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

THE INDONESIAN JOURNAL OF CANCER CONTROL

Official Journal of The Indonesian Society of Oncology

InaJCC Vol.02 No.01 Page: 1-49

Jakarta, January – April 2022

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

THE INDONESIAN JOURNAL OF CANCER CONTROL

Official Journal of The Indonesian Society of Oncology

InaJCC Vol.02 No.01 Page: 1-49

Jakarta, January – April 2022

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.

All manuscripts published in The Indonesian Journal of Cancer Control are under the terms of the Creative Commons Attribution License. This permits anyone to copy, distribute, transmit and adapt the published work, provided the original work and source are appropriately cited.

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

THE INDONESIAN JOURNAL OF CANCER CONTROL

Official Journal of The Indonesian Society of Oncology

Volume 02 **Number 01, January – April 2022**

TABLE OF CONTENT

THE INDONESIAN JOURNAL OF CANCER CONTROL

Official Journal of The Indonesian Society of Oncology

Editorial Board

Person-in-Charge
Aru Wisaksono Sudoyo

Editor-in-Chief
Aida SD Hoemardani

Vice Editor-in-Chief
Evlina Suzanna

Editor
Elisna Syahruddin
Marlinda Adham
Demak Lumban Tobing
Edi Setiawan Tehuteru
Nadia A Mulansari Salim
Adityawati Ganggaiswari
Maria A Witjaksono
I Wayan Sudarsa
Solikhah
Dik Puspasari
Johan Kurnianda
Danang Tri Wahyudi

Journal Manager
Fadhli Aulia Mughni

Language Editor
Aru Wisaksono Sudoyo

Layout Editor
Ika Setiawati

Secretariat
Mutiara Inraw Stefani

Reviewers

Malcolm J Moore
Toh Han Chong
Kuniaki Ohara
Siti Boedina Kresno
Abdul Kadir
Zubairi Djoerban
Soehartati Gondhowiardjo
Arry Harryanto Reksodiputro
IB Tjakra Wibawa Manuaba
Septelia Inawati Wanandi
Andi Fachruddin
Cosphiadi Irawan
Laila Nuranna
Sigit Purbadi
Noorwati Sutandyo
Sonar Soni Panigoro
Nurjati Chairani Siregar

InaJCC The Indonesian Journal of Cancer Control

Editorial

Challenges and opportunities of palliative care

Advances in Medicine – its knowledge and technology – have brought about many benefits for cancer patients. Survival has, among other achievements, greatly increased. But has brought about a heightened responsibility in the care of patients who struggled during and after their treatments. And this is where palliative care, long a stepchild in Indonesia's medical world, will have to be taken more seriously. Patients who not so long ago have to accept a statistically short survival, are now showing up in clinics in ever-increasing numbers, taxing not only the medical staff's energy but time and funds.

Adham's article in this edition of our journal is a case in point. The collaborative efforts of several disciplines in medicine as shown in this article reveals the complexities of cancer care in this time and age. Not anymore that we see a purely clinical approach to a certain disease, but rather a changing landscape that evolves throughout a patient's journey with a rather ambiguous transition from physical to psychosocial.

In Indonesia, a country of more than 277 million people scattered over an archipelago of seventeen thousand islands and categorized as an "LMIC" or Low and Middle Income Country, palliative care faces a daunting challenge. Healthcare workers have to overcome a multitude of barrier, not the least of which a culturally-bound resistance towards palliation as an "endgame care" philosophy.

One of the solutions is education – both for doctors and patients. Another solution is shown in Adham's approach, in which palliative care is given and introduced to patients earlier in the disease. And this approach has a more tangible benefit which is a better quality of life as revealed in her article.

Palliative care is here to stay and it is not just the responsibility of the oncologist but the whole multidisciplinary team.

Aru W Sudoyo

InaJCC The Indonesian Journal of Cancer Control

Original Article

Prognostic value of tumor-infiltrating lymphocytes among HER-2+ breast cancer patients receiving trastuzumab-based adjuvant therapy

Diah A Safitri[1], Ahmad Ghozali[2], Johan Kurnianda[1]*

Check for updates

p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v1i2.47

Received: February 23, 2021
Accepted: March 25, 2022

Authors' affiliations:
[1]Division of Hematology-Medical Oncology, Department of Internal Medicine, Faculty of Medicine Public Health and Nursing Universitas Gadjah Mada / Dr Sardjito Hospital Yogyakarta
[2]Department of Anatomical Pathology, Faculty of Medicine Public Health and Nursing Universitas Gadjah Mada / Dr Sardjito Hospital Yogyakarta

Corresponding author:
Johan Kurnianda
E-mail: *johan.kurnianda@yahoo.com*

Abstract

Background: Tumor-infiltrating Lymphocytes (TILs) have prognostic value on HER2 positive breast cancer (BC). The absence of standardized method for evaluating TILs causes variations in results of previous studies. This study is performed to evaluate the prognostic value of TILs in HER2 positive BC treated with trastuzumab-based adjuvant therapy using standardized method recommended by the *International TILs Working Group*.
Aim: To analyze the prognostic value of TILs in HER2 positive BC patients receiving trastuzumab-based adjuvant therapy at Dr. Sardjito General Hospital, Yogyakarta and to analyze proportion differences between high TILs (≥30%) and low TILs (<30%).
Methods: This is a retrospective cohort study on HER2 positive, stage 1-3 BC patients who received trastuzumab-based adjuvant therapy. Histopathology slides from 6 hospitals/laboratories were analyzed by two pathologists.
Results: 73 data were available for analysis. TILs stroma <30% was 65,8% and most patients received combination of anthracyclines, taxanes and trastuzumab (67,1%). There was no difference of overall survival between high and low TILs (p log rank: 0,331).
Conclusion: The proportion of HER2 positive breast cancer with high TILs was lower than those with low TILs. HER2 positive BC with high TILs did not show better overall survival compared to those with low TILs. Our study did not support the theory that different TILs score has prognostic value in HER2 positive breast cancer. Since no formal recommendation for a clinically relevant TIL threshold has been given, further study with bigger samples and better concordance rate among pathologists should be done.

Keywords: *adjuvant, breast cancer, HER2, trastuzumab, tumor-infiltrating lymphocytes*

Abstrak

Latar Belakang: *Tumor-infiltrating Lymphocytes (TILs)* pada penderita kanker payudara HER2 positif mempunyai nilai prognostik. Belum adanya metode penilaian TILs yang terstandarisasi menyebabkan hasil penelitian sebelumnya bervariasi. Penelitian ini dilakukan untuk mengetahui nilai prognostik TILs pada kanker payudara HER2 positif yang mendapat terapi adjuvan berbasis trastuzumab dengan menggunakan metode yang telah distandardisasi International TILs Working Group.
Tujuan: Menganalisis nilai prognostik TILs pada penderita kanker payudara HER2+ yang mendapatkan terapi adjuvan berbasis trastuzumab di RSUP Dr. Sardjito Yogyakarta serta menilai perbedaan proporsi antara penderita kanker payudara HER2 positif dengan TILs tinggi (≥30%) dan penderita kanker payudara HER2 positif dengan TILs rendah (<30%).
Metode: Penelitian ini adalah penelitian kohort retrospektif yang dilakukan terhadap data pasien kanker payudara HER2 positif stadium 1-3 yang mendapat terapi adjuvan trastusumab, dengan slide histopatologi yang lengkap yang didapat dari 6 lokasi RS/laboratorium dan dianalisis oleh 2 ahli patologi anatomi.
Hasil: Dari 73 data yang dianalisis, terdapat 65,8% TILs stroma <30% dan sebagian besar pasien mendapat emoterapi dengan kombinasi antrasiklin, taxan dan trastuzumab (67,1%). Tidak terdapat perbedaan angka ketahanan hidup antara penderita dengan TILs tinggi dibanding TILs rendah (p log rank: 0,331).
Kesimpulan: Proporsi penderita kanker payudara HER 2 positif dengan TILs tinggi lebih kecil dibandingkan proporsi penderita kanker payudara HER 2 positif dengan TILs rendah. Penderita kanker payudara HER2 positif dengan TILs yang tinggi tidak memiliki angka ketahanan hidup yang lebih baik dibandingkan dengan penderita kanker payudara HER2 positif dengan TILs yang rendah. Saat ini belum ada ambang nilai TILs yang direkomendasikan, sehingga diperlukan penelitian lanjut dengan jumlah sampel yang lebih besar dan tingkat kesepakatan antar ahli patologi yang lebih baik.

Kata kunci: *ajuvan, HER2, kanker payudara, trastuzumab, tumor-infiltrating lymphocytes*

Background

Breast cancer (BC) is a heterogenous disease with multiple subtypes. Clinically, classification of BC is determined by expression of 3 biomarkers, i.e. estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth 2 (HER2). Breast cancer with negative ER, PR, and HER2 is called triple negative breast cancer (TNBC) and it accounts for 15-20% of all new cases.[1] In 20-30% of BC, there is amplification of HER2 resulting in overexpression of HER2. Long before an effective anti-HER2 treatment was discovered, this pattern was associated with more aggressive disease with worse prognosis.[2]

Trastuzumab-based adjuvant chemotherapy is still a treatment of choice for HER2 positive invasive BC, either with positive ER/PR or negative ER/PR. The recommended regimen usually contains of combination of trastuzumab and taxane, or trastuzumab, anthracycline, and taxane[3]. The use of anthracycline and taxane in adjuvant chemotherapy also give benefit to survival. The additional of trastuzumab in adjuvant chemotherapy regimen decreases risk in recurrence if it is administered both simultaneously and consecutively. Trastuzumab that is administered for a year is more effective than 6 months. Two years administration of trastuzumab is not more effective than one-year administration.[4]

Tumor infiltrating lymphocytes (TILs) plays the main role in response to cancer cells so that TILs might be the main marker of immune balance of host and tumor.[5] TILs consist all mononuclear cells (including lymphocyte and plasma cell) that are found in tumor tissue.[6] According to its infiltration site, TILs are classified into intratumor TILs and stroma TILs.[7]

TILs are related to improvement of survival in various kind of cancer. This shows that TILs play a role in antitumor immunity.[8,9,10] Some studies have also shown that high level of TILs in BC could predict better response after neoadjuvant chemotherapy.[6,10] High level of TILs is also able to give prognostic value. Triple negative BC and HER2 positive BC with high TILs show a better survival.[6,11]

However, the prognostic and predictive value of TILs are found inconsistent and there is no exact examination method for TILs.[5] Lately, there is a standardized approach that is recommended by international panel to assess TILs on routine histopathology slide as biomarker of BC.[12].

Methods

This is a retrospective cohort on HER2 positive breast cancer patients in Dr. Sardjito Hospital, Yogyakarta. Patients with stage 1-3 (T1-4/N0-3/M0) that received adjuvant trastuzumab and were diagnosed in 2007-2015 period with complete clinical and histopathological data were enrolled to this study while patient with stage 4 and incomplete data were excluded from this study. The ethical clearance of this study was obtained from the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Gadjah Mada University – Dr. Sardjito Hospital with approval letter number: KE/FK/409/EC/2016.

Collection of clinical data was performed as the development of organ specific cancer registry in Dr. Sardjito Hospital for period of 2007-2015 and was continued by 1-year follow-up. Collection and selection of histopathology slide and parafin block were performed at Pathology Department of Dr. Sardjito Hospital, Faculty of Medicine Universitas Gadjah Mada, Waskitha Laboratorium Yogyakarta, Cito Laboratorium, Panti Rapih Hospital, and Bethesda Hospital. TILs calculation was performed at Pathology Department of Dr. Sardjito Hospital.

Minimum sample size is 60 samples. TILs were assessed with hematoxilin-eosin staining. The analysis of breast tissue was performed blindly by two pathologists from Pathology Department Dr. Sardjito Hospital. The mean of those assessment was analyzed. The expected coefficient of Spearman correlation is more than 0.60.

HER2 positive BC is diagnosed clinically and pathologically as breast cancer with HER2 +3 from immunohistochemistry examination. TNM staging is assessed based on American Joint Committee on Cancer (AJCC) criteria for patient's pathology report after surgery. The trastuzumab-based regimen consists of trastuzumab (H) in combination with anthracycline (A), cyclophosphamide (C), platinum (P), taxane (T), 5-fluorouracil (F), and methotrexate (M). The combination that had been used i.e., AC-TH, FAC-TH, CMF-TH, TCH, TPH, AT-H, AC-H, CAF-H, and TAC-H.

Numeric data is described in mean ± standard deviation (SD) or median with range of minimum to maximum value. Chi-square test or Fisher's exact test is used to analyze categorical data to compare all parameters to clinicopathological parameter. Overall survival is analyzed using Kaplan Meier method

continued by log-rank test to analyze the significance of difference. Univariate and multivariate analysis is performed with Cox's proportional hazards model to determine hazard ratio (HR) with 95% confidence interval.

Results

We collected 73 patients that met the inclusion criteria. The patient's age range was 27-74 years old with median age of 50 years old. Population of study subjects was dominated by those with age of ≥ 40 years old (87,7%), N0-1 (75%), negative ER and PR status (81,9%), degree of histology 3 (68%), and stroma TILs <30% (65,8%). The most administered chemotherapy regimen was combination of anthracycline, taxane, and trastuzumab (67,1%) (Table 1). The pathology slide that was eligible for assessment was from 2009-2015 period.

Table 1. Baseline characteristics of HER2+ breast cancer subjects

Parameter		N	(%)
Age (year), median, range	50 (27-74)		
Age when diagnosed (n=73)	• <40 years old	9	12,3%
	• ≥40 years old	64	87,7%
Tumor size (n=70)	• T ≤ 5 cm	31	44,3%
	• T > 5cm	39	55,7%
Nodal (n=60)	• N0-N1	45	75,0%
	• N2-N3	15	25,0%
ER/PR (n=72)	• negative	59	81,9%
	• positive (+/+, +/-, or -/+)	13	18,1%
Histological feature (n=71)	• Non-ductal	5	7,0%
	• Ductal	66	93,0%
Histological grade (n=50)	• 1-2	16	32,0%
	• 3	34	68,0%
TILs stroma (n=73)	• <30%	48	65,8%
	• ≥30%	25	34,2%
Chemotherapy type (in combination with trastuzumab) (n=73)	• antracycline and taxane combination	49	67,1%
	• other than antra cycline and taxane combination	24	32,9%

Coefficient of Spearman correlation from two pathologists showed that there was significant yet weak correlation (0,354; p=0,003) even though an international guideline to equalize technique and TILs reading had been used.

Most of study subjects were diagnosed as BC at the age of ≥ 40 years old (87,7%). Most of study subjects had T >5 cm and 75% of subjects had N0-N1. In this study most samples had poor histology profiles (68%) with invasive ductal carcinoma dominated the samples (93%).

The proportion of HER2 positive BC with TILs ≥30% in this study was higher than the previous study accounting for 34,2% of cases and the clinicopathological parameters based on TILs level is shown in Table 2. Some of TILs level in this study are shown in picture 1,2, and 3. Most of subjects in this study received combination of anthracycline, taxane, and trastuzumab.

Table 2. Clinicopathological parameters based on TILs level

Variables		TILs		p*
		<30%	≥30%	
Age when diagnosed (n=73)	• <40 years old	9	0	0,017*
	• ≥40 years old	39	25	
Tumor size (n=70)	• T ≤ 5 cm	19	12	0,329*
	• T > 5cm	27	12	
Nodal (n=60)	• N0-N1	29	16	0,093*
	• N2-N3	13	2	
ER/PR (n=72)	• negative	38	21	0,301*
	• positive (+/+, +/-, or -/+)	10	3	
Histological feature (n=71)	• Non-ductal	4	1	0,419*
	• Ductal	42	24	
Histological grade (n=50)	• 1-2	11	5	0,291*
	• 3	19	15	
Chemotherapy type (in combination with trastuzumab) (n=73)	• antracycline and taxane combination	35	14	0,116*
	• other than antracycline and taxane combination	13	11	

*Fisher exact test

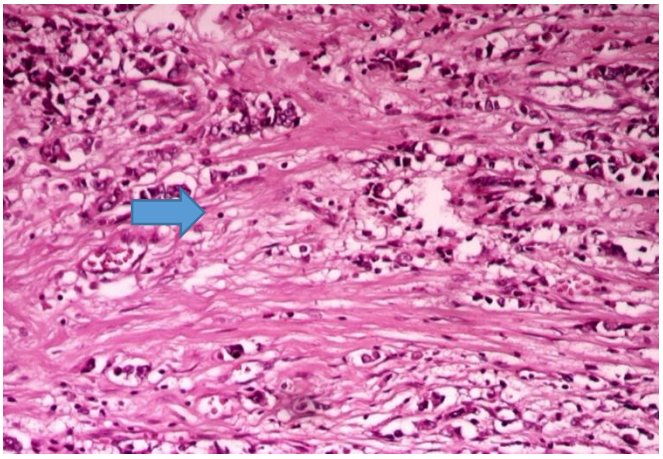


Figure 1. A hematoxylin and eosin (H&E) stained histopathology slide of a breast cancer under a microscope, showing 5% tumor-infiltrating lymphocytes (TILs) in the stromal area.

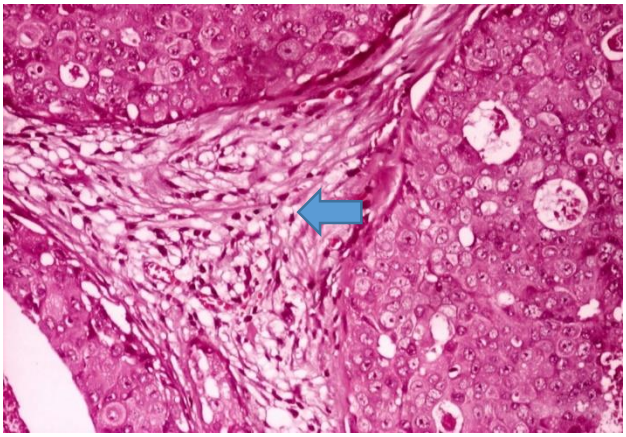


Figure 2. A H&E stained slide of breast cancer, showing 40% stromal tumor-infiltrating lymphocytes (TILs).

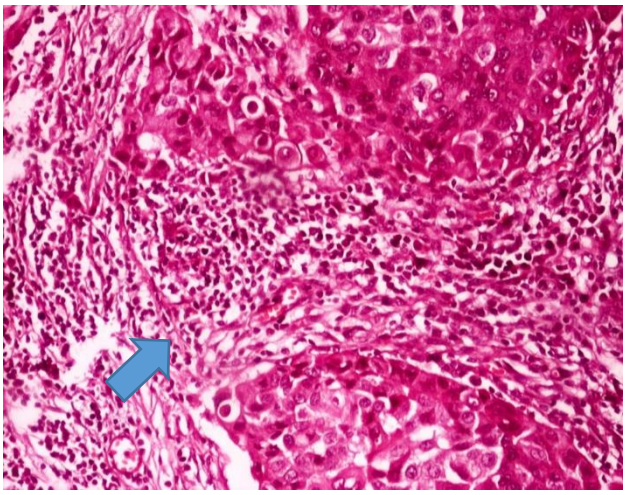


Figure 3. A H&E stained slide of breast cancer with high stromal TILs (80%). Almost all stroma was covered with inflammatory cells.

Follow-up was performed in range of 8,03 to 97,17 months with median of 38,52 months. Subjects with high TILs showed no difference in survival rate to low TILs (p log rank= 0,331) (Figure 4). This result is not consistent with this study's hypothesis.

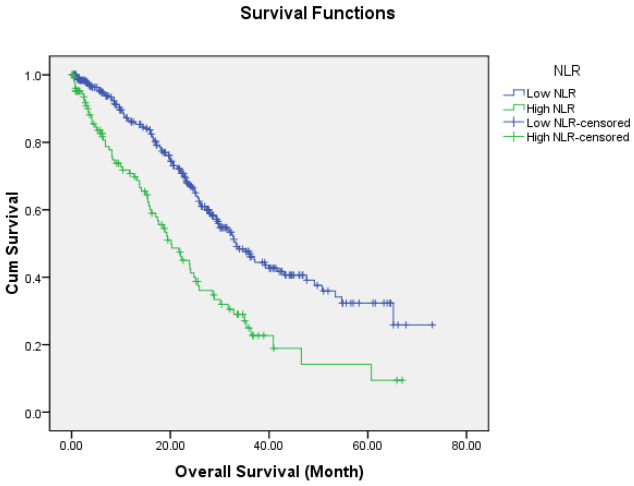


Figure 4. Overall survival of HER2+ breast cancer based on TILs level.

Discussion

The role of infiltrating immune cells is to control tumor growth and progression. However, infiltrating immune cells can also help to create an immunosuppressive environment in which the tumor can thrive.[13]

Even though there is a standardized approach on how to assess TILs on routine histopathology slide, heterogenous TILs' characteristics still might cause variability among assessors.[12,14]

Heterogenity in lymphocyte distribution, technical slide-related issues, scoring outside the tumor boundary, tumors with minimal assessable stroma, lymphocytes associated with other structures, and including other inflammatory cells also may lead to discordant sTIL assessment. [14]

There is no difference between high TILs and low TILs group based on clinicopathology factor (tumor size, nodal status, ER/PR, histology type, histology degree, and ductal or non-ductal carcinoma) and treatment regimen, except for age at first diagnosis.

Our study showed that most subjects were diagnosed at the age of of ≥ 40 years old and is consistent with previous studies that showed that BC at young age rarely occurred. Around 6,6% of BC was diagnosed in women at the age of < 40 years old, 2,4% at the age of < 35 years old, and 0,65% at the age of < 30 years old.[15]

Our study showed that invasive ductal carcinoma dominated the samples (93%) and supports a study done in Dr. Cipto Mangunkusumo Hospital which showed that 89,14% of 515 cases was invasive ductal carcinoma.[16]

The proportion of HER2 positive BC with TILs ≥30% in this study was higher than the previous study accounting for 34,2% of cases. The proportion of HER2 positive/ER negative BC and HER2 luminal B BC were 21% and 8% respectively on a study by Ohtani et al.[8] In another study by Liu et al. the proportion of HER2 positive BC patients was 31%.[17] However, there has not been any formal recommendation for a clinically relevant TIL threshold.[13]

Table 3. Univariate analysis for prognostic factors in HER2+ breast cancer

Parameters	*Hazard ratio*	CI 95%	p value
TILs stroma			
• <30%	1,597	0,615-4,143	0,336
• ≥30%			
Age			
• < 40 years old	0,994	0,227-4,351	0,993
• ≥ 40 years old			
Tumor size			
• T ≤ 5 cm	1,406	0,521-3,791	0,501
• T > 5cm			
Nodal			
• N0-N1	1,406	0,768-2,576	0,269
• N2-N3			
Hormonal status			
• negative	0,270	0,036-2,035	0,204
• positive			
Histological feature			
• non-ductal	0,646	0,147-2,845	0,564
• ductal			
Histological grade			
• 1-2	0,939	0,224-3,939	0,931
• 3			
Chemotherapy type (in combination with trastuzumab)			
• antracycline and taxane combination	1,125	0,411-3,074	0,819
• other than antra-cycline and taxane combination			

We carried out a univariate analysis for prognostic factors in HER2+ breast cancer to investigate the relationship between TILs stroma and prognosis. The result showed non-significant relationship (p: 0,336) (Table 3). Our study showed that higher TILs level (≥30%) did not relate to a better overall survival of HER2+ breast cancer subjects as shown in Figure 4.

Consistent to our study, some studies had shown that higher TILs level in stroma around tumor was not related to better prognosis in HER2 positive BC.[11,18-20] FinHER trial showed that associations between TILs and good prognosis was observed in the TNBC but not in luminal or HER2+ subtypes. However, in this study, TILs were measured as a continuous variable. Each 10% increase in TILs was associated with 13% reduction in the relative risk of distant recurrence, but there was no statistical significance observed for overall survival (OS) likely due to the small number of events observed.[11] The BIG 02-98 study showed that there was no significant prognostic effect in the global population, in those with ER positive/HER2 negative disease, or in the HER2 positive subgroup. In contrast, for the ER negative/ HER2 negative BC subtype, TILs were strongly for both disease free survival (DFS) and OS.[18] In a study by Hida et al., TILs score was classified as low (<10 %), intermediate (10–50 %), and high (>50 %) based on the area infiltrated by lymphocytes within the tumor itself plus the adjacent stroma. TILs proved to have significant prognostic value regarding relapse-free survival (RFS) in TNBC, but not among HER2+ BCs.[20]

A meta-analysis from 17 studies that evaluated level of TILs and prognostic parameter for BC revealed that high TILs were not correlated with clinicopathology of BC even though some subtypes could be correlated. Positive PD-1 T cell subtype was linked to high tumor grade, big tumor size, positive lymph node, negative hormonal receptor status, and HER2 status.[21]

Univariate analysis in various prognostic values showed that there was no significant correlation to death risk in stroma TILs ≥30% group compared to those with <30% of stroma TILs (HR 1,597; p=0,336; 95% IK 0,615-4,143). Age, tumor size, hormonal status, nodal status, histology type and degree were also not correlated with death risk (Table 3).

