studies showed that final-year medical students and oncology fellows lacked sufficient knowledge regarding cancer survivor care, with final-year students answering only 56% of questions correctly, while oncology fellows performed slightly better with 67%.[75]

To effectively provide palliative care in primary services, there needs to be better integration of palliative and survivor care into the medical education curriculum, alongside training for healthcare providers working in primary care. This aligns with the mission of comprehensive cancer centers, which focus not only on treatment but also on education and training. The Entrustable Professional Activities (EPA) concept mentioned earlier for cancer prevention could also strengthen oncology education related to palliative and survivor care for medical students, particularly those with limited exposure to cancer patients. A study demonstrated that implementing an EPA-based curriculum for medical students in the Netherlands increased their opportunities for case exposure, decision-making participation, and familiarity with seeking feedback on their learning. The feedback and sense of accomplishment from applying EPA principles helped boost students' confidence in managing patients in the future.[76]

Improving the quality and quantity of oncology education through the EPA approach can produce graduates prepared to implement preventive, promotive, survivorship, and palliative care strategies in comprehensive cancer management at various service levels, including primary care. This is expected to address WHO's recommendations for strengthening palliative care and cancer survivor services in primary health settings.[60]

In terms of training, a systematic review indicates that training in cancer survivor care can enhance the skills and confidence of healthcare providers. This training should utilize a standardized curriculum, tailored to local needs, and be conducted periodically with appropriate learning models to ensure better long-term outcomes.[73]

Additionally, primary care services need to be equipped with safe, effective, and cost-efficient medications and tools to adequately respond to palliative care needs. However, there should also be arrangements for primary care health workers to consult with more experienced doctors regarding complex or unusual palliative care issues. The consultation mechanism should be straightforward to

ensure there are no barriers to providing palliative care at the primary level. Furthermore, it is essential to establish a system that enables primary care providers who are actively engaged in the community to transfer patients quickly and efficiently to higher-level healthcare institutions when necessary to address challenging health issues. Therefore, involving and strengthening primary care services in cancer management is crucial.[71]

Various issues related to cancer care currently include the increasing incidence of cancer among individuals under 50 years old, the high proportion of cancer patients diagnosed at advanced stages, and delays in cancer treatment.[2,5,10] These problems are closely linked to the quality of cancer services, research, and oncology education. As mentioned in various studies, the high proportion of patients diagnosed at advanced stages and the issues of delayed treatment are significantly influenced by public knowledge about cancer.[13] This aspect of public knowledge is tightly connected to the educational competence of healthcare professionals, which should encompass not just prevention but also early detection, diagnosis, treatment, survivorship, and palliative care. The implementation of Entrustable Professional Activities (EPA) in education can assist in assessing the competencies of students.[52]

The national cancer control plan, which includes prevention, screening, diagnosis, treatment, survivorship, and palliative care as recommended by the WHO, can be implemented through comprehensive cancer centers. These centers not only focus on service delivery but also on research and education.[60,62] Medical schools, such as the Faculty of Medicine Universitas Indonesia, along with educational hospitals like Rumah Sakit Kanker Dharmais and Rumah Sakit Dokter Cipto Mangunkusumo, can serve as models to support the establishment of these comprehensive cancer centers. Besides comprehensive cancer centers, the WHO also recommends that primary care services can play a role in cancer control through prevention, screening, survivorship, and palliative care.[71] The integration of primary care with comprehensive cancer centers can enhance the quality of cancer services.

As we approach the demographic bonus, the government has launched the Long-Term National Development Plan (LTNDP) 2045, known as Indonesia Emas 2045. This plan outlines a vision for Indonesia by 2045 as a sovereign, advanced, just, and prosperous nation based on four pillars: human development and mastery of science and technology; sustainable economic development; equitable development; and strengthening national resilience and governance. Comprehensive cancer management through the integration of comprehensive cancer centers and primary care aligns with the pillar of human development and mastery of science and technology, aiming to improve the quality of the Indonesian population through better education, culture, health standards, life expectancy, quality of life, productivity, and broad scientific and technological knowledge.[77]

We have just faced the COVID-19 pandemic together and successfully navigated through it. The United Nations (UN) even praised our efforts. We were able to mobilize all our strength and resources to address the COVID-19 pandemic.[78] It is certainly not impossible to undertake similar efforts to improve the quality of cancer care in Indonesia. Collaboration among healthcare professionals, the government, the private sector, and educational institutions is essential to tackle the cancer issues in Indonesia. The development of comprehensive cancer centers integrated with primary care can serve as a solution to the problems of cancer care and enhance the quality of cancer services in Indonesia. Medical students who will become general practitioners working in primary care, as well as internal medicine residents and residents from other disciplines related to cancer care, must prepare themselves with the necessary competencies to face the future challenges of cancer burden. The medical faculty along with its teaching hospitals, particularly the Faculty of Medicine of Universitas Indonesia, Dharmais Cancer Hospital, and Cipto Mangunkusumo Hospital, have a significant responsibility to produce general practitioners and specialists capable of meeting the challenges of comprehensive cancer management as advocated by the WHO. Let us unite and work together to confront the various challenges in cancer care by realizing comprehensive cancer management as part of our efforts toward achieving Indonesia Emas 2045.

For the internal medicine specialization students of FKUI-RSCM whom I cherish, the overview of cancer issues in the world and Indonesia presented above serves as food for thought for us to prepare ourselves to address these challenges. There are numerous cancer cases managed in our beloved teaching hospitals. This provides us with a foundation to study cancer cases comprehensively. With this foundation, the internal medicine students of FKUI-RSCM should become internists with enhanced capabilities in the comprehensive management of cancer in the community, while also serving as catalysts for education and training at the primary care level.

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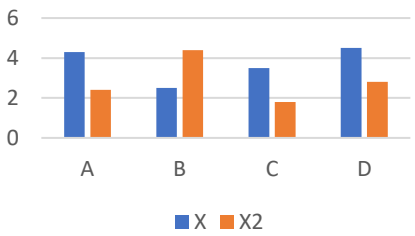

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