# THE RELATIONSHIP BETWEENHISTOPATHOLOGICAL GRADING AND METASTASIS: STUDY FROM COLORECTAL CANCER PATIENTS IN MAKASSAR INDONESIA

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# THE RELATIONSHIP BETWEEN HISTOPATHOLOGICAL GRADING AND METASTASIS: STUDY FROM COLORECTAL CANCER PATIENTS IN MAKASSAR INDONESIA

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## Abstract

*Background:* Colorectal cancer (CRC) is a malignancy in the large instestine caused by uncontrolled cell growth. The cause of death due to the metastasis, and the prognosis is determined by the stage that can be assessed using Dukes classification or TNM staging system. Determination of histopathological grading is important because of the differences in radiosensitivity, local behaviour and the metastasis tendency. The aim of this study is to determine the relationship between histopathological grading and metastasis in colorectal cancer patients.

*Methods :* This study is a cross sectional study using secondary datas from the medical record of CRC patients at the RS. Dr. Wahhidin Sudirohusodo and its networking hospital in Makassar Indonesia, that were obtained by consecutive sampling. Inclusion criterias are all patients who had surgery and have the results of histopathology, radiology and other datas that may be used as a reference for determining the staging based on the Dukes classification and TNM staging system.

*Result :* The number of CRC patients during January 2012 to April 2016 was 268 patients, 55,6% of male and most widely in 51-60 years old (25,4%). Most of the CRC location in the rectum (61,2%) and higest location of metastasis is in lymph nodes (40,4%). From 179 patients who had result of histopathological examination, founded adenocarcinoma type (100%) and moderately differentiated adenocarcinoma (45,3%) is the most frequently histopathological grading. Most of CRC stage based on the TNM saging system is stage IV (27,4%) and based on the Dukes classification is stage D (26,8%). There is a significant relationship ($p$<0,001) between histopathological grading and metastasis, and seems a trend which poorly differentiated adenocarcinoma is more frequent in advanced stage, both based on the Dukes classification and TNM staging system.

*Conclusion :* There is a significant relationship between histophological grading and metastasis. Poorly differentiated adenocarcinoma is more likely to be found in advanced stage of CRC

**Keywords:** Colorectal carcinoma, grading histopatology, metastasis

# THE RELATIONSHIP BETWEEN HISTOPATHOLOGICAL GRADING AND METASTASIS IN COLORECTAL CARCINOMA PATIENTS

## INTRODUCTION

Colorectal carcinoma (CRC) is a malignancy originated from colon caused by uncontrolled cell growth [1,2]. World Health Organization (WHO) reported that CRC incidence is quite high, so is the mortality. In 2008, CRC incidence is 3rd among other types of cancer and 4th in cause of death due to cancer in the world. In Indonesia, in 2008 mortality of CRC is estimated to be about 11,1 people per 100.000 inhabitant and also the most common malignancy in gastrointestinal [2].

The main cause of death in CRC is metastasis. The most common sites for distant metastasis in CRC are liver, then followed by lung and peritoneum. It's reported that about 5-10% of CRC patient underwent surgery with lung metastasis and about 4% with bone metastasis. Based on literatures, the prognosis of CRC patient is influenced by several parameters, including sex, age, resection of primary tumor, number of metastasis, and tumor differentiation degree [3,4].

CRC patient's prognosis could be determined by staging CRC based on Dukes Classification and TNM (Tumor Nodes Metastasis) system. Both parameters are frequently used to determined CRC's stage, which assessed CRC's cell invasion to intestinal wall, lymph nodes metastasis, and distant metastasis to other organ. Those can be determined through clinical, radiologic, and histologic evaluation, where it's important to determined tumor spread, locally or systemically [5,6].

Histologically, 98% of CRC are adenocarcinoma with most subtype are non-mucinous adenocarcinoma, mucinous adenocarsinoma dan signet ring cell carsinoma. Based on the grading, adenocarcinoma are classified to well differentiation, moderately differentiation, and poorly differentiation. Determination of histological type is important because the differences

in histological features will also vary in terms of radio sensitivity, local behavior, and a tendency for regional and systemic metastasis. CRC's degree of differentiation is an important indicator to assess the potential of local invasion and metastasis systemic [7,8].