This result is not consistent with the previous studies probably due to the difference of setting (neoadjuvant vs adjuvant), TILs cut-off, molecular subtypes, tumor

microenvironment, the choice of general or subset TILs, and amplification level of HER2.[10,22,23]

However, this current study supports the study result of Hida et al. which was performed in both adjuvant and neoadjuvant setting. TILs proved to have significant prognostic value in TNBC, but not among HER2 positive BC.[20] The similar result was also stated by N9831 study in which the prognostic value of LPBC was only found in HER2+ breast cancer that received chemotherapy only instead of trastuzumab-based chemotherapy.[19] Gene expression analysis using FinHER sample showed that IDO1 and CXCL13 were strongly associated with TILs. Even though the immune gene that is related to HER2+ breast cancer prognosis has not been found yet, the high level of PD-1 and IDO1 that is associated to the benefit of trastuzumab for DFS showed that trastuzumab could modulate the micro-environment of immune system.[24]

Furthermore, CLEOPATRA study showed that anti-tumor immunity was still going on in advanced breast cancer setting (recurrent, unresectable, or metastatic). In advanced HER2+ breast cancer, high TILs is associated with increased survival.[25] On the other hand, Kotoula et al. showed that primary metastatic HER2+ breast cancer had low TILs and was not associated with the end result but it was enriched by mutations that changed the characteristic of amino acid. Metastatic breast cancer, especially de novo, with hydrophobic mutation did not show any benefit of trastuzumab administration.[26]

One study by Ohtani et al. involved all subtypes of breast cancer while our study only included HER2+ breast cancer.[10] Miyan et al. reported that every molecular subtype is generally characterized by T cell infiltration instead of specific phenotype infiltration. There is difference of immune response among the molecular subtypes of breast cancer. The luminal subtypes were marked by low immune response showing negative or weak presentation of lymphocytic host response (LHR). Non-luminal subtypes (ER -) showed a prominent immune response presented by either moderate or strong presentation of LHR.[27]

The quality and quantity of immune response could be influenced by a lot of factors in the microenvironment of tumor and lymph node, e.g. cytokines and chemokines that will affect the cell types through its function, nutrients availability, oxygen, and lactate.[25,26] Any difficulty in controlling microenvironment could affect study result. The difference of tumor microenvironment according to the molecular subtypes could be shown by the difference of stroma lymphocyte score marked by CD3 and the difference in CD8+ density, FOXP3+, ζ–*chain*+, and CD3+.[27,30]

TILs subset CD3+, CD4+, and CD8+ have prognostic value and high score is associated with better survival.[31-33] On the other hand, other immune cells, as of macrophage and FOXP3+ Tregs, facilitate and increase carcinogenesis and tumor growth. FOXP3+ Tregs is potential to suppress T cells by suppressing antitumor immunity that is caused by T cells CD4+, CD8+, dendritic cells, and NK cells.[23] The prognostic value of TILs FOXP3+ in breast cancer is affected by the expression status of ER, HER2, and the infiltration of T cell CD8+. TILs subset FOXP3+ is the bad prognostic indicator for ER+ breast cancer but in the HER2+/ER- subtype breast cancer, it acts as good prognostic indicator.[34] In this study, the analysis was performed on both ER/PR negative and positive breast cancer. Most of the subjects (80,8%) had negative ER/PR while the rest were ER+/PR+, ER+/PR-, and ER-/PR+.

The benefit of Trastuzumab in HER2+ breast cancer is not always achieved despite of its role as the standard treatment. Xu et al. showed that the amplification level of HER2 is correlated to pathological complete response (pCR).[35] However, TILs level is not associated with the response towards trastuzumab in locally advanced HER2+ breast cancer.[35]

Conclusion

Our study did not support the theory that TILs have prognostic value on HER2 positive breast cancer. The classification into high or low TILs did not show any difference in the survival of HER2 positive breast cancer patients. Since no formal recommendation for a clinically relevant TILs threshold has been given, further study with bigger samples and better concordance rate among pathologists should be done.

Conflict of Interest

The authors have no conflict of interest to declare.

References

1. Stagg J, Allard B. Immunotherapeutic approaches in triple-negative breast cancer: Latest research and clinical prospects. Ther Adv Med Oncol. 2013;5:169–81.

2. Brown-Glaberman U, Dayao Z, Royce M. HER2-targeted therapy for early-stage breast cancer : A comprehensive review. Oncology [Internet]. 2014;28(4). Available from: https://www.cancernetwork.com/view/her2-targeted-therapy-early-stage-breast-cancer-comprehensive-review
3. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. Breast Cancer. NCCN Guidelines. 2016
4. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: An overview. BMC medicine. 2015;13:195.
5. García-Martínez E, Gil G, Benito A, González-Billalabeitia E, Conesa M, García T, et al. Tumor-infiltrating immune cell profiles and their change after neoadjuvant chemotherapy predict response and prognosis of breast cancer. Breast Cancer Res. 2014;16:488.
6. Salgado R, Denkert C, Campbell C, Savas P, Nuciforo P, Aura C, et al. Tumor-infiltrating lymphocytes and associations with pathological complete response and event-free survival in HER2-positive early-stage breast cancer treated with lapatinib and trastuzumab. JAMA Oncol. 2015;1(4):448–55.
7. Mao Y, Qu Q, Zhang Y, Liu J, Chen X, Shen K. The value of tumor infiltrating lymphocytes (TILs) for predicting response to neoadjuvant chemotherapy in breast cancer: A systematic review and meta-analysis. PLOS ONE. 2014;9(12):e115103.
8. Zhang L, Conejo-Garcia JR, Katsaros D, Gimotty PA, Massobrio M, Regnani G, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med. 2003;348(3):203–13.
9. Kondratiev S, Sabo E, Yakirevich E, Lavie O, Resnick MB. Intratumoral CD8+ T lymphocytes as a prognostic factor of survival in endometrial carcinoma. Clin Cancer Res. 2004;10:4450–6.
10. Ohtani H, Mori-Shiraishi K, Nakajima M, Ueki H. Defining lymphocyte-predominant breast cancer by the proportion of lymphocyte-rich stroma and its significance in routine histopathological diagnosis. Pathol Int. 2015;65:644–51.
11. Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: Results from the FinHER trial. Ann Oncol. 2014;25(8):1544–50.
12. Salgado R, Denkert C, Demaria N, Sirtaine F, Klauschen G, Pruneri S, et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: Recommendations by an International TILs Working Group 2014. Ann Oncol. 2015;26:259–71.
13. Hendry S, Salgado R, Gevaert T, Russell PA, John T, Thapa B, et al. Assessing Tumor-infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immunooncology Biomarkers Working Group: Part 1: Assessing the Host Immune Response, TILs in Invasive Breast Carcinoma and Ductal Carcinoma in Situ, Metastatic Tumor Deposits and Areas for Further Research. Vol. 24, Advances in Anatomic Pathology. Lippincott Williams and Wilkins; 2017. p. 235–51.
14. Kos Z, Roblin E, Kim RS, Michiels S, Gallas BD, Chen W, et al. Pitfalls in assessing stromal tumor infiltrating lymphocytes (sTILs) in breast cancer. NPJ Breast Cancer. 2020 Dec 1;6(1).
15. Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS. Epidemiology and prognosis of breast cancer in young women. J Thorac Dis. 2013;5(S1):S2–8.
16. Tjahjadi G, Sakamoto G, Thindarbumi D, Watanabe S, Prihartono J, Ohno Y, et al. Pathological aspects of breast cancer in Indonesian females, applying a modified WHO classification. A joint study between Indonesia and Japan. Med J Indones. 1999;8:102–8.
17. Liu S, Duan X, Xu L, Xin L, Cheng Y, Liu Q, et al. Optimal threshold for stromal tumor-infiltrating lymphocytes: its predictive and prognostic value in HER2-positive breast cancer treated with trastuzumab-based neoadjuvant chemotherapy. Breast Cancer Res Treat. 2015 Nov 1;154(2):239–49.
18. Loi S, Sirtaine N, Piette F, Salgado R, Viale G, van Eenoo F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol. 2013;31(7):860–7.
19. Perez EA, Ballman KV, Tenner KS, Thompson EA, Badve SS, Bailey H, et al. Association of stromal tumor-infiltrating lymphocytes with recurrence-free survival in the N9831 adjuvant trial in patients with early-stage HER2-positive breast cancer. JAMA Oncol. 2016;2(1):56–64.
20. Hida AI, Sagara Y, Yotsumoto D, Kanemitsu S, Kawano J, Baba S, et al. Prognostic and predictive impacts of tumor-infiltrating lymphocytes differ between Triple-negative and HER2-positive breast cancers treated with standard systemic therapies. Breast Cancer Res Treat. 2016;158:1–9.
21. Yu X, Zhang Z, Wang Z, Wu P, Qiu F, Huang J. Prognostic and predictive value of tumor-infiltrating lymphocytes in breast cancer: A systematic review and meta-analysis. Clin Transl Oncol. 2016;18:497–506.
22. Denkert C, Loibl S, Noske A, Roller M, Müller BM, Komor M, et al. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol. 2010;28(1):105–13.
23. Mao Y, Qu Q, Chen X, Huang O, Wu J, Shen K. The prognostic value of tumor-infiltrating lymphocytes in breast cancer: A systematic review and meta-analysis. PLOS ONE. 2016;11(4):e0152500.
24. Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, et al. Tumor infiltrating lymphocytes (TILs) indicate trastuzumab benefit in early-stage HER2-positive breast cancer (HER2+ BC). Cancer Research [Internet]. 2013 Dec 15;73(24 Suppl):Abstract S1-05. Available from: http://cancerres.aacrjournals.org/content/73/24_Supplement/S1-05.abstract
25. Luen S, Salgado R, Fox S, Savas P, Eng-Wong J, Clark E, et al. Tumour-infiltrating lymphocytes in advanced HER2-positive breast cancer treated with pertuzumab

or placebo in addition to trastuzumab and docetaxel: A retrospective analysis of the CLEOPATRA study. Lancet Oncol. 2017;18(1):52–62.
26. Kotoula V, Giannoulatou E, Alexopoulou Z, Karavasilis V, Kotsakis A, Dionysopoulos D, et al. Tumor infiltrating lymphocytes and hydrophobic amino acid changes in HER2-positive metastatic breast cancer. J Clin Oncol. 2016;34(15 Suppl):592.
27. Miyan M, Schmidt-Mende J, Kiessling R, Poschke I, de Boniface J, Ferlay J, et al. Differential tumor infiltration by T-cells characterizes intrinsic molecular subtypes in breast cancer. J Transl Med. 2016;14:227.
28. Dunn GP, Old LJ, Schreiber RD. The three es of cancer immunoediting. Annu Rev Immunol. 2004;22:329–60.
29. Hadrup S, Donia M, Thor Straten P. Effector CD4 and CD8 T cells and their role in the tumor microenvironment. Cancer Microenviron. 2013;6(2):123–33.
30. Mohammed NA, Ali SA, Saleh SM, Abood AS. Breast cancer: CD3+ tumor infiltrating lymphocytes differences among molecular subtypes. Int J Sci Eng Res. 2014;5(7):790–3.
31. Rathore AS, Kumar S, Konwar R, Makker A, Negi MPS, Goel MM. CD3+, CD4+ & CD8+ tumour infiltrating lymphocytes (TILs) are predictors of favourable survival outcome in infiltrating ductal carcinoma of breast. Indian J Med Res. 2014;140:361–9.
32. Mahmoud SM, Paish EC, Powe DG, Macmillan RD, Grainge MJ, Lee AH, et al. Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. J Clin Oncol. 2011;29:1949–55.
33. Ali HR, Provenzano E, Dawson SJ, Blows FM, Liu B, Shah M, et al. Association between CD8+ T-cell infiltration and breast cancer survival in 12 439 patients. Ann Oncol. 2014;25:1536–43.
34. Liu S, Foulkes WD, Leung S, Gao D, Lau S, Kos Z, et al. Prognostic significance of FOXP3+ tumor-infiltrating lymphocytes in breast cancer depends on estrogen receptor and human epidermal growth factor receptor-2 expression status and concurrent cytotoxic T-cell infiltration. Breast Cancer Res. 2014;16:423.
35. Xu Q, Pan B, Wang C, Zhou Y, Mao F, Lin Y, et al. HER2 amplification level is not a prognostic factor for HER2- positive breast cancer with trastuzumab-based adjuvant treatment: A systematic review and meta-analysis. Oncotarget. 2016;7(39).
36. Masini C, Bisagni G, Ragazzi M, Bisagni A, Dallaglio K, Falco G, et al. HER2-amplification level and tumor-infiltrating lymphocytes in breast cancer patients treated with neoadjuvant trastuzumab. J Clin Oncol. 2016;34(15 Suppl):596.

InaJCC The Indonesian Journal of Cancer Control

Original Article

Correlation between chemotherapy cycles and performance status based on ECOG in non-small cell lung cancer patients

Novita Andayani[1], Diana F Syafni[2], Mirfandi Amirsyah[2], Yunita Arliny[1], Rima Novirianthy[2], Murtaza[1]

Check for updates

p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v2i1.62

Received: April 26, 2021
Accepted: April 28, 2022

Authors' affiliations:
[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Syiah Kuala-Regional General Hospital, dr. Zainoel Abidin Banda Aceh
[2]Faculty of Medicine, Universitas Syiah Kuala

Corresponding author:
Novita Andayani
Email: novi@unsyiah.ac.id

Abstract

Background: Tumor-infiltrating Lymphocytes (TILs) have prognostic value on HER2 positive breast cancer (BC). The absence of standardized method for evaluating TILs causes variations in results of previous studies. This study is performed to evaluate the prognostic value of TILs in HER2 positive BC treated with trastuzumab-based adjuvant therapy using standardized method recommended by the *International TILs Working Group*.
Aim: To analyze the prognostic value of TILs in HER2 positive BC patients receiving trastuzumab-based adjuvant therapy at Dr. Sardjito General Hospital, Yogyakarta and to analyze proportion differences between high TILs (≥30%) and low TILs (<30%).
Methods: This is a retrospective cohort study on HER2 positive, stage 1-3 BC patients who received trastuzumab-based adjuvant therapy. Histopathology slides from 6 hospitals/laboratories were analyzed by two pathologists.
Results: 73 data were available for analysis. TILs stroma <30% was 65,8% and most patients received combination of anthracyclines, taxanes and trastuzumab (67,1%). There was no difference of overall survival between high and low TILs (p log rank: 0,331).
Conclusion: The proportion of HER2 positive breast cancer with high TILs was lower than those with low TILs. HER2 positive BC with high TILs did not show better overall survival compared to those with low TILs. Our study did not support the theory that different TILs score has prognostic value in HER2 positive breast cancer. Since no formal recommendation for a clinically relevant TIL threshold has been given, further study with bigger samples and better concordance rate among pathologists should be done.

Keywords: *adjuvant, breast cancer, HER2, trastuzumab, tumor-infiltrating lymphocytes*

Abstrak

Latar belakang: Prevalensi kejadian kanker paru adalah 14,3% pada laki-laki dan 8,4% pada perempuan. Rokok merupakan salah satu penyebab kanker paru. Dan kemoterapi merupakan tatalaksana lanjutan pada KPKBSK dan berpengaruh pada *performance status* pasien.
Tujuan: Penelitian ini bertujuan untuk mengetahui hubungan siklus kemoterapi terhadap *performance status* berdasarkan ECOG pada pasien kanker paru jenis karsinoma bukan sel kecil (KPKBSK) di RSUD dr. Zainoel Abidin Banda Aceh tahun 2017-2020.
Metode: Ini merupakan penelitian analitik observasional dengan desain *cross sectional*. Dengan *total sampling*. Dan data bersumber dari rekam medis sebanyak 164 subjek.
Hasil: Hasil penelitian menunjukkan 57% pasien KPKBSK setelah kemoterapi menunjukkan *performance status* yang stabil, sedangkan 41% menurun. Karboplatin + paclitaxel merupakan regimen yang paling banyak digunakan (43%), dengan rata-rata PFS < 1 tahun dan OS < 2 tahun.
Kesimpulan: Berdasarkan analisa bivariat dengan menggunakan metode spearman, didapatkan nilai p < 0,05 dengan nilai R 0,367 yang menandakan terdapat hubungan antara jumlah siklus kemoterapi terhadap *performance status* berdasarkan ECOG pada pasien KPKBSK di RSUD dr. Zainoel Abidin dengan koefisien korelasi rendah.

Kata Kunci*: kanker paru karsinoma bukan sel kecil, performance status, siklus kemoterapi.*

Background

Lung cancer is the main malignancy in the world which has a large proportion (11.4%) along with breast cancer (11.7%), colorectal cancer (10 %), prostate cancer (7.3%), and abdominal cancer (5.6%).[1] With a comparison of the incidence of lung cancer in men by 14.3% and in women by 8.4%.[2] Apart from that, lung cancer in Indonesia is also one of the highest causes of death from cancer. From WHO data in 2020, it was found that the total incidence of lung cancer was 34,783 cases (8.8%) which was dominated by men as many as 25,943 cases of lung cancer.[3] In the province of Aceh itself, there was an increase in the incidence of cancer from 2013 which was around 1.3% to 2% in 2018.[4]

Various risk factors have been studied in determining the prognosis of lung cancer, one of which is smoking. Active smokers and passive smokers can also get harmful carcinogenic effects from cigarette smoke. In addition, age, genetics, occupation, delay in diagnosis and low response of cancer cells to available cytostatic drugs are the main reasons for the poor prognosis of lung cancer.[5,6]

In addition to the speed and accuracy of diagnosis, the management of the patient is very important to note. Actions taken in lung cancer patients in the form of chemotherapy.[7] Chemotherapy is the main treatment for small cell carcinoma and advanced treatment for non-small cell carcinoma. Chemotherapy is one type of treatment used in lung cancer patients. Chemotherapy is carried out to kill cancer cells with anti-cancer drugs which must be evaluated after two to three cycles of chemotherapy or even four to six cycles with a distance of each cycle is 21 to 28 days and before doing chemotherapy the doctor must confirm the histology of the cancer cells whether small cell carcinoma or non-small cell carcinoma (NSCLC).[8] Chemotherapy has side effects that can be in the form of a worsening of the biological, physical, social status, functional status of the patient and the *performance status of the* patient.[7]

Information regarding the relationship between chemo-therapy cycles and performance status based on ECOG in non-small cell carcinoma (NSCLC) lung cancer patients at dr. Zainoel Abidin Banda Aceh is not widely known. In Aceh Province itself, especially at the Regional General Hospital, dr. Zainoel Abidin Banda Aceh which is a regional referral hospital, information about the relationship between chemotherapy cycles and performance status based on ECOG in non-small cell carcinoma (NSCLC) lung cancer patients at dr. Zainoel Abidin Banda Aceh is not widely known because no research has been done on this relationship. Based on the background described above, the researchers to examine the relationship between chemotherapy cycles and performance status based on ECOG in non-small cell carcinoma (NSCLC) lung cancer patients at dr. Zainoel Abidin Banda Aceh in 2017-2020.

Methods

This research is an analytic observational with a cross sectional design. This study looked at the correlation between the number of chemotherapy cycles and the performance status of lung cancer patients with non-small cell carcinoma in RSUD dr. Zainoel Abidin Banda Aceh Year 2017-2020. The research data collection was carried out from September 2 to September 17, 2021.

The sample population in this study were lung cancer patients with non-small cell carcinoma and undergoing chemotherapy at RSUD dr. Zainoel Abidin. The sample in this study was selected by the method, non-probability sampling namely total sampling. The data used in this study is secondary data using patient medical records.

Data analysis was carried out univariate and bivariate. Univariate analysis was carried out on variables from the results of the study resulting in the frequency distribution of each variable studied including age, gender, diagnosis, TNM staging, lung cancer stage, cycles the patient go through, performance status of the patient for each cycle undertaken, and the chemotherapy regimen used. Meanwhile, bivariate analysis was used to assess the correlation between the number of chemotherapy cycle the patient go through and the patient's performance status which would be proven using the statistical test *Spearman Rank* ($p<0.05$).

Results

Based on research that has been conducted using secondary data in the form of patient medical records, it was found that a total of 164 patients with non-small cell carcinoma who go through chemotherapy met the inclusion and exclusion criteria.

Patient Characteristics

Based on the results of the study, the frequency distribution of the characteristics of research subjects based on age and gender can be seen in table 1.

Table 1. Characteristics of Non-small Cell Lung Cancer Patients (N=164).

	N	%
Gender		
Male	139	85%
Female	25	15%
Age (Years)		
<30	5	3.04
31-40	7	4.26
41-50	25	15.24
51-60	69	42.08
61-70	43	26.22
>70	15	9.16

Characteristics of lung cancer patients with non-small cell carcinoma by age found that the highest number of study subjects was aged >40 years, namely 152 patients with a percentage of 92.7% with the most age range being 51-60 years, namely 69 subjects (42%).

Based on gender, it was found that the male sex occupied more than half of the total number of subjects, namely 85% or as many as 139 patients. This is thought to occur due to the high prevalence of smoking in men compared to women globally, and judging from the typical risk factors for lung cancer including tobacco smoking, family history of malignancy, previous lung disease, and exposure to second hand smoke, radon, asbestos, arsenic, air pollutants, or occupational carcinogens are one of the causes of the difference in the incidence of these cancers. Different subtypes of lung cancer have different epidemiology and different prognoses.[9]

Distribution of the incidence of non-small cell lung cancer presented that data shows majority of the study subjects were diagnosed with lung cancer. Squamous cell carcinoma or as many as 136 patients and 17% of the subjects were diagnosed with adenocarcinoma. Table 2 describes the characteristics of patients based on their diagnosis and treatment options.

Table 2. Distribution of Cancer Cell Types, Staging and the Number of Cycles of Chemotherapy received by patients.

	N	**(%)**
Cancer cell type		
Adenocarsinoma	28	17.07
Squamous Cell Carcinoma	136	83.93
Staging		
Stage I	0	0
Stage II	10	6.09
Stage III	48	29.27
Stage IV	106	74.64
Cycle Chemotherapy		
2	6	3.66
3	8	4.68
4	150	91.66

Based on Table 2, it is known that 65% or as many as 108 subjects were first diagnosed at stage IV, 29% at stage III, 6% at stage II, and 0% at stage I. Based on Table 3 it is known that 65% or as many as 108 subjects first diagnosed at stage IV, 29% at stage III, 6% at stage II, and 0% at stage I.

Characteristics of non-small cell lung cancer patients based on the number of chemotherapy cycles the patient go through in table 2 explained that as many as 150 subjects or 91 % of research subjects followed chemotherapy up to cycle 4. This was due to changes in the quality of life of patients and changes in the performance status of patients in each cycle. In lung cancer patients, the number of chemotherapy cycles greatly affects the patient's quality of life. Patients who do not follow chemotherapy cycles up to cycle IV can be caused by a worsening of performance status, patients lost follow-up or because the patient has died.[10]

In this study, the 95 patients who go through chemotherapy until the 4th cycle had normal performance status, 40% with a performance status decreased, namely from performance status 1 to 2, and only 2% an increase in performance status from 2 to 1. This can be influenced by several factors

including age, gender, smoker, cancer stage, and seen of the patient's cancer metastases.

For the frequency distribution of non-small cell lung cancer patients based on the treatment options listed in Table 2, it is known that as many as 72 subjects (43%) were given carboplatin and paclitaxel as a chemotherapy regimen, 31% subjects were given carboplatin and navelbine, and only 1% subjects given the chemotherapy regimen cisplatin and vinoralbin. Other regimens used by doctors in administering chemotherapy include bondronat; docetaxel, cisplatin, 5-fluorouracil; brexel, cisplatin, 5-fluorouracil; gemcitabin, kemobin; and belotaxel.