The aim of this study is to determine the relationship between histopathological grading and metastasis in CRC patients.

## METHODS

This study is a cross sectional study using secondary data from CRC's patient medical record in Dr. Wahidin Sudirohusodo hospital and other affiliation hospital in Makassar Indonesia since January 2012 until April 2016, both outpatient and inpatient obtained by consecutive sampling. Sample of this study are population studies that met the inclusion criteria i.e. patients who have undergone surgery and have had the histopathological examination result originating from the resection (surgery), patients in it's medical record already provided data on TNM classification/Dukes, or patient medical records contained the results of a CT scan of the abdomen, chest X-ray, abdominal ultrasound, endoscopy, surgery reports and other data that can be used as a reference to determine the stage by the TNM classification and Dukes

Data analysis was performed using the statistical package for social science (SPSS) version 17. The descriptive statistical method used is the calculation of the frequency distribution. The statistical test used Chi Square test (Likelihood Ratio). The test results were considered significant if the p-value <0.05.

## RESULTS

Data collection of CRC patient from Dr. Wahidin Sudirohusodo hospital other affiliation hospital in Makassar Indonesia from January 2012 until April 2016 are 268 people, with male 149 people (55.6%) dan CRC most prevalent between age 51-60 years 68 people (25.4%). (Table 1)

**Table 1. Patient's demographic characteristic**

| Characteristic | n | % |
|---|---|---|
| Total patient | 268 | 100 |
| Sex | | |
| Male | 149 | 55.6 |
| Age (years) | | |
| 11-20 | 5 | 1.9 |
| 21-30 | 15 | 5.6 |
| 31-40 | 35 | 13.1 |
| 41-50 | 58 | 21.6 |
| 51-60 | 68 | 25.4 |
| 61-70 | 58 | 21.6 |
| >70 | 29 | 10.8 |

From 268 CRC patient, only 179 people met the inclusion criteria. CRC with metastasis was found in 109 people, divided into; locoregional metastases were 60 (33.5%) and distant metastasis are 49 people (27.4%) and 70 (39.1%) with no metastasis. (Table 2)

**Table 2. Metastasis distribution**

| Metastasis | n | % |
|---|---|---|
| Locoregional metastasis | 60 | 33,5 |
| Distant metastasis | 49 | 27,4 |
| No metastasis | 70 | 39,1 |
| Total | 179 | 100 |

From histopatological pattern, all CRC patient has adenocarcinoma type (100%), which moderately differentiated is the most frequent histopatological pattern with 81 people (45.3%). (Table 3)

**Table 3. Histopathologic grading distribution**

| Histopathology type | n | % |
|---|---|---|
| **Adenocarsinoma** | **179** | **100** |
| Well differetiation | 41 | 22.9 |
| Moderately differetiation | 81 | 45.3 |
| Poor differentiation | 50 | 27.9 |
| Mucinosum type | 3 | 1.7 |
| Signet ring cell type | 4 | 2.2 |

CRC's distribution based on Dukes classification (Astler Coller Modification), found Dukes D is the most prevalent staging with 48 people (26.8%), followed by Dukes C2 with 44 people (24.6%). In this study, there were 3 people (1.7%) which can not be staging with Dukes classification. (Table 4)

**Table 4. CRC staging distribution based on DUKES classification (Astler Coller Modification)**

| Dukes | n | % |
|---|---|---|
| A | 40 | 22,3 |
| B1 | 13 | 7,3 |
| B2 | 26 | 14,5 |
| C1 | 5 | 2,8 |
| C2 | 44 | 24,6 |
| D | 48 | 26,8 |
| Unknown | 3 | 1,7 |
| Total | 179 | 100 |

CRC's staging distribution based on TNM system, stage IV is the most the prevalent with 49 people (27.4%) dan the least is stage 0 with 5 people (2.8%). (Table 5)

**Table 5. CRC staging distribution based on TNM system**

| Stadium | n | % |
|---|---|---|
| 0 | 5 | 2,8 |
| 1A | 27 | 15,1 |
| 1B | 32 | 17,9 |
| IIA | 8 | 4,5 |
| IIIA | 37 | 20,7 |
| IIIB | 21 | 11,7 |
| IV | 49 | 27,4 |
| Total | 179 | 100 |