Carboplatin and paclitaxel are the most widely used regimens. This is in line with the study of Gridelli C, et al., who explained that Paclitaxel/carboplatin was efficacious and well tolerated in 70-year-old patients with squamous NSCLC. These results are based on a previous analysis, which showed that paclitaxel /carboplatin was effective for a subgroup of difficult-to-treat patients.[11]

Table 3. Correlation between chemotherapy cycles and charges in the performance status of subjects

Cycles of Chemotherapy						
Performance status	2	3	4	Total	%	
Decreased	5	8	53	66	40.24	P<0.05
Stable	0	0	95	95	57.93	R 0.67
Increase	0	0	3	3	1.83	

In this study the use of carboplatin, paclitaxel was also associated with the performance status patient's and age. Where patients aged 60 years as many as 19 subjects had performance status 0 and as many as 91 subjects had performance status 1. Patients aged 65 years as many as 12 subjects had performance status 0 and as many as 58 subjects had performance status 1 and patients aged 70 years as many as 8 subjects. have a performance status of 0 and 22 subjects have a performance status of 1. This means that the performance status of patients when using carboplatin, paclitaxel is still said to be good for increasing patient age.[11]

Nathan R, et al conducted 10 trials with a subject of 2,855 patients. With the average results of OS and PFS are 9.8 months and 5.9 months.[12] And in the study of Akamatsu H, et al explained that the average PFS of non-small cell lung cancer patients was 12 months and the average OS of patients was 39 months. With Carboplatin + Paclitaxel, Cisplatin + S-1, and Cisplatin + Vinorelbine.[13]

Correlation between Chemotherapy Cycle and Performance Status in Non-Small Cell Lung Cancer Patients

Statistical tests based on Spearman rank correlation were used to analyze the relationship between the number of chemotherapy cycles and performance status of patients in RSUD dr. Zainoel Abidin, Banda Aceh. The following is the hypothesis for the Spearman rank correlation test:

If p < 0.05 then Ho is rejected Ha is accepted 0.05 then Ho is
If p > accepted Ha is rejected
Meaning:
Ho: There is no relationship between the dependent variable and the independent variable
Ha: There is a relationship between the dependent variable and independent variables

The data in Table 3 shows that subjects who go through 4 cycles of chemotherapy had changes in performance status. Subjects with performance status normal were 95 patients with a percentage of 57%. 32% of patients had decreased performance status and 2% had improved performance status. While in patients who go through 3 cycles of chemo-therapy as many as 8 subjects experienced a decrease in performance status. Then, a 3% decrease in performance status in subjects who go through 2 cycles and seen from the total cycles of patients and also the value of the performance status patient's as much as 57% with performance status normal, 41% experienced a decrease in performance status and only 2% of patients experienced an increase in performance status.

Performance status is said to be normal if it is 0 because the patient can still perform all physical activities without restrictions. It is said to decrease if there is a change in the value of the patient's performance status from 0 to 1 or 1 to 2, this happens because the decreasing performance status of the patient will worsen the quality of life. While the performance status of the patient is said to be increasing if the ECOG score obtained is with a value of 2 to 1 or 1 to 0. Due to the improvement in physical activity that the patient can do.

In the statistical test results using the Spearman method, P value <0.05 and R 0.367 indicated that there was a relationship between the number of chemotherapy cycles and performance status based on ECOG in lung cancer patients with non-small cell carcinoma in RSUD dr. Zainoel Abidin Banda Aceh in 2017-2020 and with a low correlation coefficient. And there is no theory that directly states the relationship between chemotherapy cycles and performance status patient. However, the value of performance status can be used as an outcome for lung cancer patients with non-small cell carcinoma. If the patient's performance status is good, the chemotherapy cycle can be continued until the 6th cycle, but if it gets worse, chemotherapy should be considered. This is done to reduce the side effects of chemotherapy drugs on patients.

Discussion

Data from patient medical records, it was found that a total of 164 patients with non-small cell carcinoma who go through chemotherapy met the inclusion and exclusion criteria. Characteristics of NSCLC patients were dominated by patients aged > 40 years as many as 152 patients or 92.7%, with the highest age range between the ages of 51-60 years with a total of 69 subjects or 42%. This is in line with research conducted by Edi Saputra Saksari's study, with a study sample of 22 lung cancer patients. It was stated that the most patients were aged >40 years as many as 19 patients (86.6%) while age <40 years were 3 patients (13.4%).[14] This is in accordance with Adam Szpechcinski's study, the average age of non-small cell lung cancer patients is 49 to 88 years.[11] This illustrates that with increasing age, the incidence of cancer will increase significantly. The peak was when entering menopause, namely at the age of 50 years.[15]

Based on gender, the results showed that the male gender dominated more than half of the total number of subjects, which was 141 patients or 85%. This is in line with other studies, namely the study of Adam Szpechcinski, et al. It consisted of 37 patients or 56% of non-small cell lung cancer patients were male.[16] Research conducted by Shah DN et al, also showed the same result, where as many 68% of lung cancer patients with non-small cell carcinoma types were male.[14] According to the research of Zhang T, et al in a retrospective study consisting of 381 patients in 2012-2014.[17] Comparison of the incidence of non-small cell lung cancer in men and women is 286/95 patients.[18] This is thought to occur due to the high prevalence of smoking in men compared to women globally, and judging from the typical risk factors for lung cancer including tobacco smoking, family history of malignancy, previous lung disease, and exposure to second hand smoke, radon, asbestos, arsenic, air pollutants, or occupational carcinogens are one of the causes of the difference in the incidence of these cancers.[18]

Conclusion

As many as 57% of cancer patients who go through chemotherapy cycles up to cycle 4 had *performance status* a normal and 41% of patients experienced a decrease in *performance status.* There is a significant relationship between chemotherapy cycles and *performance status* based on ECOG in lung cancer patients with non-small cell carcinoma in RSUD dr. Zainoel Abidin Banda Aceh with P <0.05 and R 0.367.

Suggestions

Because the assessment of *performance status* is a subjective assessment, it is necessary to have a common perception so that there are no differences in the assessment of *the performance status* and can be recorded in full in the patient's medical record.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Barta JA, Powell CA, Wisnivesky JP. Global epidemiology of lung cancer. Ann Glob Health. 2019;85(1):1–16.
3. World Health Organization. Cancer incidence in Indonesia. International Agency Research Cancer. 2020; 858:1–2.
4. Pangribowo S. Beban Kanker di Indonesia. Pusat Data dan Informasi Kemeterian Kesehatan Republik Indonesia. 2019;1–16.
5. Malhotra J, Malvezzi M, Negri E, La Vecchia C, Boffetta P. Risk faktors for Lung cancer worldwide. Eur Respir J. 2016;48(3):889–902.
6. Jusuf A, Syahruddin E, Hudoyo A. Kemoterapi Kanker Paru. J Respir Indo. 2009;29(4):219-27.
7. Setiawan DS. The effect of chemotherapy in cancer patient to anxiety. Med J of Lam Univ 2015;4(4):94–9.
8. Komite Penanggulangan Kanker Nasional. Pedoman Nasional Pelayanan Kedokteran Kanker Paru. 2017. 7.
9. Ramadhaniah F, Khairina D, Sinulingga DT, Suzanna E. Gambaran pasien kanker paru di Rumah Sakit Kanker Dharmais (RSKD) tahun 2008-2012. J Respir Indo 2019; 39(1): 44–53.

10. Mariani KS. Profil penggunaan obat sitostatika pada pasien kanker rawat inap yang menjalani kemoterapi di RSUD PROF. Dr. W. Z. Johannes Kupang tahun 2018. 2018;9–16.
11. Cheng TJD, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The international epidemiology of lung cancer: latest trends, disparities, and tumor characteristics. J Thorac Oncol. 2016;11(10):1653–71.
12. Lewis D. A long-term survival picture emerges as follow-up data from nsclc trials mature.Therapy Oncol. 2020;9(16):24.
13. Foster NR, Renfro LA, Schild SE, Redman MW, Wang XF, Dahlberg SE, et al. Multitrial evaluation of progression-free survival as a surrogate end point for overall survival in first-line extensive-stage small-cell lung cancer. J Thorac Oncol. 2015; 10(7): 1099–106.
14. Saksari ES. Karakteristik penderita kanker paru di ruang rawat inap kanker RSUD Dr. Zainoel Abidin Banda Aceh tahun 2013. Banda Aceh: 2014.
15. Sugiyono. Statistika Untuk Penelitian. Bandung: CV Alfabeta; 2016.
16. Szpechcinski A, Florczuk M, Duk K, Zdral A, Rudzinski S, Bryl M, et al. The expression of circulating miR-504 in plasma is associated with EGFR mutation status in non-small-cell lung carcinoma patients. Cell Mol Life Sci. 2019;76(18):3641–56.
17. Zhang T, Shi W, Tian K, Kong Y. Chaperonin Containing T-complex polypeptide 1 subunit 6A correlates with lymph node metastasis, abnormal carcinoembryonic antigen and poor survival profiles in non-small cell lung carcinoma. World Journal Surgical Oncology. 2020; 18(1): 1–10.
18. Bhatt PK, Fughhi I, Basu S, Mary J, Allen Borgia A, Philip DB. Mature, real world progression-free survival (pfs) and overall survival (os) milestones in stage iv, non-squamous, non-small cell lung cancer patients (nsqnsclc) treated with first line pemetrexed(pem)/platinum (plat) followed by pem +/- bevacizumab (bev). Journal Clinic Oncology. 2019; 37(15).

InaJCC The Indonesian Journal of Cancer Control

Case Report

A rare case of falcotentorial meningioma type II of the pineal region

Rahmad Mulyadi[1], Prijo Sidipratomo[1], Taufik Budianto[1], Eka Susanto[2]

Check for updates

p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v2i1.60

Received: April 21, 2021
Accepted: April 17, 2022

Authors' affiliations:
[1]Department of Radiology, Dr. Cipto Mangunkusumo Hospital/ Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2]Department of Anatomical Pathology, Dr. Cipto Mangun-kusumo Hospital/Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Corresponding author:
Rahmad Mulyadi
E-mail: *dr_rahmad_radiologi@yahoo.com*

Abstract

Background: Pineal region meningiomas are incredibly uncommon causes of pineal mass. Diagnosis is usually made when the tumours already reach huge diameters and cause mass effects, obstructing the ventricles and aquaducts.
Case Illustration: We present a case of a 32-year-old man complaining of worsening blurred visions and headaches. Brain Magnetic Resonance Imaging (MRI) disclosed a well-defined, lobulated pineal region mass that homogenously enhanced after contrast injection, with a dural adherence, close to the junction of the Vein of Galen and the straight sinus and inferior to the anterior edge of the tentorium, suggestive of a diagnosis of falcotentorial meningioma type II from the pineal region. The tumour compressed the mesencephalon and caused non-communicant hydrocephalus. The patient underwent tumour removal. Histological analysis of the tumour was consistent with meningioma WHO grade I.
Discussion : Pineal region meningioma, the falcotentorial type, can also be classified into four different types based on the tumour's adherence to the dura and the extension to its surrounding structures. Although rare, pineal region meningioma should be included as a differential diagnosis in a patient presenting with a pineal mass. MRI, both conventional and multimodal, still holds a crucial role in aiding clinicians and surgeons to make the correct diagnosis and deliver the best treatment option for the patients.
Conclusion : MRI can help differentiate pineal region meningiomas from intracranial and other pineal region tumours and aid the neurosurgeons in deciding the appropriate management approach for this rare intracranial neoplasm.

Keywords: *brain magnetic resonance imaging, meningioma, pineal region tumour, pineal region*

Abstrak

Latar Belakang: Meningioma daerah pineal adalah penyebab massa pineal yang sangat jarang terjadi. Diagnosis dapat ditegakkan ketika tumor sudah mencapai diameter yang besar dan menyebabkan efek massa, menghalangi ventrikel dan saluran air.
Ilustrasi Kasus: Seorang pria berusia 32 tahun yang mengeluhkan penglihatan kabur dan sakit kepala yang memburuk. Pada pemeriksaan Resonansi Magnetik Otak (MRI) didapatkan massa daerah pineal, lobulasi yang homogen setelah injeksi kontras, dengan perlekatan dura, dekat dengan pertemuan vena Galen dan sinus tentorial dan inferior ke tepi anterior tentorium, menunjukkan diagnosis meningioma falcotentorial tipe II dari daerah pineal. Tumor menekan mesencephalon dan menyebabkan hidrosefalus non-komunikan. Pasien menjalani pengangkatan tumor. Analisis histologis tumor konsisten dengan meningioma WHO grade I.
Diskusi: Meningioma daerah pineal, tipe falcotentorial, juga dapat diklasifikasikan menjadi empat tipe yang berbeda berdasarkan perlekatan tumor terhadap dura dan perluasan ke struktur sekitarnya. Meskipun jarang, meningioma daerah pineal harus dimasukkan sebagai diagnosis banding pada pasien yang datang dengan massa pineal. Pemeriksaan MRI baik secara konvensional maupun multimodal, masih menjadi baku emas dalam membantu dokter dan ahli bedah untuk membuat diagnosis yang benar dan memberikan pilihan pengobatan terbaik bagi pasien.
Kesimpulan: Pemeriksaan MRI dapat membantu membedakan meningioma daerah pineal dari tumor intrakranial dan tumor daerah pineal lainnya dan membantu ahli bedah saraf dalam memutuskan tatalaksana yang tepat untuk neoplasma intracranial.

Kata kunci: *daerah pineal, meningioma, pencitraan resonansi magnetik otak, tumor daerah pineal*

Background

Anatomically, the pineal region is located deeply, close to other vital structures in the brain's centre. It lies posteriorly along the midline, dorsal to the roof of the third ventricles and caudal to the tectum of the midbrain.[1,2] The incidence of the pineal region tumour is rare. It constitutes only 1% of all intracranial tumours in adult patients with various causes of lesions, such as tumours originating from pineal parenchymal tissue and various cells adjacent to the pineal gland, germinal cells, and metastatic tumours.[3-5] Although meningioma is the most commonly found central nervous system (CNS) tumour, pineal region meningioma is rare, accounting for only 2 – 8% of all pineal region tumours and 0,3 – 1,0% of all intracranial meningiomas.[2,6-8] Pineal region meningioma is characterized by meningioma that originates from falcotentorial junction or the posterior part of veluminterpositum and fills the quadrigeminal cistern with few or without adherence to the dura at all.[6,9] Pineal region meningiomas are predominantly benign with slow tumour progressivity. Thus, diagnosis is commonly made when the tumour is already large and elicits complications such as obstructive hydrocephalus.[10] Neuroimaging, particularly Magnetic Resonance Imaging (MRI), both standard and multimodal, still plays a pivotal role in diagnosing and differentiating benign and malignant mass in this deep, posterior part of the brain, including diagnosis of pineal region meningioma.[5]

Here, we report a rare case of a 32-year-old man with a falcotentorial meningioma type II of the pineal region.

Case Illustration

A 32-year-old-man had been complaining of blurred visions and headaches for three months. Blurry vision initially began with the left vision, followed by the right a month later. The Visual Analogue Scale (VAS) for his headache was 2-3. There were no vomiting and other neurology deficits, such as loss of consciousness, extremity weakness, or double vision. On examination, the patient was compos mentis with unremarkable vital signs. Both pupil size and pupillary light reflex were normal. However, his visual acuities were OD 6/30 and OS 1/300, and fundoscopy revealed bilateral papilledema. Other neurologic examinations found no contributory findings.

Magnetic Resonance Imaging (MRI) disclosed a sharply circumscribed mass lesion that was isointense and lobulated in the pineal region and enhanced after contrast injection (diameter, 3 x 3 x 3,5 cm), compressing the mesencephalon from the posterosuperior side. MRI also revealed noncommunicating hydrocephalus, deviated septum to the left, and an extra-axial cystic lesion in the left medial fossa with a differential diagnosis of an arachnoid cyst. Evans ratio was 0,4.

Serum biomarkers of pineal region tumours such as beta-HCG and alpha-fetoprotein (AFP) were normal, <1,2 mIU/mL and 2,3 ng/mL, respectively. Cerebrospinal fluid (CSF) analysis suggested clear colour, with cells count of 3 (3 MN, 0 PMN), CSF protein and glucose were 5 mg/dL and 79 mg/dL, respectively. Nonhematopoietic cells were not found.

The patient underwent a ventriculoperitoneal shunt surgery procedure and tumor removal. Tissue samples obtained from surgery confirmed our diagnosis of meningioma, WHO grade I. After surgery, the patient's vision and headache improved and he was later discharged and encouraged for routine follow-up visits.

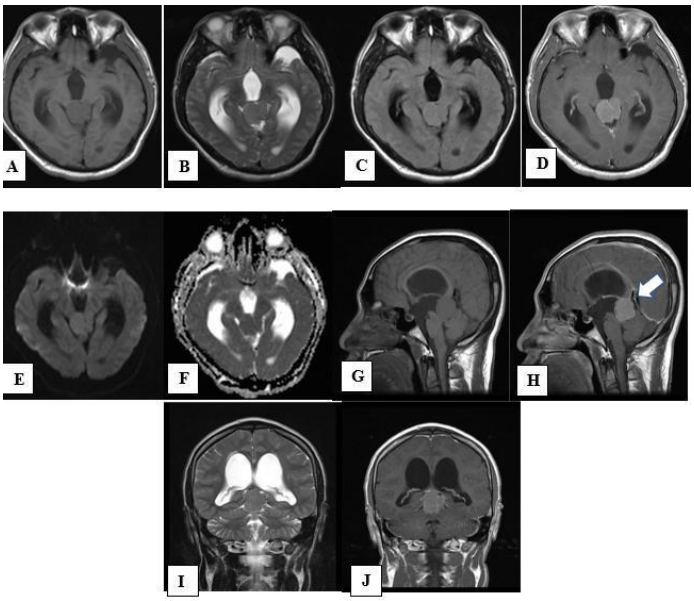


Figure 1. Brain MRI. **(A)** Axial T1-weighted, **(B)** Axial T2-weighted, **(C)** Axial FLAIR, **(D)** Axial T1weighted + gadolinium contrast, **(E)** Axial DWI, **(F)** Axial ADC image, (**G**) Sagittal T1-weighted, **(H)** Sagittal T1-weighted + gadolinium contrast, (**I**) Coronal T2-weighted, (**J**) Coronal T1-weighted + gadolinium contrast. Note that the tumor originated just beneath the anterior edge of the tentorium, near to the junction of galen vein and the straight sinus (white arrow), with a dural adherence apparent after contrast injection.

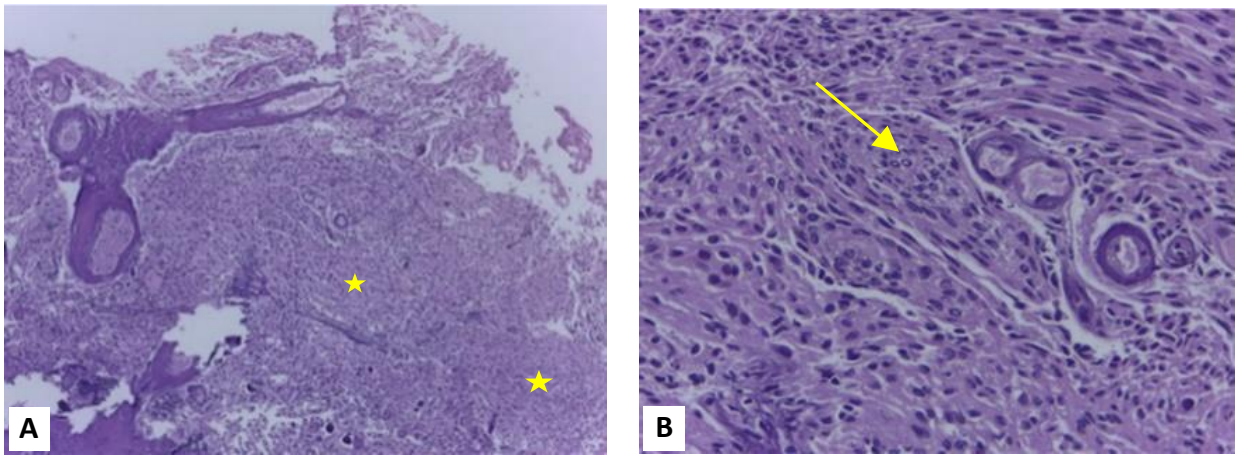


Figure 2. Histopathological finding of the tumor. (**A**) H&E 100X and (**B**) H&E 400x. The tumor shows lobular growth pattern (star). Tumor cells are largely uniform, with round to oval nuclei, fine chromatin and variable nuclear pseudo inclusions (arrow).

Discussion

As with other intracranial meningiomas, pineal region meningioma generally occurs in adulthood with a female predominance.[1,11] Some literature reports that the incidence of meningiomas increases with age, with a median age at diagnosis of 66 years.[12] Our patient presented a rarer case of pineal region meningioma in a 32year-old male.

In theory, pineal region meningiomas are broadly divided into two groups based on their origin: falcotentorial junction meningiomas and velum interpositum meningiomas. The clinical symptoms of the two do not show any difference. Thus, differentiation clinically is not plausible. The two lesions are distinguished by the relationship of the tumour to the dura at the falcotentorial junction. In falcotentorial junction meningiomas, meningiomas arise from the arachnoid membrane attached to the falcotentorial junction (dural folds of the tentorium and falx cerebri) and protrude anteriorly or posteriorly to the quadrigeminal cistern. Meanwhile, in the less common interpositum meningioma, the tumour originates from the arachnoid membrane that lines the velum interpositum.[2,6] Other literature also previously reported a case of pineal region meningioma arising from the arachnoid membrane of the vein of Galen.[6] Even with advanced imaging techniques, such as MRI and angiography, distinguishing these two types of tumours is often not possible, and the differentiation is usually confirmed after surgical operation.[2]

Pineal region meningioma, the falcotentorial type, can also be classified into four different types based on the tumour's adherence to the dura and the extension to its surrounding structures. In type I, the tumour derives from in the middle of both dural leaves of the cerebral falx, positioned superiorly to the Vein of Galen and the straight sinus junction. Type II originates from just beneath the anterior edge of the tentorium, closely positioned to the Vein of Galen and the straight sinus junction. Type III lateralized and located paramedian of one of the tentorial leaves. It originates from the dura and grows in a medial pattern towards the Vein of Galen. Type IV has a posterior direction. It is adherent to the dura in the falcotentorial junction down the straight sinus.[13] On MRI, our patient showed a meningioma closely adherent to the junction between the Vein of Galen and the straight sinus, inferior to the anterior edge of the tentorium, consistent with type II falcotentorial meningioma.

The course of the disease is generally slow, with an occult disease period of up to 25 years. Thus, pineal region meningiomas are often diagnosed when they have reached a large size and caused symptoms of mass effect and increased intracranial pressure. Obstructive hydrocephalus is caused by compression of the ventricles and aqueducts. Symptoms include headache, blurred vision, papilledema, gait disturbances, ataxia, cognitive impairment, hemifacial spasms, and Parinaud's syndrome (upward gaze paresis).[1,11,14] Consistent with the existing literature, our patient presented with symptoms of increased intracranial pressure in the form of gradually blurred vision and papilledema accompanied by headache. Furthermore, our patient did not have any extraocular movement disorders that are common in other tumours of the perineal region, confirming our suspicion of a pineal meningioma which, according to the available literature, rarely exhibits extraocular movement abnormalities.[7,11]

The radiological features of pineal meningiomas are nonspecific and similar to those of meningiomas at other CNS sites.[5,9] MRI generally shows a low to intermediate signal on T1weighted images, and the signal on T2-weighted images can vary, predominantly showing an intermediate to high signal on T2-weighted images. The lesions appear homogeneously enhanced after injection of gadolinium contrast. Because meningiomas are dura-based lesions, pineal region meningiomas exhibit a dura-tail appearance that differentiates them from other extra-axial tumours.[3,12] The presence of intratumoral haemorrhage, necrosis, or cysts with a more heterogeneous appearance indicates a more aggressive tumour.[12] On MRI examination, we found a solid, sharply-circumscribed, lobular, contrast-enhancing mass adherent to the dura that filled the pineal region, compressing the mesencephalon from a posterosuperior direction, suggestive of a mass of the pineal region origin. The tumour caused a mass effect and obstructed the normal flow of CSF, and caused noncommunicating hydrocephalus and deviated septum to the left. We also disclosed a cyst in the right and left temporal fossa, suggestive of an arachnoid cyst. The finding of an arachnoid cyst is incidental and is not related to the patient's clinical condition.

Serum and CSF biomarkers are performed to complete clinical, imaging, and pathologic findings. In our case, serum and CSF findings were unremarkable, lacking high CSF markers such as AFP and HCG. Thus, it furtherly excludes the possibility of

other pineal region tumours, such as germinoma, as the most prevalent type of all pineal region tumour that typically expressed high oncoproteins.[4]

Histopathological examination of the tumour confirmed the diagnosis of CNS WHO grade I meningioma. Based on histological criteria, the World Health Organization (WHO) in 2016 classified meningiomas into three grades: benign tumours (WHO grade I), and more aggressive meningiomas (WHO grade II), and malignant meningioma (WHO grade III).[8,12]

Definitive therapy is performed with surgery determined based on the relationship of the tumour to the deep venous system and surrounding structures, which are generally classified into two main approaches, namely the occipital transtentorial approach (OTA) and the supra-cerebellar infratentorial approach.[10,11] Due to its benign nature with slow disease progression, multistage and multidirectional surgery has also been reported and considered a safe approach for large pineal region meningiomas.[10] Most studies report improvement in patient's vision after tumour removal at the time of discharge from the hospital and follow-up.[14] In our case, the patient's headache and visual acuity had improved for both eyes after tumour removal.

Conclusion

Pineal region meningioma, falcotentorial meningioma type II in particular, is a rare case that ordinarily may not be considered a differential diagnosis in pineal region tumours. The diagnosis of pineal region meningioma is often a challenge for clinicians, surgeons, radiologists, and pathologists. MRI can help differentiate pineal region meningiomas from intracranial and other pineal region tumours and aid the neurosurgeons in deciding the appropriate management approach for this rare intracranial neoplasm.

References

1. Qiu B, Wang Y, Ou S, Guo Z, Wang Y. The unilateral occipital transtentorial approach for pineal region meningiomas: a report of 15 cases. International Journal of Neuroscience. 2014 Oct 2;124(10):741–7.
2. Yu L, Orazmyradov B, Qi S, Song Y, Fang L. Reinvestigation of the origins of pineal meningiomas based on its related veins and arachnoid membranes. BMC Neurol. 2020 Dec 20;20(1):200.
3. Fang AS, Meyers SP. Magnetic resonance imaging of pineal region tumours. Insights Imaging. 2013 Jun 3;4(3):369–82.
4. Favero G, Bonomini F, Rezzani R. Pineal Gland Tumors: A Review. Cancers (Basel). 2021 Mar 27;13(7):1547.
5. Deiana G, Mottolese C, Hermier M, Louis-Tisserand G, Berthezene Y. Imagery of pineal tumors. Neurochirurgie. 2015 Apr;61(2–3):113–22.
6. Inoue A, Ohnishi T, Kohno S, Ohtsuka Y, Nakamura Y, Mizuno Y, et al. Two cases of pineal-region meningiomas derived from arachnoid membrane over the vein of Galen without dural attachment. World J Surg Oncol. 2015 Dec 25;13(1):226.
7. Avelar T, Paiva A, Costa M, Aguiar G, Vitorino J, Veiga J. Meningioma of the Pineal Region — Differential Radiologic Aspects of Pineal Region Tumors Based on a Clinical Case. Arquivos Brasileiros de Neurocirurgia: Brazilian Neurosurgery. 2018 Jun 12;37(02):145–7.
8. Wang KY, Chen MM, Malayil Lincoln CM. Adult Primary Brain Neoplasm, Including 2016 World Health Organization Classification. Radiol Clin North Am. 2019 Nov;57(6):1147–62.
9. Lensing FD, Abele TA, Sivakumar W, Taussky P, Shah LM, Salzman KL. Pineal Region Masses—Imaging Findings and Surgical Approaches. Curr Probl Diagn Radiol. 2015 Jan;44(1):76–87.
10. Otani N, Mori K, Wada K, Tomiyama A, Toyooka T, Takeuchi S. Multistaged, multidirectional strategy for safe removal of large meningiomas in the pineal region. Neurosurg Focus. 2018 Apr;44(4):E13.
11. Nowak A, Dziedzic T, Czernicki T, Kunert P, Marchel A. Falcotentorial and velum interpositum meningiomas: Two distinct entities of the pineal region. Neurol Neurochir Pol. 2014 Nov;48(6):397–402.
12. Ogasawara C, Philbrick BD, Adamson DC. Meningioma: A Review of Epidemiology, Pathology, Diagnosis, Treatment, and Future Directions. Biomedicines. 2021 Mar 21;9(3):319.
13. Blasco García de Andoain G, Delgado-Fernández J, Penanes Cuesta JR, Gil-Simoes R, Frade-Porto N, Sánchez MP. Meningiomas Originated at the Falcotentorial Region: Analysis of Topographic and Diagnostic Features Guiding an Optimal Surgical Planning. World Neurosurg. 2019 Mar;123:e723–33.
14. Hong CK, Hong JB, Park H, Moon JH, Chang JH, Lee KS, et al. Surgical Treatment for Falcotentorial Meningiomas. Yonsei Med J. 2016;57(4):1022

InaJCC The Indonesian Journal of Cancer Control

Case Report

Palliative management of advanced stage head and neck cancer: Evidence-based case report

Marlinda Adham[1], Anita A Sari[1], Rudi Putranto[2], Indrati Suroyo[3], Henry Kodrat[4], Eka D Safitri[5]

Check for updates

p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v2i1.68

Received: March 29, 2021
Accepted: February 20, 2022

Authors' affiliations:

[1]Departement of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Universitas Indonesia / Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[2]Division of Psychosomatic Medicine, Departement of Internal Medicine, Faculty of Medicine, Universitas Indonesia / Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[3]Department of Radiology, Faculty of Medicine, Universitas Indonesia / Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[4]Department of Oncology Radiation, Faculty of Medicine, Universitas Indonesia / Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[5]Center for Clinical Epidemiology and Evidence Based Medicine (CEEBM), Faculty of Medicine, Universitas Indonesia / Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding author:
Marlinda Adham
Email:
marlinda.adham@gmail.com

Abstract

Background: Head and neck cancer is one type of cancer with high prevalence in Indonesia. So far, the therapeutic approach for patients with head and neck cancer has focused a lot on the curative approach. In patients with advanced conditions, unable to undergo curative therapy, the palliative approach plays an important role to improve the quality of life.This paper aims to better understand about palliative care in advanced head and neck cancer.
Case Illustration: Male, 43 years old, with adenocystic carcinoma of the salivary gland. The tumor has already spread to the spinal cord. The team decided to put the patient into palliative care. Treatment goals for this patient were to reduce pain.
Discussion: Therapeutic choices for head and neck cancer include surgery, radiotherapy, and chemotherapy. The palliative approach plays a role at the point where the patient's condition determines the shift in the treatment plan from curative to palliative therapy. Early palliative therapy provided a statistically greater effect on the overall quality of life, overall survival, incidence of depression and severity of symptoms.
Conclusion: In advanced head and neck cancer, early palliative intent treatment leads to improvements in quality of life.

Keywords: *head and neck cancer, quality of life, treatment advance stage, palliative treatment*

Abstrak

Pendahuluan: Kanker kepala leher merupakan salah satu jenis kanker yang banyak ditemukan di Indonesia. Selama ini pendekatan terapi pasien dengan kanker kepala leher banyak terfokus pada pendekatan kuratif. Pada pasien dengan kondisi lanjut dan tidak dapat menjalani terapi kuratif, pendekatan paliatif memegang peranan penting untuk meningkatkan kualitas hidup. Laporan kasus berbasis bukti ini bertujuan untuk memahami lebih baik mengenai terapi paliatif pada kanker kepala leher.
Ilustrasi Kasus: Laki-laki, usia 43 tahun dengan karsinoma kistik adenoid kelenjar liur. Pasien dengan perluasan tumor ke daerah kanalis spinalis. Tim dokter memutuskan untuk memilih terapi paliatif sebagai tatalaksana pada pasien dengan tujuan akhir untuk mengurangi nyeri.
Diskusi: Pembedahan, radioterapi dan kemoterapi merupakan pilihan terapi utama pada kasus keganasan kepala leher. Dalam beberapa kasus lanjut dimana pasien tidak lagi mampu menjalani terapi kuratif, terapi paliatif merupakan pendekatan terapi terpilih. Pendekatan paliatif memiliki efek positif terhadap kualitas hidup, kesintasan, insidensi depresi dan derajat keparahan gejala.
Kesimpulan : Pada kasus kanker kepala leher stadium lanjut, pendekatan terapi paliatif sejak dini dapat meningkatkan kualitas hidup pasien.

Kata Kunci*: kanker kepala leher, kualitas hidup, tata laksana stadium lanjut, terapi paliatif*

Background

Head and neck cancers are the sixth most common types of cancers in the world. In Indonesia, the prevalence of cancers of the head and neck is high. According to GLOBOCAN 2018, head and neck cancers make up 8.63% of all new cancer cases yearly, with nasopharyngeal carcinoma being the most prevalent (5.2% of all new cancer cases). Cancer of the salivary glands, however, make up roughly 0.67% of all new cancer cases annually.[1]

Salivary gland cancers are rarely occurring cancers, making up about 3-6% of all head and neck cancers globally. About 15-20% of salivary gland cancers originate from the submandibular glands. Cancer of the salivary glands can be classified into two groups: cancers of the major salivary glands, including parotid, submandibular and sublingual glands, and minor glands that surround the cavities of the mouth, pharynx, larynx, nasal cavities, and paranasal sinuses. Cystic adenoid carcinoma is histologically the most commonly occurring salivary gland cancer of the submandibular region and the minor salivary glands.[2,3]

Management of head and neck cancers, including salivary gland cancers, involves a combination of surgery, radiation therapy, chemotherapy and palliative therapy. Multiple indications in support of palliative therapy for head and neck cancers exist, including the presence of distant metastasis at the time of diagnosis, advanced locoregional disease, history of surgical or extensive radiation intervention, patient comorbidities, poor tolerance towards curative therapies and patient autonomy. These conditions can lower the social function of patients, and thereby lower the overall quality of life.[4,5]

Adenoid Cystic Carcinoma of the Salivary Gland

Epidemiology

Adenoid Cystic Carcinoma *(*ACC*)* is a type of head and neck cancer that arises from the salivary gland. ACC occurs among 1% of head and neck malignancies and 10% of all salivary gland cancers.[2] ACC occurs in all populations. No definite risk factors exist that increase the occurrence of ACC.[2,3]

Histopathology

Histopathologically, ACC can be divided into three types; tubular, cribriform and solid. Microscopically, ACC is made up of small basaloid epithelium, non-luminal, hematoxyphillic cells, with small and medium sized cytoplasm. [2,3]

Cribriform type ACC most commonly demonstrates a “swiss cheese” like histopathologic pattern. Tubular type carcinoma is characterised by the presence of tubules that are layered by luminal cells with clear cytoplasm. Solid type tumors are made up of basaloid cells that grow in sheets without lumina.

All types of ACC show perineural invasion, allowing the tumor to follow the neuronal path. Cancer cells also exhibit intraneural invasion.[2,3]

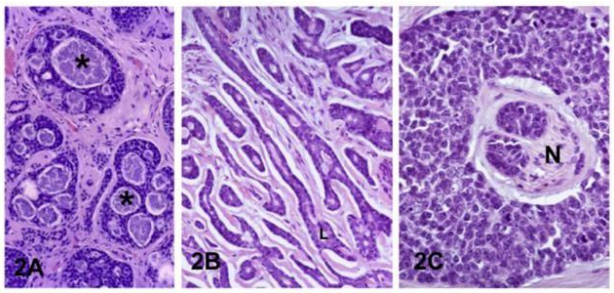


Figure 1. Histopathologic image of ACC, A: cribriform type, B: tubular type, C: solid type

The prognosis of ACC can be predicted based on its grading. According to Szanto et al, ACC can be classified into:

- Grade I: cribriform and tubular patterns without solid components
- Grade II: purely cribriform patterns or mixed with >30% solid components
- Grade III: dominated by solid patterns

Low grade tumors are usually found on the palate or the parotid gland, whereas high grade tumors usually occur in the submandibular glands. [2,3]

Diagnosis

ACC is a type of malignancy that grows slowly, however, is progressive and tends to involve nerves, often reoccurs, and can cause distant metastasis. To determine the diagnosis, a histopathologic examination of the tumor sample is required, which is obtained via incision biopsy.[2,3]

Ultrasonography (USG) examination can be used to detect ACC early, despite the lack of specificity in differentiation between ACC and other head and neck cancers: irregular borders and heterogenous

hypoechogenic structures, often with cystic patterns, form the general description of many malignancies. USG guided fine needle aspiration biopsy can differentiate between malignant and benign lesions with a sensitivity of 88%-93% and specificity of 75%-99%.[2,3]

Magnetic Resonance Imaging (MRI) can provide sensitive images, which can be used to predict malignancy and differentiate the tumor from surrounding structures such as nerves, cartilages, and bones. CT scans are preferred to evaluate tumor invasion into bone. PET scan can be conducted to determine the presence of distant metastasis.[2,3,6]

From the MRI examination, ACC is seen as an unclear mass, with diffuse infiltration from nearby structures and worsening with contrast. Solid type histological patterns generally display lower signals upon T2-weighted sequence MRI imaging. The combination of irregular borders, local invasion and hypointense t2-weighted MRI sequence is characteristic of salivary gland carcinomas. [2,3,6,7] MRI is superior to the CT scan in detecting perineural invasion of ACC to the skull base (sensitivity 95%-100%).[2,3]

Management

Primary management of Head and Neck ACC is surgery, followed by post-operative adjuvant radiotherapy. Radiotherapy is the treatment of choice for salivary gland tumors that are inoperable.[2,3,6,7] Management of inoperable, unresectable or recurrent salivary gland cancer poses a complex challenge. ACC is a predominant subtype of these challenging tumors due to the perineural invasion, which is often extensive and involves the primary structures of the skull base.[2,3]

ESTRO ACROP guidelines 2022 for external beam radiotherapy divides two types of patients into patients with uncomplicated and complicated bone metastases. Bone metastases, regardless of size, should be considered uncomplicated if: 1) painful; 2) no impending or pre-existing pathologic fracture; 3) no compression of the spinal cord or cauda equina, regardless of size.[8] ESTRO ACROP guidelines 2022 recommends the use of single dose of 8-10 Gy conventional external beam radiotherapy for inoperable metastatic spinal cord compression (MSCC) patients while stereotactic body radiotherapy (SBRT) should not be used routinely outside clinical trials for MSCC. MSCC re-irradiation is safe at 6 months if the cumulative BED is 100-135.5 Gy.[9]

Tumor stage, lymph node status, age and tumor grade remain as the most important prognostic variables of salivary gland malignancies. Multiple studies have also shown that the presence of perineural invasion is an independent predictor of survival.[4,6]

Palliative Approach

According to the World Health Organization (WHO), palliative therapy is a therapeutical approach designed to improve the quality of life of patients and their families in facing life-threatening illnesses through prevention and recovery that is performed via early assessment towards the patient condition, as well as management physical, psychosocial, and spiritual complaints.[10]

Supportive therapy for head and neck cancer patients generally aims to manage symptoms including pain, dysphagia, dyspnea, bleeding, and ulceration. These complaints significantly affect the patient's quality of life. Administration of analgesics, performing tracheostomies to ensure airway patency, and nasogastric tube (NGT) placement to provide adequate nutrition to head and neck cancer patients are some types of palliative therapies that can be performed.[4,5,8]

Palliative therapy does not only focus on the patient but also on the caretaker, who loyally accompanies the patient. Information provided to the patient and family regarding the disease, as well as its complications, may aid in reducing fear among the patients and their families. As a result, the management of patients with head and neck cancers, especially those with advanced stage disease, requires multidisciplinary teamwork between otorhinolaryngologist-head and neck surgery, radiology, surgery, radiotherapy, medical oncology, palliative medicine, medical rehabilitation, pain management teams or anesthesiology, and psychiatry.[5]

Medical teams play a role in discussing patient management, including determining which patients can be admitted and which illnesses are categorised as incurable. Radical therapy of advanced stage or recurrent head and neck cancer is considered “futile” and can lead to a lower quality of life. Determination of effective decision making in palliative conditions is highly essential. Patients and their families must completely understand the diagnosis and prognosis of the disease.[11,12]

Competent and completely conscious patients have the right to make decisions regarding their management. In cases where patients lack autonomy, medical decisions can be made by representatives. This right is given to spouses, followed by adult children, and finally, other family members.[11,12]

Symptom control and proper psychosocial function can aid in choosing sensible therapies. Palliative care is associated with less aggressive cancer treatment.[13]

Palliative therapy targets

Palliative therapy requires a holistic and multidisciplinary approach. All members of the palliative care team must have the ability to communicate effectively. The end goal of palliative therapy includes the treatment of symptoms and the management of psychological and social problems of the patients. Following are some types of palliative approaches in patients with advanced head and neck cancer:[13]

Symptom control

1. Palliative surgery

Advanced stage head and neck cancer may cause significant discomfort to the patient. Surgery aims to reduce the size of the tumor, reduce the pain and bleeding risk, to improve swallowing, nutrition, and airway. Debulking surgery for head and neck cancers can provide benefits in symptom control. However, major resection rarely provides any benefit. Endovascular techniques, including embolization and vascular stents, can be the treatment of choice for bleeding control.[13]

2. Non-surgical palliative therapy

Radioterapy. Palliative radiotherapy may help to reduce pain experienced by patients with advanced stage head and neck cancers. ESTRO ACROP guidelines 2022 for external beam radiotherapy of patients with complicated bone metastases recommends radiation therapy should be used in combination with appropriate pharmacological and neurostimulation therapy for neuropathic pain due to bone metastases. For neuropathic pain, a single dose of 8 Gy should be used using conventional techniques. In patients with uncomplicated bone metastasis, ESTRO ACROP guidelines 2022 reccomends 1) Conventional radiation therapy should be used to treat uncomplicated painful bone metastases, especially when pain is not adequately controlled by analgesics or when analgesic reduction is desired. 2) For diffuse pain due to multiple bone metastases, single fraction hemibody or widefield radiation should be considered. Patients with uncomplicated painful bone metastases should be treated with a single dose of 8 Gy. 3) Patients with inadequate pain relief, no pain relief, or recurrence of pain after initial radiotherapy should be considered for reirradiation with a single dose of 8 Gy. 4) There is no advantage of high-dose conventional radiotherapy or SBRT over conventional single-dose radiotherapy for pain responses in oligometastatic bone disease. [8,9]

Chemotherapy. Chemotherapy, both monotherapy and when combined with radiotherapy, provides significant symptom control and higher quality of life; however, it also increases toxicity and side effects of the therapy.[13]

3. Dysphagia management

Roughly 40% of head and neck cancer patients experience dysphagia due to mechanical or functional obstruction, side effects of medicines, fistulas or pain. Functional endoscopic evaluation of swallowing (FEES) performed on head and neck cancer patients is essential in ensuring safe oral intake for the patient. Aspiration and silent aspiration are uncommon among advanced stage head and neck cancer patients. If results from the FEES show the presence of dysphagia, then nutrition may be provided enterally via the nasogastric tube (NGT).[13]

4. Airway Management

Indications for tracheostomy in palliative patients are not drastically different from those in non-palliative patients. In patients at risk of respiratory failures, such as with oral, oropharyngeal, laryngeal and thyroid tumors that are not operated on, fixation of vocal cords by invasive tracheal tumors, as well as the presence of cervical metastases, may require establishing patency of the airway. In chronically intubated patients, chronic aspiration may occur, warranting the need for a "*pulmonary toilet*." The decision to perform tracheostomies should be based on consent from the patient and their family. Tracheostomies in patients with advanced stage head and neck cancer can increase the quality of life.[13]

5. Pain Management

Pain is the dominant symptom suffered by patients with advanced stage cancer. Pain may cause agitation, frustration, and fear. In patients with advanced stage

head and neck cancer, holistic pain management can be achieved using the WHO analgesic ladder strategy. Despite that, pain management in head and neck cancer patients is often not sufficient. Lack of knowledge and skill in evaluating pain, inappropriate analgesic agents, unavailability of morphine, and myths regarding opioid addiction are some barriers to successful pain management in cancer patients.[14]

6. Nausea and Vomiting

Treatment of nausea and vomiting with anti-emetic medications such as metoclopramide and domperidone can be provided to relieve the symptoms.[13]

7. Constipation

In patients with advanced stage head and neck cancer, constipation is one of the most common complaints, which is caused by prolonged immobilisation, dehydration and use of constipation causing medicines, such as opioids and anti-cholinergics. Laxatives should be provided to the patient, along with opioid administration.[13]

Intensive communication between patients and physicians and early palliative treatment may increase the chance that patients accept their conditions and are satisfied with their patient-doctor relationship, increasing the patient's acceptance of symptom control and psychosocial intervention, resulting in reduced pressure. Reducing pressures experienced by patients is consistently associated with quality of life and survival. Furthermore, patients and their families that undergo early palliative care receive information regarding treatment and end-of-life decisions making; hence patients and their families are able to make careful decisions by respecting patient autonomy.[15]

Bioethic Principles of Palliative Therapy

Doctors and other medical professionals often face ethical challenges in applying palliative therapy to patients. Multiple dilemmas and medical issues arise in the implementation of palliative therapy.[13]

Medical bioethics is a field of applied ethics that studies the moral values and evaluation that is applied in the field of medicine. Medical bioethics aims to provide guidelines to doctors in performing their duties responsibly. [14]

There are four pillars of medical bioethics that are used in palliative therapy[14]

1. *Autonomy* – patient has the right to continue or terminate treatment
2. *Beneficence* – moral principles that prioritise interventions that benefit the patient
3. *Non-maleficence* – moral principles that prohibit interventions that worsen patient conditions, also known as the "*primum nonnocere*" principle
4. *Justice* – moral principal that prioritises fairness in the distribution of resources.

In addition to the four basic bioethical principles, other principles include dignity and honesty.

In cases of terminal advanced head and neck cancer, it is important for a doctor to understand the clinical decision-making process to stop and delay medical interventions. In terminal cases, patients and their families may experience difficulties in accepting the terms of curative treatment, thereby warranting effective communication regarding the disease process.[14]

Screening of palliative cases can be performed using several scoring systems. At Cipto Mangunkusumo National General Hospital (RSCM), palliative screening is scored based on:

1. Main disease
2. Comorbidities
3. Patient functional status based on the ECOG (Eastern Coorperative Oncology Group) performance status
4. Other criteria that must be considered (appendix 1).

Patients with a palliative score of 0 to 2 do not require palliative intervention. A score of 3 means that patient is still in the observation stage. If a patient score is $\geq$4, palliative consultation is required.

Case Report

A 43-year-old male patient, complaints of masses behind the ear and right lower jaw. Upon physical examination, the patient was found to have paresis of the right peripheral facial nerve (N.VII) and tetraparesis. CT scan results showed 2 uncorrelated masses. The masses extended into the spinal cavity, having solid multifocal malignant characteristics, located in the right mastoid, left mandibula, left parapharyngeal space and C1-T2 vertebra, with evidence of level I-II bilateral

cervical lymphadenopathy. Based on the immuno-histochemistry examination, the masses were shown to be solid type adenoid cystic carcinoma of the salivary glands.

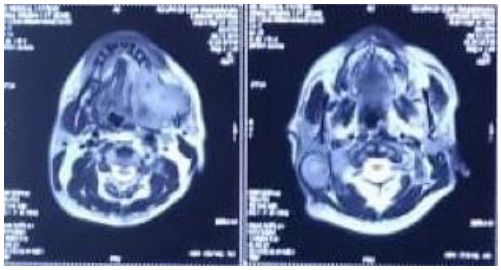


Figure 2. Mastoid MRI with contrast

Based on meetings with multiple disciplines, the patients were decided to undergo palliative care with the target of controlling pain. The pain medication given to the patient included 4x10mg of immediate release morphine, 3x600mg of gabapentin and 1x25mg of Duragesic patch. Throughout the treatment, a nasogastric tube (NGT) was also placed to ensure adequate nutritional needs were met. The urinary catheter was also placed throughout treatment.

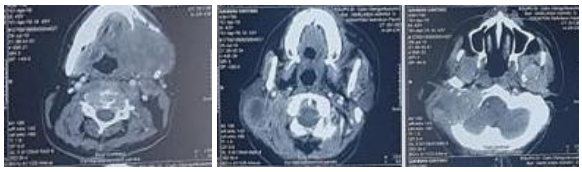


Figure 3. Neck CT scan

Literature Review

Clinical Question

Based on the case described above, a clinical problem exists with regard to patient treatment, especially with deciding to choose palliative therapy. Hence, the clinical question is as follows, "In patients with advanced stage head and neck cancer, does early palliative care improve the quality of life?"

P : Patients with advanced stage head and neck cancer
I : Early palliative head and neck cancer care
C : Head and neck cancer management
O : Quality of life

Based on the above clinical question, the eligibility criteria for the literature were created, which included:

1. Study design: systematic review, RCT, Observational study (cohort or case control)
2. Literature written in English or Bahasa Indonesia
3. Subjects were patients with advanced stage head and neck cancer
4. Received palliative care
5. Outcomes were measured using validated quality of life scoring tools

Search Strategy

The literature search was conducted using two databases: PubMed/Medline and Cochrane. Keywords used in the search strategy included *head and neck cancer, head and neck carcinoma, head and neck neoplasm, early palliative care, palliative care referral and quality of life.* Initial search results showed 5 literatures. The screening was conducted to remove duplicated articles, limit the search based on human subjects and availability of full text, resulting in 4 included articles. The articles were evaluated, and only 1 article met the eligibility criteria set by the authors.

Critical Appraisal Method

Critical appraisal of the included article was conducted by two researchers using the CEBM Oxford critical appraisal tool.