Correlation between CRC histopathological grading and staging based on Dukes Classification can not be tested, but the result is this study showed tendency of poorly differentiation CRC are more prevalent in advanced stage (C1, C2 and D) compared to early stage. While well differentiation CRC tend to be more common in early stage (A1, B1 and B2). (Table 6)

**Tabel 6. Correlation between histopathological grading with CRC staging based on DUKES classification (Astler Coller Modification)**

| | | | Adenocarsinoma | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Well Diff. | Moderately Diff. | Poorly Diff. | Mucinosum | Signet Ring Cell | Total |
| Dukes | A | n (%) | 21 (52.5) | 16 (40.0) | 1 (2.5) | 0 (0.0) | 2 (5.0) | 40 (100) |
| | B1 | n (%) | 5 (38.5) | 8 (61.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 13 (100) |
| | B2 | n (%) | 5 (19.2) | 18 (69.2) | 1 (3.8) | 1 (3.8) | 1 (3.8) | 26 (100) |
| | C | n (%) | 1 (33.3) | 2 (66.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (100) |
| | C1 | n (%) | 0 (0.0) | 2 (40.0) | 3 (60.0) | 0 (0.0) | 0 (0.0) | 5 (100) |
| | C2 | n (%) | 4 (9.1) | 22 (50.0) | 15 (34.1) | 2 (4.5) | 1 (2.3) | 44 (100) |
| | D | n (%) | 5 (10.4) | 13 (27.1) | 30 (62.5) | 0 (0.0) | 0 (0.0) | 48 (100) |
| Total | | n (%) | 41 (22.9) | 81 (45.3) | 50 (27.9) | 3 (1.7) | 4 (2.2) | 179 (100) |

*Can not be tested due to many cells with value 0.* Diff; differetiation

Correlation between CRC histopathological grading with staging based on TNM system also can not be tested, the this study showed tendency of poorly differentiation CRC are more prevalent in stage IIIA and above, while well differentiation are more common in stage IIA and below (Table 7)

**Table 7 . Correlation between histophatological grading with CRC staging based on TMN system**

| Stadium | | Adenocarsinoma | | | | | |
|---|---|---|---|---|---|---|---|
| | | Well Diff. | Moderately Diff. | Poorly Diff. | Mucinosum | Signet Ring Cell | Total |
| 0 | n (%) | 4 (80.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (100) |
| IA | n (%) | 12 (44.4) | 13 (48.1) | 0 (0.0) | 1 (3.7) | 1 (3.7) | 27 (100) |
| IB | n (%) | 12 (37.5) | 19 (59.4) | 0 (0.0) | 0 (0.0) | 1 (3.1) | 32 (100) |
| IIA | n (%) | 2 (25.0) | 5 (62.5) | 1 (12.5) | 0 (0.0) | 0 (0.0) | 8 (100) |
| IIIA | n (%) | 4 (10.8) | 22 (59.5) | 8 (21.6) | 2 (5.4) | 1 (2.7) | 37 (100) |
| IIIB | n (%) | 2 (9.5) | 8 (38.1) | 10 (47.6) | 0 (0.0) | 1 (4.8) | 21 (100) |
| IV | n (%) | 5 (10.2) | 13 (26.5) | 31 (63.3) | 0 (0.0) | 0 (0.0) | 49 (100) |
| Total | n (%) | 41 (22.9) | 81 (45.3) | 50 (27.9) | 3 (1.7) | 4 (2.2) | 179 (100) |

*Can not be tested due to many cells with value 0*

From the analysis of correlation between CRC histopathological grading with metastasis, there was a significant correlation between CRC differentiation with metastasis ($p<0,001$). Distant metastasis is the most prevalent in poorly differentiation CRC (62%), while no metastasis is the most prevalent in well differentiation CRC (73.2%). (T able 8)