Critical Appraisal Results

The article by Haun et al,[15] is a systematic review consisting of 7 randomised controlled trials (RCTs) which aimed to understand the benefit of early palliative therapy in patients with advanced stage head and neck cancer. Outcome measures included quality of life, survival, depression, and severity of symptoms.

Table 1. Search method

Database	Seach Strategy	Hits	Selection
PubMed	(((head neck cancer[Title/Abstra ct]) OR head neck carcinoma[Title/Ab stract]) OR head neck neoplasm [Title/Abs tract])) AND ((early palliative care [Title/Abstract])OR palliative care refferal[Title/Abstract]))) AND quality of life[Title/Abstract]	1	1
Cochrane	Head and neck cancer AND earlypalliative care AND quality of life	4	1

They performed a search strategy in Medline, CENTRAL, EMBASE, PsycINFO, CINAHL and OPENGREY. EU databases, and from the references of the selected articles. Potential articles were searched from the bibliography of individual articles included in the systematic review and meta-analysis, so it could be entered into the systematic review. Articles that were included met the inclusion and exclusion criteria, which consisted of RCT study design on a group of advanced stage cancer that could not undergo curative treatment, recruited adults over the age of 18 and were receiving palliative care.

The authors excluded articles whose subjects were diagnosed with cancer since childhood or were predicted to have a remaining life expectancy of under three months since the start of the study.[13]

Data was extracted using a structured form by two independent researchers. Two researchers analysed the obtained data, and the accuracy was confirmed using the kappa statistic to determine if an eligibility criterion was required. Any disagreement between the researchers was discussed with a third independent researcher.[13]

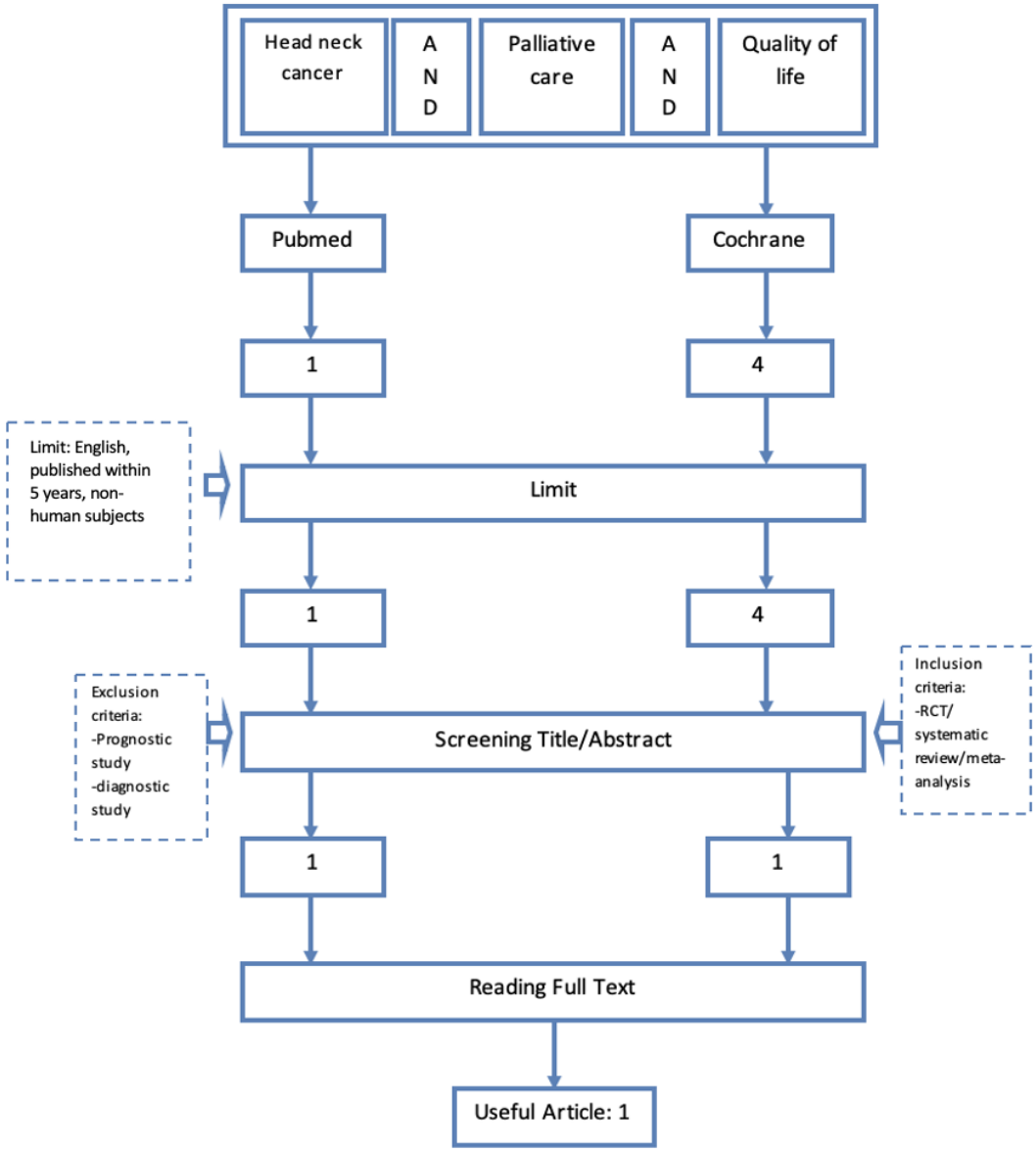


Figure 4. Search flow chart

In order to evaluate the quality of the study, the authors determined the eligibility of the study using a bias risk assessment based on the criteria stated in the *Cochrane Handbookfor Systematic Reviews of Interventions* and resolved differences in opinions through discussion. This study uses the Oxford Quality Score as the bases of the eligibility assessment. This article stated the combined effect of multiple studies as the standard mean differences (SMD).

Table 2. Critical appraisal

Q-FAITH Method Critical Appraisal	***YES/NO/NOT CLEAR***
Q*uestion*- Can the clinical question in this systematic review be defined clearly and specifically?	YES
F*ind*- Is the relevant search strategy stated clearly?	YES
A*ppraise*- Have the studies included been appraised critically?	YES
I*nclude*- Have the researchers obtained only high quality studies?	YES
T*otal up*- Are the results presented in a summary table and plots?	YES
H*eterogeneity*- Is there any heterogeneity between the studies?	YES

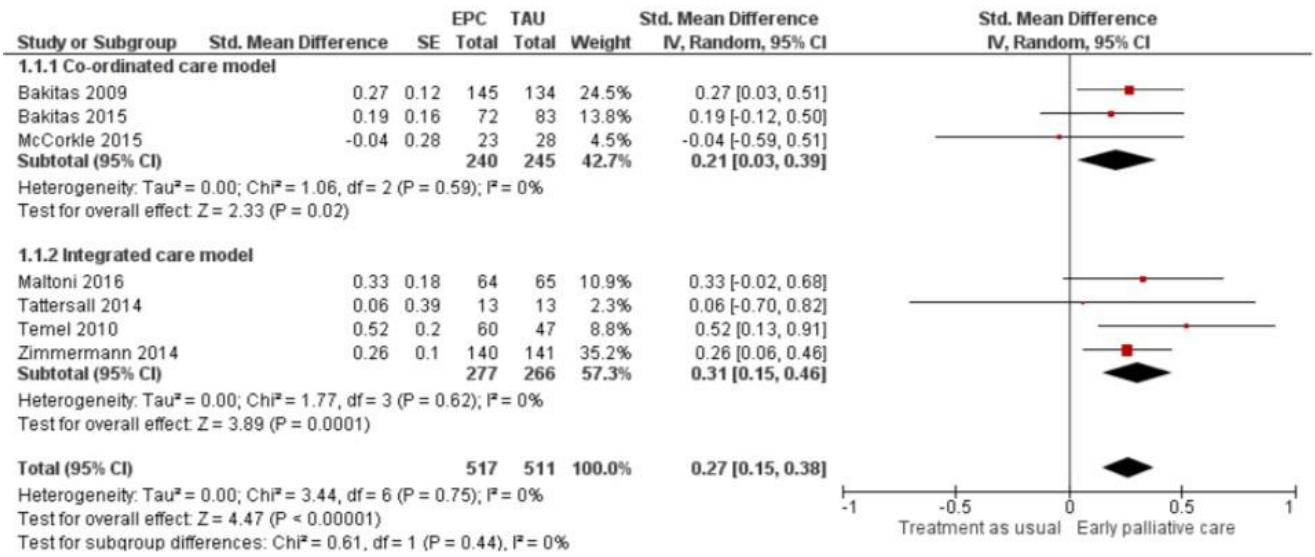


Figure 5. Forest plot comparing early palliative therapy vs without palliative therapy and overall patient quality of life.

Assessment of the trust level is conducted using the GRADE (Grading of Recommendations, Assessment, Development and Education) tool and is summarised in the table "Summary of Findings".[15]

Based on the search by Haun et al, it was found that patients receiving early palliative care had a significantly higher quality of life compared to cancer patients who were not receiving early palliative care (SMD 0.27, 95% CI 0.15-0.38). This result was statistically significant (Figure 3).[15]

In this article, the risk of bias is quite low (Figure 6). Among all the seven included studies, all studies were randomised using a random sequence generator to avoid selection bias. In this systematic review, the blinding of personnel was not included into the bias risk assessment. However, the authors were blind to the subjects and result assessment.[15]

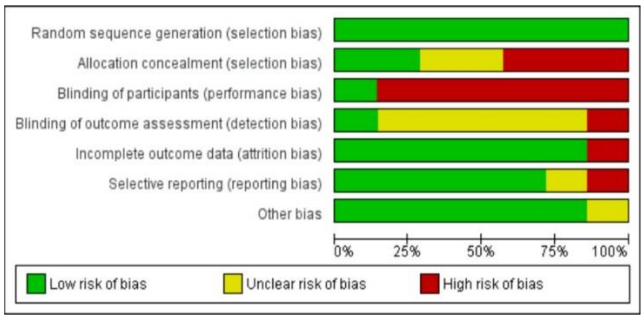


Figure 6. Bias risk

Discussion

Management of the patient in this case report is focused on palliative treatment since, in this case, tumor invasion into the spinal cavity had occurred, causing difficulty in mobilisation. Furthermore, the presence of spinal decompression from C1 to T2 in this patient increased the risk of respiratory depression if the intervention was performed without cervical stabilisation. Hence, palliative care played an important role in managing the patient described in the case report, including the family.[7,16,17]

Therapeutic choices for head and neck cancer include surgery, radiotherapy, and chemotherapy. The palliative approach plays a role at the point where the patient's condition determines the shift in the treatment plan from curative to palliative therapy. Conditions where the intervention may have a greater risk than the benefit towards the patient.[17]

Based on the article by Haul et al, from the 7 RCTs included in the study, results generally showed that early palliative therapy provided a statistically greater effect on the overall quality of life. Positive SMD values demonstrate a greater quality of life, whereas negative SMD values denote a lower quality of life. From the 7 RCTs in this systematic review, all studies used different standard effect size measures of quality of life, using scoring tools that were validated individually. [13]

Based on conventional criteria, a SMD score of 0.2 shows a small effect size, 0.5 denotes a moderate effect size, and 0.8 demonstrate a large effect size. Despite the small effect size obtained from the studies, this effect may be clinically relevant in advanced stage disease, where the prognosis is limited and overall quality of life tends to be lower. [15]

Apart from the quality of life, in this systematic review, overall survival, incidence of depression and severity of symptoms were also assessed. From the overall results, it can be concluded that there is a positive effect of palliative care, even though the size may not be large.[15]

Cancer is often diagnosed at a late stage of the disease. Patients may choose to start or continue curative treatments with potential side effects that may arise. However, patients may also choose to receive early palliative care. This approach, known as early palliative management, begins at or soon after the patient is diagnosed with advanced stage cancer. Palliative treatment is often combined with chemotherapy and radiotherapy. Early palliative management involves empathetic communication with patients regarding the prognosis, treatment plan and evaluation and control of symptoms.[15,18,19]

WHO has recommended all nations to implement comprehensive palliative care programs to increase the quality of life of patients, however, referral of patients for palliative care is often late. Quality of life is the focus of palliative care, and hence is chosen as the outcome measure in this study.[10]

In palliative care, it is essential to always evaluate each patient individually and to create a care plan according to the individual, disease stage, personal preference, and family's wishes. Meeting with family members to create a shared understanding between medical personnel and patient and family members is the first step of the palliative approach. By understanding the target and wishes of the patient and the family, treatment towards the patient can be maximised and guided. All decisions are made based on the results of the discussion between the patient and the medical personnel.[19,20]

Care for patients with head and neck cancer is quite challenging to the complex nature of nutritional needs, risk of airway obstruction, bleeding and psychosocial problem associated with chronic pain, communication difficulty, disability and addiction.[20]

Based on the results of this systematic review, further reviews with larger study sizes are required to obtain greater and more accurate effect size.

Conclusion

In patients with advanced stage head and neck cancer, whereby the patient's condition is inoperable, a palliative approach becomes the treatment of choice. Palliative therapy aims to increase the quality of life, via the control of symptoms experienced by the patient, as well as a spiritual and psychosocial approach.

Despite the small effect size obtained from this study, the results may be clinically relevant in patients with advanced stage head and neck cancer and limited prognosis. With these results, the addition of palliative care should be considered as a part of the protocol or recommended management of advanced stage head and neck cancer patients, especially in RSCM.

References

1. World Health Organization. The Global Cancer Observatory 2018. https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf. Published 2018. Accessed September 17 2019
2. Coca-Pelaz A, Rodrigo JO, Bradley PJ, Vander Poorten V, Triantafyllou A, Hunt JL, et al. Adenoid cystic carcinoma of the head and neck - An update. Oral Oncol. 2015;51(7):652-61.
3. Kokemueller H, Eckardt A, Brachvogel P, Hausamen JE. Adenoid cystic carcinoma of the head and neck – a 20 years experience. Int J Oral Maxillofac Surg. 2004;33(1):25-31
4. Grewal AS, Jones J, Lin A.Palliative radiation therapy for head and neck cancers. Int J Rad Oncol. 2019:1-12.
5. Begbie FD, Douglas CM, Finlay F, Montgomery J. Palliative intent treatment for head and neck cancer: An analysis of practice and outcomes. J Laryngol Otol. 2019:1-4.
6. Garg M, Tudor-Green B, Bisase B. Current thinking in the management of adenoid cystic carcinoma of the head and neck. Br J Oral Maxillofac Surg: 2019:1-6.
7. Wang X, Luo Y, Li M, Yan H, Sun M, Fan T. Management of salivary gland carcinomas – a review. Oncotarget. 2017;(8):3946-56.
8. van der Velden J, Willmann J, Spałek M, Oldenburger E, Brown S, Kazmierska J, Andratschke N, Menten J, van der Linden Y, Hoskin P. ESTRO ACROP guidelines for external beam radiotherapy of patients with uncomplicated bone metastases. Radiother Oncol. 2022 Aug;173:197-206
9. Oldenburger E, Brown S, Willmann J, van der Velden JM, Spałek M, van der Linden YM, Kazmierska J, Menten J, Andratschke N, Hoskin P. ESTRO ACROP guidelines for external beam radiotherapy of patients with complicated bone metastases. Radiother Oncol. 2022 Aug;173:240-253.
10. World Palliative Care Alliance. Global atlas of palliative care at the end of life. http://www.who.int/cancer/publications/palliative-care-atlas/en/. Published 2014. Accessed September 17, 2019.
11. Satija A, Lorenz K, DeNatale M, Spruyt O, Deo SVS, Bhatnaga S. Role of early palliative care in advance head and neck cancer. Indian J Palliat Care. 2019;25(1):153–5.
12. Levy MH, Back A, Benedetti C, Billings JA, Block S, Boston B, et al. NCCN clinical practice guidelines in oncology: Palliative care. J Natl Compr Cancer Netw. 2009;7:436-73.
13. Cocks H, Ah-See K, Capel M, Taylor P. Palliative and supportive care in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016; 130:198-207.
14. Mohanti BK. Ethics in palliative care. Indian J Palliat Care. 2009;15(2):89-92.
15. Haun MW, Estel S, Rucker G, Friederich HC, Villalobos M, Thomas M, et al. Early palliative care for adults with advance cancer. Cochrane Database Syst Rev. 2017;(6):1-32.
16. Trilling GM, Cho H, Ugas MA, Saeed S, Katunda A, Jerjes W, et al. Spinal metastasis in head and neck cancer. Head Neck Oncol. 2012;4:36.
17. Shuman AG, Yang Y, Taylor JM, Prince ME. End of life care among head and neck cancer patients. Otolaryngol Head Neck Surg. 2011;144(5):1-9.
18. Gardiner C, Ingleton C, Gott M, Ryan T. Exploring the transition from curative to palliative care: A systematic review of the literature. BMJ Support Palliat Care. 2015;5:335-42.
19. Davies L, Rhodes LA, Grossman DC,Rosenberg MC, Stevens DP.Decision making in head and neck cancer care. Laryngoscope. 2010;120:2434-45.
20. O'Sullivan EM, Higginson IJ. ''I'll continue as long as I can, and die when I can't help it'': a qualitative exploration of the views of end-of-life care by those affected by head and neck cancer (HNC). BMJSupport Palliat Care. 2016;6:43-51.

Appendix 1

<table>
<tr><td colspan="3">1. Main Disease</td><td colspan="2">2. Comorbidity</td></tr>
<tr><td colspan="3">Cancer (metastasis/recurrent)
Advanced COPD
Stroke (functional loss > 50%)
Chronic Kidney Disease
Severe heart disease : congestive heartfailure, severe coronary artery disease, cardiomyopathy (left ventricle ejection fraction < 25%)
HIV/AIDS
Severe congenital disorder
*Every point gets a score of 2. Score:_____</td><td colspan="2">a. Chronic Liver Disease
b. Moderate Kidney Disease
c. Moderate COPD
d. Congestive Heart Failure
e. Other conditions or complications

* Every point gets a score of 1
Score:_____</td></tr>
<tr><td colspan="3">3. Functional status
Using the ECOG performance status tool
(European Cooperative Oncology Group)</td><td>4. Other criteria under consideration
*Score 1 for each consideration</td><td>SCORE</td></tr>
<tr><td>Degree</td><td>Scale</td><td>Specific score</td><td>a. Will not undergo curative therapy</td><td></td></tr>
<tr><td>0</td><td>Active, can perform without difficulty like before the disease</td><td>0</td><td>b. Severe disease and chooses to terminate therapy</td><td></td></tr>
<tr><td>1</td><td>Some difficulty faced upon heavy activity, but can perform light work, such as light house and office work</td><td>0</td><td>c. Pain lasting for over 24 hours</td><td></td></tr>
<tr><td>2</td><td>Able to walk and care for self, but cannot perform activities for >50% hours awake</td><td>1</td><td>d. Experiences uncontrolled symptoms such as nausea and vomiting</td><td></td></tr>
<tr><td>3</td><td>Limited care for self, spends most of the time in bed or wheelchair > 50% of hours awake</td><td>2</td><td>e. Requires psychosocial and spiritual care</td><td></td></tr>
<tr><td>4</td><td>Cannot care for self, spends most of the time in bed, severe disability</td><td>3</td><td>f. Frequent emergency room visits > 1x/month for the same diagnosis</td><td></td></tr>
<tr><td colspan="2" rowspan="3">TOTAL SCORE</td><td rowspan="3"></td><td>g. More than once for the same diagnosis in 30 days</td><td></td></tr>
<tr><td>h. Prolonged hospital admission without significant improvement</td><td></td></tr>
<tr><td>i. Prolonged ICU admission without significant improvement</td><td></td></tr>
</table>

Score Interpretation
Score 0 - 2 : does not require palliative treatment
Score 3 : observation
Score ≥4 : requires palliative consultation

InaJCC The Indonesian Journal of Cancer Control

Special Article

See and Treat: Cervical cancer prevention strategy in Indonesia with VIA-DoVIA screening and prompt treatment

Laila Nuranna

Check for updates

p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v2i1.70

Received: June 30, 2021
Accepted: April 15, 2022

Authors' affiliations:
Gynecology Oncology Division, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia / Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding author:
Laila Nuranna
Email: lairalil@gmail.com

Abstract

Cervical cancer, as the second most common type of cancer in Indonesia after breast cancer, is a major problem for Indonesian women. Cervical cancer can be prevented with HPV vaccination and various screening/early detection methods, such as Pap smear, VIA (visual inspection with acetic acid) test, and HPV-DNA test. Currently, VIA test is the chosen screening method for cervical cancer in Indonesia, as it is easy, cheap, accurate, and can be implemented in all regions of the country. The VIA method was developed using VIA documentation (DoVIA) and VIA documentation telemedicine (TeleDoVIA). It is established that positive findings should be treated with cryotherapy. This serial of diagnosis using VIA screening and treatment with cryotherapy is termed See and Treat. Subsequently, it is developed into Screen and Treat. The gas supply for cryotherapy may become a challenge, which drive the search for an alternative therapeutic method, such as using TCA (trichloroacetic acid). Strategies for the prevention of cervical cancer includes implementation of HPV vaccination (90%), 70% coverage of screening, and treatment after positive findings (90%). The involvement of the authorities is crucial for the achievement of strategical target and its public implementation, by setting regulations for the success of screening coverage.

Keywords*: cervical cancer, DoVIA, see and treat, TeleDoVIA, VIA*

Abstrak

Kanker serviks menjadi masalah bagi kesehatan perempuan Indonesia, menduduki peringkat kedua setelah kanker payudara di Indonesia. Kanker serviks dapat dicegah, dengan vaksinasi HPV, upaya skrining/deteksi dini kanker serviks dengan beberapa metode skrining a.l. pap smear, tes IVA (inspeksi Visual dengan Asam Asetat), tes HPV-DNA. Saat ini untuk Indonesia dipilih metode skrining kanker serviks dengan tes IVA, karena metode ini mudah, murah, akurat, dan dapat dilaksanakan di seluruh pelosok negeri. Metode tes IVA dikembangkan dengan dokumentasi IVA (DoIVA) dan untuk konsultasi, dengan Telemedisine Dokumentasi IVA (TeleDoIVA). Telah ditetapkan temuan positif diterapi dengan krioterapai, maka rangkaian diagnosis dengan skrining IVA, dan dilakukan terapi dengan krioterapi, menjadi rangkaian See and Treat. Pengembangan nya menjadi Screen and Treat. Adanya kendala pengadaan gas untuk krioterapi, mendorong upaya mencari metode terapi lain, yaitu dengan TCA (Tri Chloro Acetic acid). Terlaksananya Vaksinasi HPV (90%), tercapainya 70% cakupan skrining, terapi pada temuan skrining positif (90%), menjadi strategi bagi upaya pencegahan kanker serviks. Dalam penerapannya di masyarakat agar pencapaian target strategi dapat tercapai, kiranya diperlukan keterlibatan peran otoritas untuk menetapkan regulasi agar cakupan skrining dapat tercapai.

Kata kunci: DoIVA, IVA, kanker serviks, see and treat, TeleDoIVA

This article is translated from the author's professorial inauguration speech on April 24th 2021 at the Auditorium Room of FMUI Salemba campus, Jakarta.

Background

Cervical cancer is the second most prevalent cancer in Indonesian women, just after breast cancer.[1,2] A successful method for detection most commonly used in developed countries is the Pap test, which is difficult to implement in Indonesia. In the US, for example, 50 million Pap tests are conducted yearly with an estimated cost of 1.5 billion USD,[3,4] which is approximately 21 trillion IDR, the equivalent of about a third of Indonesia's Ministry of Health's expenditure in 2020.[5]

The government of Indonesia has allocated 49 million USD, approximately 704 billion IDR, as the budget for cervical cancer management in 2020.[6] In order to execute Pap tests with the aforementioned amount, the US employs 18,640 dual anatomic pathology and clinical pathology specialists and 5,729 anatomic pathologists, totaling at 24,360 anatomic pathologists with the capacity to perform Pap tests.[7] Additionally, approximately 10,000 cytotechnologists, certified associate bachelor of science, are presented to help.[8] Accounting for population differences, implementing the same resource in Indonesia requires 19,800 anatomic pathologists.[9,10] In 2016, there were only 681 anatomic pathologists in Indonesia.[11] Thus, noting the available resources and the country's unique geographic terrain, the Pap test cannot yet be performed as a routine screening program in Indonesia; an alternative method is needed.

Cervical cancer differs from most malignancies in that its cause is well known. Harald zur Hausen was awarded a Nobel prize in 2008 for discovering that Human Papilloma Virus (HPV) is the cause of cervical cancer.[12] Its transmission widely suggests that sexual activity is a risk factor for cervical cancer.[13–15]

Cervical Cancer As A Challenge for Women's Health in Indonesia

There are several main discussion points regarding cervical cancer in Indonesia

1. Cervical cancer as a challenge for women's health
2. The need for early education for students regarding reproductive health and malignancies of the reproductive organs.
3. Direct mass education: cervical cancer prevention, early detection with VIA, Pap test, or HPV DNA test. Early detection, do not wait until a symptom appears.
4. Health professional training to raise capability and competence for cervical cancer screening.
5. Choosing an easy, affordable, accurate, and accessible screening method, such as VIA.
6. Implementation of *See and Treat.* Viable therapeutic modality includes cryotherapy, trichloroacetic acid (TCA), and cold coagulation.[16-17]
7. The need for mandatory screening regulation for married Indonesian women in areas capable of running a screening program resource-wise.

Based on the 2020 survey data of GLOBOCAN, it is estimated that there are 604,127 new cases of cervical cancer and 341,831 deaths relating to cervical cancer, most of which are from low and medium-low-income countries.[18] In Indonesia in 2020, there were 36,633 new cases of cervical cancer and 21,003 cervical cancer-related deaths. This nearly doubles from 2012, when new cases of cervical cancer were only around 20,000.[19] Cervical cancer is the second leading cause of cancer-related death in Indonesian women, just after breast cancer.[18] The high death rate in Indonesia's cervical cancer cases can be attributed to the fact that most cases (70%) are found already in the late stages.[20]

On April 21st 2015, the national movement for prevention and early detection of cancer in women (*Gerakan Nasional Pencegahan dan Deteksi Dini Kanker pada Perempuan*) was planned by First Lady Iriana Joko Widodo at Puskesmas Nanggulan public health center, Kulonprogo, Yogyakarta.[21] The execution of this program is regulated under The Minister of Health of The Republic of Indonesia Number 34 of 2015 concerning Breast Cancer and Cervical Cancer Management. Early detection using Visual Inspection with acetic acid (VIA) or pap smear and management of precancerous lesions with cryotherapy is collectively known as See and Treat.

A positive finding in screening is futile if not followed by prompt treatment. However, in a pilot national cervical cancer program, an area showed that only 30% of those who were screened positive continued to cryotherapy. Data from Faculty of Medicine, Universitas Indonesia, the Female Cancer Program (FMUI-FCP) shows that only 60% of patients who tested positive for VIA were treated.[22] Meanwhile, the World Health Organization (WHO) recommended that at least 90% of precancerous lesion cases be treated.[23]

Cryotherapy requires N_2O/CO_2 gases, which have limited availability in certain areas. Therefore, an alternative treatment method is required. One viable modality is Trichloroacetic acid (TCA), known for its cosmetic use in chemical peeling.[24] TCA is more

commonly used to treat condyloma acuminate (genital warts), but an 85% concentration of TCA can be used to treat cervical precancerous lesions. A study by Suwartono shows that 97.2% of patient with TCA treatment undergoes conversion to VIA-negative after three months. Compared to cryotherapy, there appears to be no significant difference in using TCA on VIA-positive cases.[16]

Basic Concepts and Target of Cervical Cancer Prevention

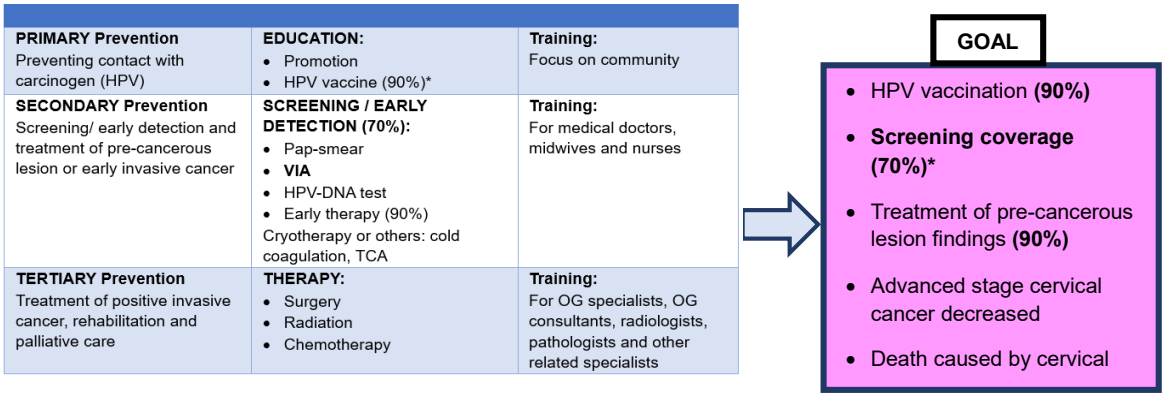


Figure 1. Concepts and Targets *) Target established by WHO for the year 2030.[25]

Purpose of Program:

Institutions responsible for cervical cancer prevention programs must have united long-term goals for Indonesia, which are adapted from WHO's target for the year 2030:[25]

1. HPV vaccination (90%)
2. Screening coverage (70%)
3. Therapy for those screened positive (90%).
   Cervical cancer has a clinical progression that starts from the precancerous lesion and ends with invasive cancer in 3 to 17 years. The broad period of time for detection gives birth to the concept of *kenalilah aku pada tahap prakanker* (Recognize Me in Precancerous Stage), as treatment is relatively easy and can reach 100% clearance in precancerous lesions.
4. Reduction of late-stage cervical cancer cases.
   Currently, most cases (70%) are in the late stages.[20]
5. Reduction of cervical cancer-related death.
6. Assurance of program sustainability.
7. Data surveillance for cervical cancer screening.
8. Building a national cervical cancer prevention network.

Developing a cervical cancer prevention strategy in Indonesia and possible solutions to challenges involved is essential. The basic concept of cervical cancer management is as follows:

1. Primary prevention.

Efforts to prevent the causative agent, HPV, from entering the target organ, the cervix. This includes health education to create healthy living habits away from possible HPV infection, such as safe sexual practices, lower promiscuous tendencies, no smoking, and consumption of nutritious foods. A brief and to-the-point message is developed for the public:

a. "All married women or engaged in sexual activity must undergo cervical cancer screening."
b. "Early detection, do not wait for a symptom."

This leads to the notion that the knowledge and education to prevent cervical cancer should be formally taught to students in secondary education within the school's curriculum. Another important primary prevention method includes the HPV vaccine, which has been available since 2006. Available vaccine variant includes the bivalent vaccine (against HPV type 16 and 18) and the quadrivalent vaccine (against HPV type 16,18, and low-risk HPV type 6 and 11). A nine-valent vaccine (against HPV type 6,11, 16, 31, 33, 45, 52, 58) has also recently made available.[26,27] In Indonesia, efforts to implement the HPV vaccine for students started with the Student Immunisation Month program (BIAS) on October 4th, 2016.

2. Secondary Prevention.

Secondary prevention entails early detection in populations where HPV exposure was not prevented. This is done with screening, such as with the VIA method. The following should be accounted for in secondary prevention:

a. **Screening coverage** ideally reaches at least 70% of the target. The target for this coverage is at-risk women, i.e., those married and aged 30-50. However, the Indonesian society of oncology and gynecology (HOGI) suggests that the screening should be broadened to include 25 to 65-year-olds since the prevalence of cancer in those aged 50 years above is still high.[28,29] To achieve the targeted screening coverage, the screening method must be relatively easy to do, affordable, accessible, and applicable while still having good sensitivity and specificity.

b. **Choice of screening method.** Several methods for cervical cancer screening are known; Pap smear, HPV DNA test, visual inspection with acetic acid (VIA), and colposcopy. Historically, there was also what was known as gynoscopy (using a magnifying glass with a 2.5x power) and cervicography (using a camera equipped with a ring light). Cytology methods also vary from conventional cytology, liquid-based cytology, and examination of the cancer etiology, the HPV.

The USA spearheaded the movement toward HPV genotyping-based screening, where the majority of screeners agreed to change regulation from cytology-based to primarily based on HPV genotyping (Genotyping-HR HPV).[30] The Eurogin conference in Europe 2015 had also agreed on HPV-based screening and increasing HPV vaccination. The introduction of the HPV vaccine in the early 21st century showed that wide vaccine coverage caused a decline in HPV infection and precancerous lesions.[31]

Among all the available screening methods, VIA appears inferior at first. However, the power of looking at the cervix using VIA, combined with documentation (DoVIA), is now considered to be capable of being a confirmatory test before definitive testing in high-degree lesions. Equipment required for VIA includes speculum, light source, and 3-5% acetic acid solution. The advantage of the VIA method is the immediate result. VIA has also shown good sensitivity and specificity (94% and 95%, respectively).[32]

Conventionally, VIA does not include documentation, thus making confirmation difficult to do. Current development adds the use of camera, which is available in most person's phone nowadays. With a few tweaks, the camera can shine a light on the cervix for visual clarity and take a photo for documentation. This is known as documented VIA (DoVIA), and the documentation quality is regarded as equivalent to colposcopy.[33] With the documentation photo, it is possible to communicate and consult the finding by sending the DoVIA photo through applications such as WhatsApp messenger, creating telemedicine DoVIA (TeleDoVIA), and allowing long-ranged consultation. Our team has trained an area in Ambon, Fakfak Papua, for this method; they can send a picture from there and get answers in less than an hour, even in minutes.[34]

Documentation of visual inspection with acetic acid (DoVIA)

DoVIA reduces the possible bias from the VIA examiner and provides material for long-ranged communication and consultation. For example, a midwife or a doctor in Fakfak Papua can send a DoVIA photo to Jakarta with WhatsApp messenger applicaiton, and get an answer instantly. The entirety of this method is dubbed telemedicine documentation of VIA (TeleDoVIA). TeleDoVIA also monitors and evaluates the examiner's performance after VIA training, using long-range communication.

When screened positive, apply prompt treatment: See and treat

The protocol for a positive VIA finding is to treat in at least 90% of the cases,[29] for example, using cryotherapy. However, one issue in cryotherapy is the unavailability of N_2O or CO_2 gas. Currently, cold coagulation or trichloroacetic acid (TCA) is being considered.[24] This is the implementation of See and Treat, assuring that the positive finding in screening is not for naught. Most positive results in screening (90-95%) are caused by precancerous lesions, which are relatively easy to treat, with a recovery rate of nearly 100%. The available method in primary health care facilities in Indonesia is cryotherapy, usingN_2O or CO_2 gas to freeze the cervix. This method is simple, effective, and takes no longer than 20 minutes (3'-5'-3'). In practice, however, there are problems regarding gas availability, especially in secluded areas. With the See and Treat concept, Nuranna practices in a regional health care facility in Northern Jakarta using VIA screening followed by cryotherapy. She dubbed

this approach "Proaktivo," proactively screening with VIA and treating with cryotherapy.[32]

3. Tertiary Prevention

This stage of prevention is done in cases of confirmed invasive cancer. The prevention here refers to the prevention of death, and it is hoped that the patient's well-being can increase with adequate therapy. The therapy mainly consists of operative procedures, radiation, or combination with chemotherapy. This paper will not discuss tertiary prevention in detail.

Answering cervical cancer challenges in Indonesia

To achieve successful screening practice, there are a few notes to remember:

1. Goal determination, which is commonly women between 30 – 50 years old (± 1/6 of the population), in accordance to WHO. However, cervical cancer can occur as soon as three years after sexual activity, and in Indonesia, cervical cancer patients aged 50 years above are plentiful. Thus, the recommended screening age is 25 – 65 years old, or ±1/3 of the population. Because the VIA screening method is relatively easy dan affordable, the broader target age range of 25-65 years is still doable.
2. Develop documentation on VIA. There may be times when VIA interpretation is hindered and subjected to bias. DoVIA can solve that and enable VIA examiners to send photos to experts with TeleDoVIA. Interpretation can then be given without concern for distance.
3. The main challenge would be raising awareness in the women population on the importance of screening so that they come to their health care centers to check themselves. Stricter regulation in the form of legislation bills and government regulation (at the hands of the house of representatives or regional house of representatives) may be needed. Implementing the regulation nationally is a bit difficult, but it can be tried on a regional level in areas with adequate healthcare resources.
4. Building a national cervical cancer prevention data network would detail the precancerous lesion finding, any given therapy, and follow-up observations. It should also be possible to know if there is a recurrent lesion or if any lesions have become invasive cancer.

Implementation of Cervical Cancer Prevention Program with the Five Pillar Model

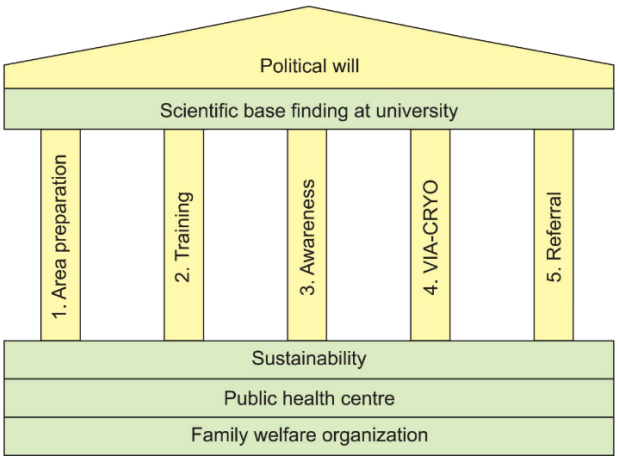


Figure 2. The Five Pillar Model for Cervical Cancer Prevention[35]

Coordination is necessary to practice cervical cancer prevention. The various activities we do with FMUI-FCP are coordinated under one model: The Five Pillar Model for Cervical Cancer Prevention.[35]

Conclusion

1. From a decade's study, it is found that the screening method applicable in Indonesia without sacrificing accuracy is VIA.
2. To increase objectivity in VIA tests, documentation on VIA (DoVIA) can be done with cell phone cameras. Furthermore, DoVIA can be used for telemedicine (TeleDoVIA).
3. A positive finding from VIA should be promptly treated. This approach is known as See and Treat. Aside from cryotherapy, the current modality in development is trichloroacetic acid (TCA).
4. A message to the public, especially to the women population:
   a. All women at risk (those who are married or have done sexual intercourse) must check themself for early detection of cervical cancer with a VIA test, Pap test, or HPV DNA test
   b. Early detection of cervical cancer should not wait for a symptom to appear.
5. The involvement of the government is essential. Strict regulation should impose mandatory periodic screening.

6. As a lecturer at Universitas Indonesia, while sailing the ocean of knowledge and life, I want to leave the following message for myself and my students: Your knowledge and your skill are essential, but your character is more. With a strong and sturdy character, keep learning and acquire valuable knowledge and skills. The most beautiful life is a beneficial one.

References

1. Kementrian Kesehatan Republik Indonesia: Komite Penanggulangan Kanker Nasional. Panduan Penatalaksanaan Kanker Serviks. 2019
2. Sunanti N. Deteksi dini kanker serviks: studi cross sectional pada ibu rumah tangga di pedesaan. J Kesehat "Samodra Ilmu. 2016;7:133–41.
3. Insinga R, Glass A, Rush B. Pap screening in U.S. health plan. Cancer Epidemiol Biomarkers Prev. 2004;13:355–60.
4. University of Pittsburgh Medical Center. Pap test cost. Health & Personal Care Information. A Conventional Pap test $25 to $40, liquid – based (ThinPrep) $ 45 to $60.
5. Kementrian Kesehatan Republik Indonesia, 2020
6. Setiawan D, Andriyono, Hadinegoro S, Meyta H, Sitohang R, Tandy G. Cervical cancer prevention in Indonesia: an updated clinical impact, cost-effectiveness and budget impact analysis. PLoS One. 2020;15.
7. American Medical Board of Specialties Certification Report 2016-2017 AP/CP 18.640 AP 5.720.
8. Stevens S. Maping the literature of cytotechnology. Bull Med Libr Assoc. 2000;88:172–7.
9. Badan Pusat Statistik. Sensus Kependudukan Indonesia. 2020.
10. Worldometer US Population. United States Population [Internet]. [cited 2021 Apr 12]. Available from: www.worldometers.info
11. Badan PPSDM Kesehatan. Informasi SDM Kesehatan. 2016.
12. Nobelförsamlingen. The Nobel Assembly at Karolinska Institutet. The Nobel Prize in Physiology or Medicine 2008. Is awarded with one half to Harald zur Hausen for his discovery of "human papilloma viruses causing cervical cancer".
13. Burk R, Ho G, Beardsley L, Lempa M, Peters M, Bierman R. Sexual behaviour and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. J Infect Dis. 1996;174:679–89.
14. Bosch F, Qiao Y, Castellsagué X. The epidemiology of humanpapilloma virus infection and its association with cervical cancer. Int J Gynecol Obs. 2006;94:S8– 21.
15. Gladden P, Tedesco A. Encyclopaedia of Personality and Individual Difference: Chapter Sexual promiscuity. In: Ziegler-Hill V, Shackelford TK eds. New York Springer Int. 2018;
16. Herdhana S, Andrijono. Eficacy of Trichloroacetic Acid (TCA) Compared to Cryotherapy in Treating Patients with Positive IVA Result. INAJOG. 2020;8(4):249–53.
17. L. Dolman, C. Sauvaget, R. Muwonge, and R. Sankaranarayanan. Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review BJOG, 2014; 121: pages 929–942; DOI: 10.1111/1471-0528.12655)
18. Cancer TIA for R on. GLOBOCAN 2020 : New Global Cancer Data [Internet]. 2020 [cited 2020 Apr 12]. Available from: UICC.org/news/globocan-2020
19. Internatioanal Agency for Research on Cancer For Worldh Health Organization. Global Cancer Observatory (GLOBOCAN) : Indonesia 2012 [Internet]. Available from: http://globocan.iarc.fr/Pages/online.aspx
20. Nuranna L, Fahrudin A. Survival Rate of Cervical Cancer in National Referral Hospital in 2012-2014. Acta Med Indones [Internet]. 2019; 51(2). Available from: http://www.actamedindones.org/index.php/ijim/article/view/1058
21. Menteri Kesehatan Republik Indonesia. *Buletin Jendela Data Dan Informasi Kesehatan*. Kementerian Kesehatan Republik Indonesia; 2015.
22. Ditjen P2P, Kemenkes RI. Laporan Kinerja: Direktorat Pencegahan dan Pengendalian Penyakit Tidak Menular. 2020.
23. Female Cancer Foundation. Female Cancer Program, Indonesia : Report. 2019.
24. Yonei N, Kanazawa N, Ohtani T, Furukawa F, Yamamoto Y. Induction of PDGF- B in TCA-treated epidermal keratinocytes. Arch Dermatol Res. 2007;299(9):433– 40.
25. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. 2020.
26. Cheng L, Wang Y, Du J. Human papillomavirus vaccines: an update review. Vaccines. 2020;391(8).
27. Sangar V, bivalent and quadrivalent human papillomavirus (HPV) vaccines: a review. Int J Pharm Sci Rev Res. 2013;23:247–53.
28. Nuranna L, Donny N, Purwoto G, Winarto H, Utami T, Anggaraeni T, et al. Prevalence, Age Distribution, and Risk Factors of Visual Inspection With Acetic Acid-Positive From 2007 to 2011 in Jakarta. J Cancer Prev. 2017;22(6):103–7.
29. Anggraeni T, Nuranna L, Sobur C, Al E. Distribution of Age, Stage, and Histopathology of Cervical Cancer: A Retrospective Study on Patients at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, 2006-2010. Obs Gynecol. 2011;35(1).
30. Wentzensen N, Arbyn M, Berkhof J, Bower M, Al E. Eurogin 2016 Roadmap: how HPV knowledge is changing screening practice. Int J Cancer. 2016;140:2192–200.
31. Giuliano AR, Nyitray AG, Kreimer AR, Pierce Campbell CM, Goodman MT, Sudenga SL, et al. EUROGIN 2014 roadmap: Differences in human papillomavirus infection natural history, transmission and human papillomavirus-related cancer incidence by gender and anatomic site of infection. Int J Cancer. 2015;136(12):2752–60.
32. Nuranna L. Penaggulangan Kanker Serviks yang Sahih dan Andal dengan Model ProAktif-Vo (Proaktif, Koordinatif dengan Skrining IVA dan Terapi KRIO). Disertasi. 2005.

33. Nuranna L, Wardany RS, Purwoto G, Utami TW, Peters L. Agreement Test of Documentation of visual Inspection with Acetic Acid “DoVIA” and Colposcopy findings as a Screening Tool for Cervical Cancer. Indones J Obstet Gynecol. 2020;8(1):61–5.
34. Nuranna L, Purwoto G, Sukana A, Peter A. TeleDoVIA Meeting the Challenge of Early Detection on Cervical Cancer: A Pilot Study in Indonesia. Scitepress. 2020;13–6.
35. Tim Penerima Hibah Kajian Strategis Universitas Indonesia, HOGI DOGF, Female Cancer Program. Model Lima Pilar Menjawab Tantangan Pencegahan Kanker Serviks. DRPM. Universitas Indonesia; 2018.

InaJCC The Indonesian Journal of Cancer Control

Review Article

Perianal infections in acute leukemia patients who received induction and consolidation chemotherapy: Clinical manifestations, pathogenesis, complications, management, and prevention

Diah Pitaloka[1], Adhimukti T. Sampurna[1], Aida SD Hoemardani[2], Nandita Melati[3]

Check for updates

p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v2i1.54

Received: January 25, 2022
Accepted: April 25, 2022

Authors' affiliations:
[1]Department of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia / Dr. Cipto Mangunkusumo National Central General Hospital, Jakarta, 10430, Indonesia
[2]Medical Staff Group of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia/Dharmais National Cancer Hospital, Jakarta, 11420, Indonesia
[3]Department of Plastic Surgery, Faculty of Medicine Universitas Indonesia / Dr. Cipto Mangunkusumo National Central General Hospital, Jakarta, 10430, Indonesia

Corresponding author:
Diah Pitaloka
Email: jdpitaloka@gmail.com

Abstract

Perianal infection (PI) is one of the complications often found in acute leukemia patients who received induction and consolidation chemotherapy. Perianal mucosal damage in these patients can be a port of entry of pathogenic microorganism. Clinical manifestations of PI can range from abscess and fistula to life-threatening complications of tissue necrosis and sepsis. Patients with neutropenia sometimes do not show profound signs of inflammation so that diagnosis sometimes requires imaging studies. These conditions not only cause death, but also decreases the patient's quality of life. Management of PI includes surgical and nonsurgical procedures, both of which show good results in most patients, however complications such as sepsis and necrosis can still be found. Prevention and early diagnosis of PI in leukemia patients are important and need to be developed.

***Keywords**: acute leukemia, chemotherapy, management, neutropenia, perianal infections*

Abstrak

Infeksi perianal (IP) merupakan salah satu komplikasi yang sering ditemukan pada pasien leukemia akut yang mendapatkan kemoterapi induksi dan konsolidasi. Pasien tersebut mengalami kerusakan mukosa perianal yang dapat menjadi *port de entrée* mikroorganisme patogen. Manifestasi klinis IP dapat berupa abses dan fistula hingga komplikasi nekrosis jaringan dan sepsis yang mengancam nyawa. Pasien dengan neutropenia terkadang tidak menunjukkan tanda inflamasi yang jelas sehingga penegakan diagnosis membutuhkan pemeriksaan penunjang dengan pencitraan. IP tidak hanya menyebabkan kematian, namun juga menurunkan kualitas hidup pasien. Tata laksana IP meliputi tindakan non-bedah dan bedah. Kedua tindakan tersebut menunjukkan hasil yang cukup baik pada sebagian besar pasien, namun komplikasi berupa nekrosis dan sepsis tetap dapat ditemukan. Untuk mengatasi hal tersebut perlu dikembangkan cara pencegahan dan diagnosis dini.

***Kata kunci**: infeksi perianal, kemoterapi, leukemia akut, tata laksana, pencegahan*

Background

Leukemia is a group of hematologic malignancy characterized by abnormal leukocyte proliferation and development. Until recently chemotherapy is one of the treatment options for leukemia. During induction-consolidation chemotherapy, neutropenia occurs and causes patients with leukemia become susceptible to infections.[1-3] One of the infections that frequently found is perianal infections (PI) which can manifest as abscess and fistula.[1,3] If it is not treated quickly, it will cause widespread infection and life-threatening sepsis.[3,4]

A study by Chen et al in Taiwan in 2013, which involved 1,102 adult patients with acute leukemia from 2001 to 2010 showed PI prevalence of 6.7% (74 patients). Twenty-three (31%) of 74 patients had recurrent PI.[2] A retrospective study from Turkey in 2016, with 79 acute leukemia patients who received chemotherapy, found that 34 patients had anorectal infection.[3] Other data from a study in Canada by Renzi et al In 2019, found 233 pediatric patients with acute myeloid leukemia (AML), 7% of the subjects experienced PI in the form of abscesses.[1] Based on data from Global Burden Cancer Study (GLOBOCAN) in 2020, the increase in the new number of leukemia cases in Indonesia was 14,979 cases with number of deaths of 11,530 cases.[5] However, there are no data that show the prevalence of PI either in adults or children.

Clinical Manifestation of Perianal Infections

The most common clinical manifestation of PI are abscess and fistula.[1,3,4,6] It is often accompanied by severe pain, swelling, and constipation.[2]

1. Abscess

An abscess is a localized collection of fluid. Perianal abscess occurs due to infection of cryptoglandular glands by bacteria. The inflammatory response begins with a neutrophil response, followed by the formation of pus which then formed an abscess. Abscess may form in submucosa, intermuscular, supralevator, and ischiorectal. The infection may resolve with an immune response or may become more severe, causing pain, swelling, and drainage.[4] In 2017, Chang et al. conducted a retrospective study of 292 patients data and found that in acute leukemia patients who received chemotherapy, the incidence of perianal abscess (PA) ranged from 5–9%. This study showed a low mortality rate of 14.3%, but it showed that patients with AP had a 10-fold risk experienced recurrent abscess after subsequent chemotherapy.[6,7]

2. Fistula

An abscess may heal permanently, but it may relapse in the same location and form drainage. This drainage or channel connects glands of cryptoglandular anal and perianal skin, this channel is called a perianal fistula (PF). It is estimated that one third of patients with PA may experience PF formation. PA is the acute manifestation of PI, and PF is the chronic manifestation.[2,4]

Pathogenesis

Leukemia is a group of blood malignancy disease characterized by the growth of immature progenitor cells in the bone marrow. Based on the degree of cell differentiation, leukemia can be classified into acute and chronic leukemia, while based on the dominant cell type involved, it can be divided into myeloid and lymphocytic. This disease may often cause thrombocytopenia, anemia and leukopenia. The exact cause of leukemia is unknown, non-specific symptoms include fever, fatigue, weight loss, bone pain, bruising, or bleeding. Acute leukemia can be divided into three types including, acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL) and the rare form which mixed form or mixed phenotype acute leukemia (MPAL).[9]

Patients with leukemia are susceptible to infection. Infection is caused by complex interaction between disease, immune system, and pathogenic bacteria, causing significant morbidity and mortality. The severity of infection is influenced by several factors, the disease-related factors, patient-related factors and treatment-related factors.[9] (Figure 1)

Leukemia treatment, particularly chemotherapy is divided into induction phase, consolidation phase and maintenance phase. Induction phase chemotherapy is the first chemotherapy that aims to destroy leukemia cells in the bone marrow. Consolidation phase is a follow-up treatment to remove residual leukemia cells after induction phase, while maintenance phase is provided to prevent recurrence and maintain long-term remission.

1. Disease-related factors

In patients with leukemia, the normal function of bone marrow become disrupted so that proliferative cells experience abnormal maturation (immature) and

result in the interference of granulocyte function and decrease in the number of immune cells in the blood circulation. It makes the organism more susceptible to infection. Furthermore, abnormal cells have the potential to inhibit response of antigen specific T-cells, in addition there is a decrease in the humoral immune system, therefore most patients will experience immunoglobulin deficiency.[9] In AML there is a unique immune dysregulation which can avoid the body's immune system by controlling and actively suppresses the immune response (immune editing and immune evasion).[10] Certain chemotherapy regiments at induction phase in AML also causes neutropenia that last longer than the induction phase in ALL, so that the incidence and the severity of infection in AML patients is higher than in ALL patients.[9,10]

2. Patient-related factors

a. Age

Patient's age is important in assessing the risk of infection in acute leukemia patients. The natural function of the immune system declines with increasing age, such as the function of B and T cells. In elderly people the condition of imbalance between inflammatory and anti-inflammatory mechanisms leads to remodeling and the up regulation of pro-inflammatory cytokines. This condition known as immunosenescence and caused a modification of apoptotic lymphocytes.[10] Elderly patients also often have comorbidities that affect the choice and dose of treatment, thereby increase the risk of disease morbidity and mortality.[11]

b. Nutrition

Nutrition is also considered as one of the factors that influence infection susceptibility. Nutritional problems are often associated with side effects of leukemia treatment, such as nausea and vomiting. Reduced food intake, low baseline body mass index (BMI) and weight loss during treatment are strong indicators of low survival rates and bacterial and fungal infection.[15]

3. Treatment-related factors

Leukemia treatment requires intensive chemotherapy with certain drug doses and might last for certain period of time so that result in prolonged neutropenia. The risk of infection is influenced by the degree and duration of the neutropenia. Gill et al found cytopenia in patient with chronic lymphocytic leukemia (CLL) namely the decrease in the number of mature blood cells, which lasts more than 3 months after combination chemotherapy with fludarabine.[16] This condition is associated with susceptibility to infection including prolonged neutropenia. A study by Solmaz showed that leukemia patients in the neutropenic period were more susceptible to anorectal infections that manifest as abscess or fistula.[3]

Leukemia patients who receive chemotherapy will experience mucosal barrier injury, or often called mucositis.[17,18] Under normal circumstances mucosa will protect the body against pathogenic micro-organisms and at the same time it provides defense against normal microorganisms (resident micro-organisms). Damage on the mucosa of gastro-intestinal tract could be a place for microorganisms to enter (*port de entrée*) and potentially causing infection. As a result, infection in leukemia patients is frequently caused by normal microorganisms that inhabit the skin, oral cavity, and gastrointestinal tract, such as, *E. coli, Klebsiella spp.* and *Viridans group streptococci.* These organisms under normal circumstances can be found in large numbers but it does not cause any infection symptoms.[19]

Leukemia treatment also affects the colonization of bacteria or the normal flora of the gastrointestinal tract (GIT) which we call the commensal microbiota. Furthermore, the decrease in the number of the normal flora will reduce microbial diversity which plays a role in suppressing infection.[19] The change in GIT microbiota happened through indirect and direct mechanism (Figure 1)

Indirect mechanisms (Fig. 2 A–C) involve the gut microbiota in defense against pathogenic bacteria through direct and indirect mechanisms of action. Commensal bacterial species and their products interact with the host by producing antimicrobial peptides, maintaining the epithelial barrier, and modulating bile acids. Antimicrobial proteins are REG3 gamma protein and angiogenin-4 (ANG4). The proinflammatory cytokine IL-18 increases the production of antimicrobial peptides, including ANG4. Certain commensal bacteria, such as *Clostridium scindens*, can cause hydroxylation of primary bile acids to secondary bile acids using the 7α-hydroxysteroid dehydrogenase enzyme, which inhibits the growth of *C. difficile*. The microbiota also maintains the epithelial barrier by producing mucus, and transcription activation of nuclear factor-κB (NF-κB) in epithelial cells to delay apoptosis and repair tissue.

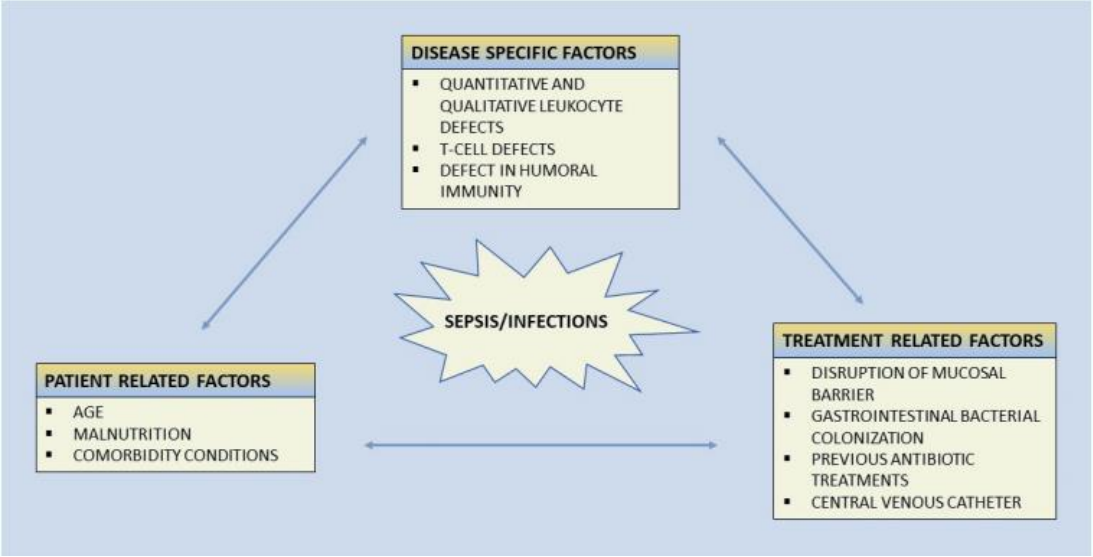


Figure 1. Interactions of factors that influences the pathogenesis of PI in leukemia patients. Quoted with modification from reference no. 9

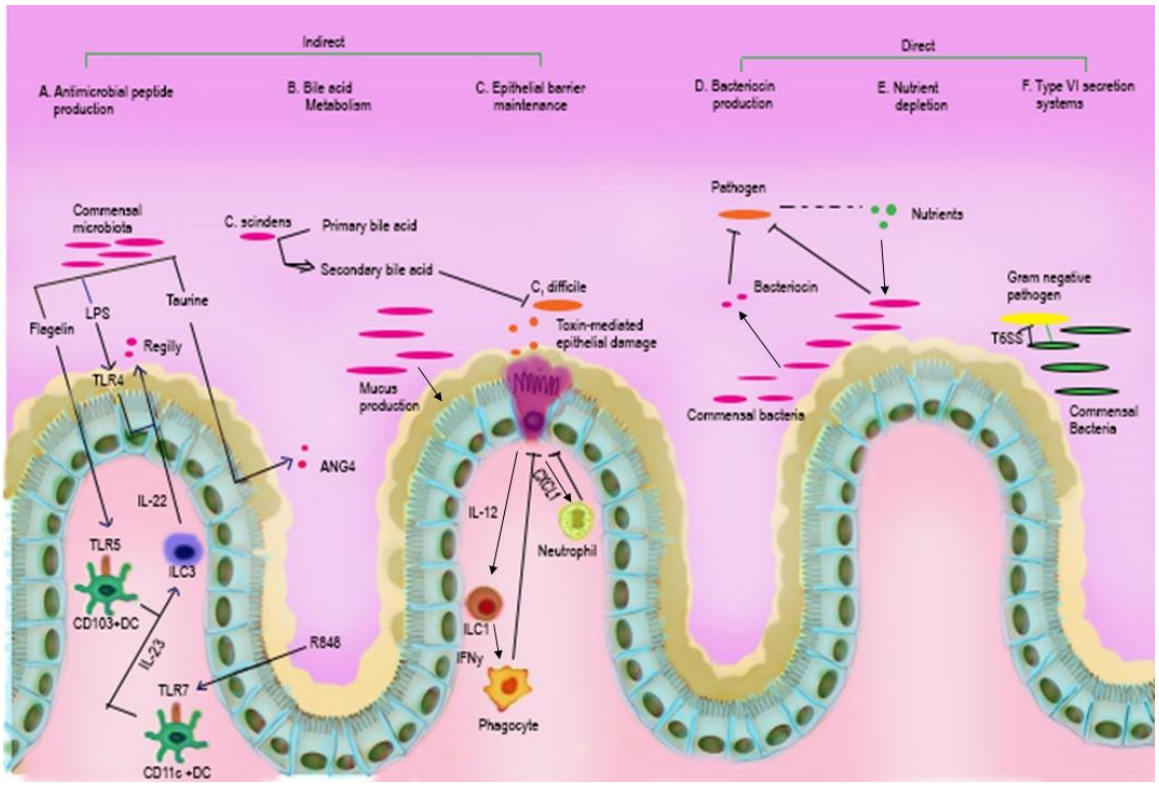


Figure 2. **A-C:** Indirect mechanisms, **D-F**: Direct mechanisms. Quoted with modification from references no. 2

Direct mechanisms of colonization resistance include bacteriocin production, nutrient depletion, and the type VI secretion system (Fig. 2 D-F). Several commensal bacterias have been identified to produce bacteriocins with a narrow spectrum of activity, which inhibit specific pathogens with minimal impact against other commensal microbiota (Fig. 2 D). In addition, commensal microbiota will compete with pathogens in receiving various nutrients, including food and carbohydrates that are obtained from the host, as well as producing metabolites such as succinate, that decrease pathogens colonization (Fig.2 E).[17-19]

The use of broad-spectrum antibiotics, particularly beta-lactams and cephalosporins, is a routine practice to prevent opportunistic infection in patients. However, there are consequences of inappropriate antibiotics use. Its administration will affect the number of gastrointestinal tract microbiota, so that the colonization of certain bacteria such as *Clostridium difficile* will increase and cause infection. Other nosocomial pathogens bacteria can also grow and enter the bloodstream, causing systemic infections. Table 1 contains the names of common GIT bacterias that frequently cause infections.[19,20]

A study by Chen et al reported that perianal infections were most often caused by bacteria (99%) and Candida species (1%). Overall, 68% of patients had polymicrobial infection, and 24% had bacteremia. The most frequently isolated bacteria in this study were *Escherichia coli* (25%), followed by *Enterococcus* species (22%), *Klebsiella pneumonia* (13%), and *Bacteroides* species (11%).[17]

In addition to the microorganisms mentioned above, infection can also be caused by other skin commensal bacteria, one of which is *S. epidermidis*. These bacteria not only cause skin infection around the perianal, but infection can also be caused by medical action such as the installation of a central venous catheter (CVC).[9]

Table 1. Common gastrointestinal bacteria that cause infections in leukemia patients

	Microorganisms	**Source**
Gram-negative bacteria	*E. faecalis* *E. faecium*	Gastrointestinal tract[19,24]
	C. difficile	Lower gastrointestinal tract[19,25]
	Viridans group streptococci	Oral/ Gastrointestinal tract[19,26-29]
Gram-negative bacteria	*E. coli*	Gastrointestinal tract, urogenital [19,24,30-35]
	Klebsiella spp	Gastrointestinal tract, urogenital [19,24,30-35]
	P. aeruginosa	Gastrointestinal tract[19,24,36,37]

Diagnosis

History and physical examination

Signs of infection include fever (temperature >38°C), complaints of perianal pain. In physical examination, it was found perianal mass, induration, erythema, fluctuation, and purulent fluid was found when ruptured. These signs may not appear simultaneously. Neutropenia in patients may cause an inflammatory response that is different with immunocompetent patients so that the symptoms of perianal erythema and induration may be less prominent. [1,2,21]

Diagnostic examination

- Blood culture

Cultures (blood, fluid) will help identifying cause of infection. Blood culture should ideally be taken during fever and before antimicrobial administration. The discovery of microbes and their sensitivity to antimicrobials becomes important for patients' treatment.

- Imaging examination

If clinical signs are not characteristic, imaging studies can be performed. Magnetic Resonance Imaging (MRI) with contrast administration supporting investigation, produces optimal imaging of the soft tissues.[1,2,22,23] A study by Plumb et al (2015) found high signal intensity in patients with PA, which was significantly greater in patients with hematological malignancies compared to patients' control. MRI can also show the location of the fistula and then facilitate surgery.[23]

Supporting investigation with computed tomography scan (CT scan) is also useful in diagnosing PA. Large PA will be seen on CT scan, however if the size of the

PA and fistula is small, there is a possibility that the abnormality is not visible. Moreover, soft tissue resolution with CT scan is not as good as MRI examination.[23]

Another examination that also helpful is imaging with ultrasonography (USG). A study by Cheng et al showed that imaging with USG itself is quite helpful. This procedure is inexpensive and has a low radiation risk. But still it has some limitations in detecting small PA and PF, and since sound doesn't penetrate well through bone, USG is not effective at imaging PA and PF that are hidden by bones. In addition, patients with severe pain or pediatric patients may require sedation.

Complications

Blood Stream Infection

Blood stream infection (BSI) that originates from the gastrointestinal tract can occur in patients with compromised immune systems. The combination of chemotherapy, antibiotics and dysregulation of the immune system in leukemia patients results in impaired immune system and gastrointestinal mucositis. Pathogenic microorganisms enter through *port de entrée* in gastrointestinal tract and spread systemically.[2,9,19]

Sepsis

Sepsis is a life-threatening condition, caused by response of the body to infection, which is characterized by organ failure.[38] Finding signs of sepsis in leukemia patients is challenging because leukemia causes altered inflammatory response. However, sepsis should still be suspected in patients with either fever symptoms (>38°C) or hypothermia (<36°C), heart rate (>90 per minute), tachypnea (>30 breaths per minute), altered mental status, signs of significant edema or positive fluid balance (>20 ml/ kg over 24 hours), and hyperglycemia (plasma glucose >110 mg / dl or 7,7 mmol / l) in patients without a history of diabetes. In addition, it is necessary to pay attention to symptoms of infection such as respiratory symptoms (cough, rhinorrhea, and respiratory disorders), digestive symptoms (nausea, vomiting, diarrhea, and stomachache), and impaired consciousness.

Hemodynamic parameters can indicate organ dysfunction and sepsis development; hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70 mmHg, or decreased systolic blood pressure >40 mmHg in adults or <2 standard deviations (SD) below normal for age, mixed venous oxygen saturation >70%, heart index (cardiac index >3,5 l / min / m^2, arterial hypoxemia (PaO2 / FiO2 <300), and acute oliguria (urine output <0,5 ml / kg / hour or 45 ml for at least 2 hours).[39, 40]

Laboratory testing helps estimate the severity of the infection and may show the source of the infection. Inflammatory markers that show sepsis are leukocytosis (white cell counts (WBC)> 12 x 10^9/l), leukopenia (WBC <4 x 10^9/l), normal white blood cell count with >10% immature form, and C-reactive protein (CRP) or procalcitonin >2 Standard Deviation. Organ dysfunction can also be verified by laboratory testing including creatinine increase ≥0,5 mg / dl, coagulation abnormalities (International Normalized Ratio (INR) >1,5 or activated partial thromboplastin time (APTT) >60 seconds), thrombocytopenia (platelets <100 000 / µl), and hyperbilirubinemia (plasma bilirubin total >4 mg / dl or 70 µmol / l). Hyperlactatemia (>3 mmol / l) may indicate decreased tissue perfusion.[39,40]

Fournier gangrene

Fournier gangrene (FG) is a necrotizing fasciitis that occurs in the genital area, perineum, anus, and sometimes in the skin of the lower abdomen. Immune deficiency is one of the risk factors for FG. In PI, there is skin discontinuity, therefore it can become *port de entrée* for variety of pathogenic microorganisms. Both conditions allow the occurrence of FG in leukemia patients who received chemotherapy and experienced PI.[41]

A case report by Mantadakis et al, showed that FG may occur in young adult patients who were receiving induction phase chemotherapy. In 2016, Solmaz et al investigated perianal complication that occurred in 92 acute leukemia patients who were undergoing induction-consolidation phase chemotherapy. The study showed that 19 patients who had PA, 1 patient had necrosis on perianal area or FG.[3,42] Another study by Renzi et al, with research subjects of 235 pediatric patients, showed that 7% of the subjects or 19 patients had perianal infections, and there were two patients with PA which progressed into FG.

Management

Management of PI in leukemia patients differs from immunocompetent patients. This is due to immunosuppression and pancytopenia conditions that occur during chemotherapy. It is important to conduct multidisciplinary management that involves collaboration

between oncologists, surgeons, and infectious disease experts.

Management includes surgical treatment (ST) and non-surgical treatment (NST). The criteria for selecting the two managements are still unclear. Studies of the two management options showed varied results. Some studies suggest that ST should be performed immediately in leukemia patients with PI, but other studies showed that NST alone is sufficient.[7,43]

- Surgical treatment (ST)

The ST approach in leukemia patients should consider neutropenia and thrombocytopenia conditions. ST is performed very selectively for patients with obvious clinical manifestations of abscess. Patients who do not show improvement with the NST approach itself may be considered for receiving ST.[7,43]

A study by Barnes et al suggested early surgical intervention and abscess drainage. The study involved 16 patients with perianal abscess. Fifteen of 16 leukemia patients experienced improvement. The authors suggested that drainage was an important procedure that would eliminate source of infections and induce neutrophil recovery.[43]

A more recent study by Badgwell et al attempted to determine factors or predictors for PI management. This study is a retrospective study which involved 100 patients with neutropenia (Absolute Neutrophil Count < 1000 cells/ml), the study found that abscess and signs of erythema are indications of ST.[44] Both studies suggested that ST should be conducted on patients that had a prominent abscess on clinical manifestations nor supporting investigations, significant necrosis, and soft tissue infection despite appropriate antibiotics administration. ST selection should still consider the condition of neutropenia and the patient's bleeding risk.

- Non-surgical treatment (NST)

The NST approach relies on antimicrobials. Once a potential source of infection is identified, either from laboratory tests or blood cultures, the patient should begin antimicrobial therapy immediately. The recommended antibiotics should have broad spectrum activity gram-positive, gram-negative, anaerobic bacteria, and antifungals. Administration of broad-spectrum antibiotics is important because in patients with leukemia, polymicrobial pathogens are common.[2,19,24-37]

Patients without signs of erythema, abscess, and perianal fluid on physical examination, but showed the presence of PI features from supporting investigation of MRI and CT scan can be considered for NST management. This treatment can be used as an alternative option, considering the presence of neutropenia, thrombocytopenia, poor vital signs and poor laboratory results. However, this approach requires close monitoring to avoid complications such as BSI and sepsis.

The knowledge of microbiological patterns and microbial resistance in hospital is important for the selection of antimicrobial therapy. When a particular pathogen is identified from laboratory and culture results, the selection of antimicrobial should be based on these results and clinical manifestations.

A study by Lehrnbecher et al of National Cancer Institute (NCI), USA, examined 82 episodes of PI in 64 leukemia patients after induction chemotherapy. The study showed antibiotics therapy alone was successful in PI treatment of 52/82 (63%) episodes. The combination of ST and NST was needed in 25/82 (31%) episodes, and only 5 patients needed ST management alone.[47]

Table 2. The use of antibiotics based on European Conference on Infections in Leukemia guidelines (ECIL) and Infectious Disease Society of America (IDSA)

Microbes		Recommended antibiotic treatment options
Gram-negative bacteria	ESBL	Carbapenems
	CPE	Two or more combinations, aminoglycosides, polymyxins, tigecycline, fosfomycin, and meropenem
	P. aeruginosa	Combination therapy, using a beta-lactam with an aminoglycoside or a fluoroquinolone
	S. maltophilia	Trimethoprim-sulfamethoxazole (combination with ticarcillin/clavulanate or ceftazidime)
	MDRO *A.baumanii*	Colistin Combination with ampicillin/sulbactam or imipenem or meropenem. Tigecycline Combination
Gram-positive bacteria	CoNS	Glycopeptides; vancomycin and teicoplanin (daptomycin, linezolid, and tigecycline)
	MRSA	
	VRE	Linezolid and daptomycin (Quinupristin–dalfopristin, tigecycline, fosfomycin, tedizolid, oritavancin, dalbavancin and telavancin)

ESBL: *Broad-Spectrum β-Lactamase-Producing Enterobacteriaceae*. CPE: *Carbapenemase-Producing Enterobacteriaceae*. MRSA: *Methicillin-resistant Staphylococcus aureus*. CoNS: *Coagulase-negative Staphylococcus*. VRE: *Vancomycin Resistant Enterococci*. MDRO: *Multidrug-resistant Organism.*
Quoted with modification from references no. 9, 24, 26-37.

Table 3. The use of antifungals based on European Conference on Infections in Leukaemia guidelines (ECIL) and Infectious Disease Society of America (IDSA)

Microbes		Recommended antifungal treatment options
Fungal infection	*P. jiroveci*	Trimetoprim-sulfamethoxazole (Primaquine + clindamycin, pentamidine)
	Candida spp.	Echinocandins (Fluconazole)
	Aspergillus spp.	Voriconazole, isavuconazole (Liposomal, amphotericin B, caspofungin)

Drugs in parentheses are second-line alternatives
Quoted with modification from references of no. 9, 45, 46.

- Sitz bath

Sitz bath (SB) is a therapeutic method of warm water added with certain drugs or substances to clean area around perineum and genitals. Patients can soak the perineum area with the solution. In post-chemotherapy leukemia patients with signs of PI, SB can be performed to treat and prevent worsening of PI. Substances that are added to warm water are generally potassium permanganate (PP) with a concentration of 1:5000.[48.49]

In 2020, Zhou et al conducted a retrospective study of SB effectiveness using matrine compounds (matrine sitz bath/MSB) compared to PP. This study involved 216 leukemia patients with PI. The results showed that perianal pain, systemic symptoms, PA size and consistency improved in both treatment groups. However, the group with MSB therapy showed a more significant improvement compared to the PP group (control) ($p < 0,05$). Analysis was also conducted by examining blood inflammatory markers, namely level of proinflammatory factor of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor (TNF-α), erythrocyte sedimentation rate (ESR) and prostaglandins E2 (PEG2). All of these blood inflammatory markers decreased in both the MSB and PP groups, so it was concluded that the SB method could reduce inflammation.[48]

Prevention

PI is common in leukemia patients after chemo-therapy, and it caused significant morbidity and mortality.[2,3,6] On the other hand, the management of ST and NST shows varied results. Therefore, it is

necessary to think about PI prevention strategies in leukemia patients.

A study in China has compiled a concept of prevention which involves doctors, nurses, laboratory technicians and residents. This concept is called a quality control circle (QCC) or can also be called a plan-do-check-act (PDCA). The steps contained in the QCC including, planning, analysis of causes, implementation, and standardization. With the QCC concept, PI prevention is performed by teaching patients to recognize PI signs as early as possible.[49]

The followings are the steps in QCC or PDCA:

1. Planning

The QCC team members consist of 5-9 doctors, analysts, nurses and medical students. The QCC team will provide questionnaires to patients to recognize several factors that can influence the severity of PI. Some of these factors will become the basis for the management or actions that are arranged in the PDCA.

2. Cause analysis

The causes or factors that have been obtained by giving questionnaires will be the focus of the QCC team's intervention. In a study by Jiang et al at Nanfang Hospital, China, the factors that cause the high incidence of PI including the lack of patient knowledge about PI, lack of standard operating procedures (SOP) for skin disinfection, and lack of disinfection tools and materials. The QCC team then uses the "5W1H" principles (who, what, when, where, why, and how) to compile actions to intervene these issues.

3. Implementation

At this phase the QCC team conducts the interventions that have been compiled. To overcome the patient's lack of knowledge about PI, doctors, nurses, and medical students educate patients to recognize and treat PI signs and provide tools and materials for PI treatments. The QCC team also educates the patient's family. The education is performed in group discussions, giving notes or brochures of proper PI treatments.

4. Standardization

PI prevention efforts are assessed and reviewed every 9 months. If there is a procedure that does not give benefits, then the procedure is eliminated. On the contrary, procedures that are assessed to be able to reduce the severity of PI are maintained. Then the procedure is used as a standard of treatment and documented in the form of videos or recordings that are shared with other patients.

The objective of QCC is to reduce the incidence of PI which will also reduce mortality, length of hospital stays, and cost of treatment. This QCC study involved 253 patients with hematological malignancies and was conducted for one year. After one year of follow-up, it was obtained that PI incidence rate decreased from 17.20% to 5.93% and remained at 5.25% during the following year.[49]

Conclusion

PI is a complication that is common in acute leukemia patients who receive induction and consolidation chemotherapy. The pathogenesis of PI involves the interaction of many factors, namely, disease, patients, and treatment factors. Early diagnosis is challenging and requires supporting examinations. Management of PI consist of NST and ST procedures, both showed varied results. It is necessary to think of preventive measures on PI to reduce the incidence rate, morbidity, length, and cost of treatment in hospital. QCC methods can be used as a guide for the prevention of PI in leukemia patients who receive induction and consolidation chemotherapy.

Conflict of Interests

There is no conflict of interests that need to be declare.

References

1. Renzi S, Bartram J, Ali S, Portwine C, Mitchell D, Dix D, et al. Perianal Infections in Children with Acute Myeloid Leukemia: A Report from the Canadian Infection in Acute Myeloid Leukemia Research Group. J Pediatric Infect Dis Soc. 2019;8(4):354-7.
2. Chen CY, Cheng A, Huang SY, Sheng WH, Liu JH, Ko BS, et al. Clinical and microbiological characteristics of perianal infections in adult patients with acute leukemia. PLoS One. 2013;8(4):e60624.
3. Solmaz S, Korur A, Gereklioglu C, Asma S, Buyukkurt N, Kasar M, et al. Anorectal Complications During Neutropenic Period in Patients with Hematologic Diseases. Mediterr J Hematol Infect Dis. 2016;8(1):e2016019.
4. Sahnan K, Adegbola SO, Tozer PJ, Watfah J, PhillPI s RK. Perianal abscess. BMJ. 2017;356:j475.

5. International agency for research on cancer. https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf 2020.
6. Chang H, Kuo MC, Tang TC, Lin TL, Wu JH, Hung YS, et al. Clinical Features and Recurrence Pattern of Perianal Abscess in Patients with Acute Myeloid Leukemia. Acta Haematol. 2017;138(1):10-3.
7. Amato A, Bottini C, De Nardi P, Giamundo P, Lauretta A, Realis Luc A, et al. Evaluation and management of perianal abscess and anal fistula: SICCR position statement. Tech Coloproctol. 2020;24(2):127-43.
8. Lyengar V, Shimanovsky A. Leukemia. Treasure Island (FL): StatPearls Publishing. 2020;PMID: 32809325.
9. Hansen BA, Wendelbo O, Bruserud O, Hemsing AL, Mosevoll KA, Reikvam H. Febrile Neutropenia in Acute Leukemia. Epidemiology, Etiology, Pathophysiology and Treatment. Mediterr J Hematol Infect Dis. 2020;12(1):e2020009.
10. Ventura MT, Casciaro M, Gangemi S, Buquicchio R. Immunosenescence in aging: between immune cells depletion and cytokines up-regulation. *Clin Mol Allergy*. 2017;15:21.
11. Barrett AJ. Acute myeloid leukaemia and the immune system: implications for immunotherapy. Br J Haematol. 2020;188(1):147-58.
12. Atkins S, He F. Chemotherapy and Beyond: Infections in the Era of Old and New Treatments for Hematologic Malignancies. Infect Dis Clin North Am. 2019;33(2):289-309.
13. Kayser S, Levis MJ. Advances in targeted therapy for acute myeloid leukaemia. Br J Haematol. 2018;180(4):484-500.
14. Halpern AB, Culakova E, Walter RB, Lyman GH. Association of Risk Factors, Mortality, and Care Costs of Adults with Acute Myeloid Leukemia With Admission to the Intensive Care Unit. JAMA Oncol. 2017;3(3):374-81.
15. Baumgartner A, Zueger N, Bargetzi A, Medinger M, Passweg JR, Stanga Z, et al. Association of Nutritional Parameters with Clinical Outcomes in Patients with Acute Myeloid Leukemia Undergoing Haematopoietic Stem Cell Transplantation. Annals of Nutrition and Metabolism. 2016;69(2):89-98.
16. Gill S, Carney D, Ritchie D, Wolf M, Westerman D, Prince HM, et al. The frequency, manifestations, and duration of prolonged cytopenias after first line fludarabine combination chemotherapy. Ann Oncol. 2010;21(2):331-4.
17. France MM, Turner JR. The mucosal barrier at a glance. J Cell Sci. 2017;130(2):307-14.
18. Van der Velden WJ, Herbers AH, Netea MG, Blijlevens NM. Mucosal barrier injury, fever, and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. Br J Haematol. 2014;167(4):441-52.
19. Kim S, Covington A, Pamer EG. The intestinal microbiota: Antibiotics, colonization resistance, and enteric pathogens. Immunol Rev. 2017;279(1):90-105.
20. Luo R, Greenberg A, Stone CD. Outcomes of Clostridium difficile infection in hospitalized leukemia patients: a nationwide analysis. Infect Control Hosp Epidemiol. 2015;36(7):794-801.
21. Iqbal S, Walcott J, Chan S. Acute Myelomonocytic Leukemia Presenting as Perianal Pain. Case Rep Surg. 2018:2151492.
22. Haliloglu N, Gulpinar B, Ozkavukcu E, Erden A. Typical MR imaging findings of perianal infections in patients with hematologic malignancies. Eur J Radiol. 2017;93:284-8.
23. Tolan DJ. Magnetic Resonance Imaging for Perianal Fistula. Semin Ultrasound CT MR. 2016;37(4):313-22.
24. Satlin MJ, Walsh TJ. Multidrug-resistant Enterobacteriaceae, Pseudomonas aeruginosa, and vancomycin-resistant Enterococcus: Three major threats to hematopoietic stem cell transplant recPI ients. Transpl Infect Dis. 2017;19(6).
25. Bartlett JG: Narrative review: the new epidemic of Clostridium difficileassociated enteric disease. Annals of internal medicine 2006, 145(10):758-64.
26. Torfoss D. Carbapenems and febrile neutropenia - author's reply. Clin Microbiol Infect. 2017;23(3):214.
27. Torfoss D, Fladhagen T, Holte H, Brinch L, Schjesvold FH, Floisand Y, et al. Benzylpenicillin plus an aminoglycoside versus meropenem in neutropenic lymphoma and leukaemia patients with a suspected bacterial infection: a randomized, controlled trial. Clin Microbiol Infect. 2017;23(3):179-87.
28. Torfoss D, Hoiby EA, Holte H, Kvaloy S. The Norwegian experience with penicillin G plus an aminoglycoside as initial empiric therapy in febrile neutropenia; a review. Acta Oncol. 2012;51(4):433-40.
29. Torfoss D, Hoiby EA, Tangen JM, Holte H, Bo K, Meyer P, et al. Tobramycin once versus three times daily, given with penicillin G, to febrile neutropenic cancer patients in Norway: a prospective, randomized, multicentre trial. J Antimicrob Chemother. 2007;59(4):711-7.
30. Perez F, Adachi J, Bonomo RA. Antibiotic-resistant gram-negative bacterial infections in patients with cancer. Clin Infect Dis. 2014;59 Suppl 5:S335-9.
31. Gudiol C, Royo-Cebrecos C, Tebe C, Abdala E, Akova M, Alvarez R, et al. Clinical efficacy of beta-lactam/beta-lactamase inhibitor combinations for the treatment of bloodstream infection due to extended-spectrum beta-lactamase-producing Enterobacteria-ceae in haematological patients with neutropaenia: a study protocol for a retrospective observational study (BICAR). BMJ Open. 2017;7(1):e013268.
32. Bassetti M, Giacobbe DR, Giamarellou H, Viscoli C, Daikos GL, Dimopoulos G, et al. Management of KPC-producing Klebsiella pneumoniae infections. Clin Microbiol Infect. 2018;24(2):133-44.
33. Gutiérrez-Gutiérrez B, Salamanca E, de Cueto M, Hsueh P-R, Viale P, Paño-Pardo JR, et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. The Lancet Infectious Diseases. 2017;17(7):726-34.
34. Gutierrez-Gutierrez B, Perez-Galera S, Salamanca E, de Cueto M, Calbo E, Almirante B, et al. A Multinational, Preregistered Cohort Study of beta-

Lactam/beta-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-beta-Lactamase-Producing Enterobacteriaceae. Antimicrob Agents Chemother. 2016;60(7):4159-69.
35. Averbuch D, Cordonnier C, Livermore DM, Mikulska M, Orasch C, Viscoli C, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recPI ients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). Haematologica. 2013;98(12):1836-47.
36. Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yanez San Segundo L, Pabst T, Ozcelik T, Klyasova G, Donnini I et al: Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant RecPI ients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. Clin Infect Dis 2017, 65(11):1819-1828
37. Mikulska M, Averbuch D, Tissot F, Cordonnier C, Akova M, Calandra T, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. J Infect. 2018;76(1):20-37.
38. Huerta LE, Rice TW. Pathologic Difference between Sepsis and Bloodstream Infections. J Appl Lab Med. 2019;3(4):654-63.
39. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29(4):530-8.
40. Kim M, Ahn S, Kim WY, Sohn CH, Seo DW, Lee YS, et al. Predictive performance of the quick Sequential Organ Failure Assessment score as a screening tool for sepsis, mortality, and intensive care unit admission in patients with febrile neutropenia. Support Care Cancer. 2017;25(5):1557-62.
41. LaChance A & Kroshinksy D. Necrotizing Fasciitis, Necrotizing Cellulitis, and Myonecrosis. In: Kang S, Amagai M, Bruckner AL, Enk AH, Morgolis DJ, McMichael AJ, et al, editors. Fitzpatrick's Dermatology 9th Ed: McGraw-Hill Education. 2019;2770-81
42. Mantadakis E, Pontikoglou C, Papadaki HA, Aggelidakis G, Samonis G. Fatal Fournier's gangrene in a young adult with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2007;49(6):862-4.
43. Baker B, Al-Salman M, Daoud F. Management of acute perianal sepsis in neutropenic patients with hematological malignancy. Tech Coloproctol. 2014;18(4):327-33.
44. Badgwell BD, Chang GJ, Rodriguez-Bigas MA, Smith K, Lupo PJ, Frankowski RF, et al. Management and outcomes of anorectal infection in the cancer patient. Ann Surg Oncol. 2009;16(10):2752-8.
45. Maschmeyer G, Helweg-Larsen J, Pagano L, Robin C, Cordonnier C, Schellongowski P, et al. ECIL guidelines for treatment of Pneumocystis jirovecii pneumonia in non-HIV-infected haematology patients. J Antimicrob Chemother. 2016;71(9):2405-13.
46. Tissot F, Agrawal S, Pagano L, Petrikkos G, Groll AH, Skiada A, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017;102(3):433-44.
47. Lehrnbecher T, Marshall D, Gao C, Chanock SJ. A second look at anorectal infections in cancer patients in a large cancer institute: the success of early intervention with antibiotics and surgery. Infection. 2002;30(5):272-6.
48. Zhou Y, Gao H, Hua H, Zhu W, Wang Z, Zhang Y, et al. Clinical effectiveness of matrine sitz bath in treating perianal infection after chemotherapy for acute leukemia. Ann Palliat Med. 2020;9(3):1109-16.
49. Jiang Q, Zhang D, Majaw J, Zhao C, Chai Y, Xu Z, et al. Minimization of the perianal infection rate of hematological malignancies with agranulocytosis by quality control circle activity and patient-hospital-student win-win concept. J Int Med Res. 2018;46(6):2338-45.

Author Guidelines

Manuscripts are submitted through online submission; Please register/make an account first (don't forget to checklist "Author" in "Register as" field, when you fill/edit your profile). After you have an account, please do log in, then in your profile, you can click "New submission", follow the step for uploading your manuscript. If you have any difficulties please contact submission@inajcc.com for help.

The maximum file size for the manuscript is 5MB, full-resolution photographs should be uploaded separately as supplementary files.

Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. Accepted manuscripts become the permanent property of The Indonesian Journal of Cancer Control without permission from the publisher.

Author Responsibility

All accepted manuscripts are subject to copy editing. The author is responsible for all statements in his work.

Manuscript Preparation

All manuscripts should be prepared in accordance with "Uniform Requirements for Manuscript Submission to Biomedical Journals" (also known as "Vancouver Style"), as agreed by the International Committee for Medical Journal Editors. The entire manuscript must be typewritten, double spaced, on white bond paper, 216 x 279 mm (8 ½ x 11 in.) or ISO A4 (212 x 297 mm), with margins of at least 25 mm (1 in.), including the abstract, footnotes, references, figure legends and tables (superscript). If a word processor is used, do not justify lines.

All manuscripts should include (1) title page, (2) short title page, (3) abstract in English (4) body of paper, (5) acknowledgements, (6) references, (7) tables, (8) figure legends, and (9) clear photocopies of figures and illustrations. Manuscripts should be consistent in style, spelling, and use of abbreviations. Slang, medical jargon, and obscure abbreviations are to be avoided. The word count should not exceed 5000 words including figures and tables.

Abstract and key words

Provide an abstract (250 words maximum) of the article. Original articles consist of statements of the problem (background), method of study, findings and conclusions. Observation and others (review article) consists of statement of the problem and the way of study performed. Abstract replaces the summary. Key words must be included after abstract and maximal 5 words.

References

List references in consecutive numerical order (not alphabetically). Once a reference is cited, all subsequent citations should be to the original number. All references must be cited in the text or tables. Unpublished data and personal communications should not be listed as references. Reference to journal articles should include: (1) authors (abbreviation of middle name), (2) title, (3) journal name (as abbreviated in Index Medicus), (4) year, (5) volume number, (6) inclusive page numbers. References to book should include: (1) author[s], (2) chapter title (if any), (3) editor (if any), (4) title of book, (5) city of publication, (6) publisher, and (7) year. Volume and edition numbers, specific pages, and name of translator(s) should be included when appropriate.

Further explanation and examples could be seen, e.g., in thefile "Quick references guide to Vancouver citing & referencing style" (Vancouver - Citing and referencing - Library guides at Monash University), that can be obtained from the Monash University site.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. The material has not been previously published and is not under simultaneous consideration for publication elsewhere
2. The submission file is in Microsoft Word.
3. Where available, URLs for the references should be provided.
4. The text is single-spaced; uses a 10-point font; employs italics, rather than underlining (except with URL addresses); and all illustrations, figures, and tables are placed within the text at the appropriate points, rather than at the end.
5. The text adheres to the stylistic and bibliographic requirements outlined in the Author Guidelines.
6. The manuscript has been structured based on the template.
7. For original article, ethical clearance and informed consent statement must be included in the submission.
8. For case report, patient's informed consent must be included in the submission.
9. Ethics Statement, Authorship Agreement and Copyright Statement forms must be filled and submitted together with the manuscript.
10. Provide a cover letter for submission.

Download article submission kit/template here

Instructions For Authors

Article Type (10 pt, colored gray 50%, bold, underlined)

Article title (First letter capitalized, 14 pt, bold, centered, max 15 words)

(one blank line, 14 pt)

First Author, Second Author, Third Author, etc. (12 pt)

(one blank line, 12 pt)

1. Department, Faculty, University, Address, City, Zip Code, Country (10 pt)
2. Research Group, Institution, Address City, Zip Code, Country (10 pt)

(one blank line, 12 pt)

Email: author@address.com (10 pt, italic, underlined)

(two blank line, 12 pt)

Abstract (12 pt, bold)

(one blank line, 12 pt)

Abstract must be written in English and should not exceed 250 words. The font is Arial size 9 with single spacing. Original articles consist of statements of the problem (background) including aim of the journal, method of study, results and conclusions. Case reports consist of background, case illustration, discussion and conclusion. Observation and others (review article) consists of statement of the problem and the way of study performed.

(one blank line, 12 pt)

Keywords: (10 pt, bold, italic) *maximum 5 words in English must be provided in alphabetical order, chosen according to the Medical Subject Headings (MeSH) terms* (10 pt, italic)

(three blank line, 12 pt)

Submission Requirements (12 pt, bold)

(one blank line,10 pt)

Manuscripts are submitted through online submission; Please register/make an account first (don't forget to checklist "Author" in "Register as" field, when you fill/edit your profile). After you have an account, please do log in, then in your profile, you can click "New submission", follow the step for uploading your manuscript. If you have any difficulties please contact submission@inajcc.com for help.

The maximum file size for the manuscript is 5MB, full-resolution photographs should be uploaded separately as supplementary files. The word count should not exceed 5000 words including figures and tables.

Manuscripts are received with the understanding that they are not under simultaneous consideration by another publication. Accepted manuscripts become the permanent property of The Indonesian Journal of Cancer Control without permission from the publisher. All accepted manuscripts are subject to copy editing. The author is responsible for all statements in his work. Criteria of acceptance for all papers are the originality, quality and significance to the readers.

It must be stated that all the protocols for research project have been approved by the Ethic Committee of the institution. Research that includes human subjects must preserve anonymity of the subjects and a statement that all subjects gave informed consent. Case reports should include informed consent by the patient.

Background (12 pt, bold)

(one blank line, 10 pt)

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

abstract, footnotes, references, figure legends and tables (superscript). All pages must be numbered on bottom right-hand corner. If a word processor is used, do not justify lines.

Generally, the body of paper should be divided in sections with these following headings: **Background, Methods, Results, Discussion,** and **Conclusion**. Acknowledgements must be written if present.

Parts of Manuscript (12 pt, bold)

(one blank line, 10 pt)

All manuscripts should include (1) title page, (2) short title page, (3) abstract, in English and Indonesian (4) body of paper, (5) acknowledgements, (6) references, (7) tables, (8) figure legends, and (9) clear photocopies of figures and illustrations.

Original Articles

a. Abstract: maximum 250 words, single spaced, divided by subheadings Background, Methods, Results, and Conclusion. Key words must be included below the abstract maximal 5 words.
b. Background: 1-3 paragraphs consists of the background of the study, objectives of the study, and hypothesis which will be proved with the study. Background should show the importance of the study, novelty of the manuscript and the gap analysis.
c. Methods: explains the details on how the study was conducted. Statistical methods of the study must be explained in this section including the software used. Statistical terms, symbols and abbreviations should be defined clearly.
d. Results
e. Discussion
f. Conclusion: conclusion related to the objectives of the study

Case Report

a. Abstract: maximum 250 words, single spaced, divided by subheadings Background, Case Illustration, Discussion and Conclusion.
b. Background: explanation of the main problem and the purpose of the case report. Brief description of the background of the study.
c. Case Illustration
d. Discussion
e. Conclusion

Review Article or Special Article

a. Abstract: maximum 250 words, single spaced, consists of summary of the problem considered and how the study was performed
b. Background: consist of 1-3 paragraphs
c. Content: consists of comprehensive analysis of the topics.
d. Conclusion

Result (12pt, bold)

(one blank line, 10 pt)

Data presented in the result must have been processed, and can be presented in forms of tables or figures.

Discussion (12pt, bold)

(one blank line, 10pt)

Discussion should focus on the study/case. The correlation between the result and hypothesis should be explored. The result should be compared with other studies. The implication of the study, both theoretically and implementation, should be discussed.

Tables and Figures (12pt, bold)

(one blank line, 10pt)

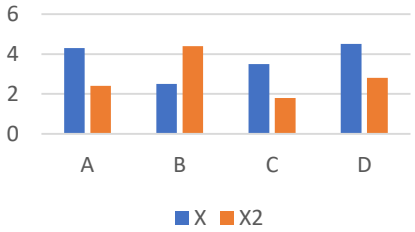
Tables should be self-explanatory and numbered consecutively based on the order of appearance (Table 1, Table 2, etc). The data contained in the tables must not be duplicated within text and figures. Tables should be written with Arial font size 10 pt, single spacing. Tables should be cited accordingly unless it is original. The title should be positioned above the table, in a center justified manner like the following example.

Table 1. Title of the Table
(one blank line, 10pt)

	A	B
A	1	2
B	3	4
C	5	6

Table content source and additional explanation (font 10)

Figures should be numbered consecutively based on the order of appearance (Figure 1, Figure 2, etc) Images must be supplied as JPEG or GIF files with minimum size of 500 KB. All figures must be supplied as a separate file with each figure labeled as Figure 1, Figure 2, etc. Images should be cropped sufficiently to prevent recognition of the subject. The use of eye bar is acceptable. Figures should be cited accordingly unless it is original. The consent from the subjects/patients whose images are used is needed. The title should be positioned below the figure, in a center justified manner like the following example.



(one blank line, 10pt)

Figure 1. Title of the Figure
(two blank line, 10pt)

Acknowledgements (12pt, bold)

(one blank line, 12pt)

Only written if present. People who are contributed to the study but does not meet the criteria for authorship must be acknowledged and listed. The source of funding, financial grants, and conflict of interest must be acknowledged and listed.

Conflict of Interests (12pt, bold)

(one blank line, 10pt)

This part should declare authors' conflicts of interest, including sources of support for the work and authors' authority to access the study data.

References (12pt, bold)

(one blank line, 10pt)

References should be done with Vancouver system of referencing. Further explanation and examples could be seen, e.g., in the file "Quick references guide to Vancouver citing & referencing style" (Vancouver - Citing and referencing - Library guides at Monash University), that can be obtained from the Monash University site. In the text, references must be cited using superscript. Once a reference is cited, all subsequent citations should be to the original number. All references must be cited in the text or tables. Unpublished data and personal communications should not be listed as references. Updated references should always be prioritized.

Examples:

Books

Author 1, Author 2, so on (last name, abbreviated first name). Title of book. Edition. Place of publication: Publisher; Year of publication. Page range.

Book Chapter

Author 1, Author 2, so on (last name, abbreviated first name). Title of chapter. In: Editor 1, Editor 2, so on (last name, abbreviated first name), editors. Title of book. Edition. Place of publication: Publisher; Year of publication. Page range.

Journal

Author 1, Author 2, so on (last name, abbreviated first name). Title of article. Abbreviated journal name. Publication year;volume number(issue number):page range.

Online Journal

Author 1, Author 2, so on (last name, abbreviated first name). Title of article. Abbreviated journal name [Internet]. Publication year [date accessed];volume number(issue number):page range. Available from: Uniform resourced locater (URL) address

Thesis or Dissertation

Author (last name, abbreviated first name). Title. [Paper, thesis, or dissertation]. University place: University name; Year

Proceeding Book

Editor 1, Editor 2, so on (last name, abbreviated first name). editors. Title of article. Conference name, Date, Month, and Year, City, Country. Publication place; Publisher; Publication year.