**Table 8. Correlation between histophatological grading with metastasis**

| Adenocarsinoma | | Metastase | | | Total |
|---|---|---|---|---|---|
| | | *Locoregional* | Distant | NM | |
| Well differentiation | n (%) | 6 (14.6) | 5 (12.2) | 30 (73.2) | 41 (100) |
| Moderately differentiation | n (%) | 32 (39,5) | 13 (16,0) | 36 (44,4) | 81 (100) |
| Poorly differentiation | n (%) | 18 (36.0) | 31 (62.0) | 1 (2.0) | 50 (100) |
| Mucinosum type | n (%) | 2 (66,7) | 0 (,0) | 1 (33.3) | 3 (100) |
| Signet Ring cell type | n (%) | 2 (50.0) | 0 (,0) | 2 (50,0) | 4 (100) |
| Total | n (%) | 60 (33.5) | 49 (27.4) | 70 (39.1) | 179 (100) |

*Likelihood Ratio test (p=0,000).* NM; no metastasis

## I. DISCUSSION

The prognosis of patient with CRC is influenced by several parameters, i.e. sex, age, resection of the primary tumor, number of metastasis lesions and the degree of differentiation [3,4]. The National Cancer Institute (2011), reported that the risk for TRC began to increase after the age of 40 years and increased sharply at the age of 50 to 55 years, the risk has doubled every next decade [9]. In our study, total of CRC, patients who were treated between 2008-2012, found male patients (56%) did not differ in number with female. Mainly found in the productive age range 20-60 years (60.1%) and CRC incidence increases with age and peaks at age 51-60 years (25.4%)

Metastasis in CRC can be grouped in to local and regional (*loco-regional*) metastasis and distant metastasis [10]. Based on metastasis, we found locoregional is 33,3% and distant metastasis 27,2%, while non metastasis CRC is 39.5%.

In this study, of 179 patients who had histopathologic examination, all of it is was adenocarcinoma (100%). Of the study evaluated 100 cases, reported that patients with poorly differentiation showed deeper invasion into the intestinal wall and lymph node metastasis

compared to moderately and well differentiation [11]. The results were consistent with the study conducted by Chung et al [12]. These findings suggested that histological assessment is very significant for the evaluation of clinical and management of CRC patient. The results of our study, found the degree of differentiation of the vast majority were moderately differentiation adenocarcinoma (45.3%) followed by poorly differentiation (27.9%) and well differentiation (22.9%), while the adenocarcinoma type mucinous only found in 3 (1.7%) and signet ring on 4 patient (2.2%).

This study showed a significant correlation between the adenocarcinoma differentiation with metastasis ($p < 0.001$), in which distant metastases are found most prevalent in poorly differentiation adenocarcinoma (62%), while no metastasis is found mostly in well differentiation adenocarcinoma (73.2%). The results are consistent with the study conducted by Riboli RE (1983), which reported an association between adenocarcinoma differentiation with metastasis to lymph nodes in patients with moderately and poorly differentiation adenocarcinoma [13]. The correlation between of differentiation and metastasis in CRC is possible due to increased mitosis and hyper-proliferation of malignant cell in poorly differentiation adenocarcinoma compared to well or moderately differentiation adenocarcinoma. Thus, malignant cell invasion to surrounding tissue and cell penetration through hematogen and lyphogen to metastasis also greater [14].

Nabi U (2010), reported a significant correlation between histology pattern in adenocarcinoma differentiation with CRC staging based on Dukes classification ($p < 0.000$), where poorly differentiation adenocarcinoma mostly found at an advanced stage (Dukes C), otherwise well differentiation adenocarcinoma only found at an early stage (Dukes A and B). [9]. Similarly, Derwinger K (2010), also reported a significant correlation ($p < 0.001$) between histology pattern in adenocarcinoma differentiation with CRC staging based on TNM system, where poorly differentiation linked to the higher number of metastasis to lymph nodes (stage

III) [16]. Although statistically the correlation between the CRC histopathology pattern with staging cannot be tested, but the results of this study showed a tendency of poorly differentiation adenocarcinoma are more prevalent in advanced stage (IIIA and above), while the well differentiation tend to be more prevalent in earlier stage (IIA or lower). Similarly, the correlation between the Dukes classification with CRC histopathology pattern, this study showed a tendency poorly differentiation adenocarcinoma more prevalent in advanced stage (C1, C2 and D), whereas well differentiation adenocarcinoma tend to be more prevalent in the early stages (A, B1, and B2). The tendency for poorly differentiated adenocarcinoma more prevalent in advanced stage CRC, either by Dukes classification and TNM system, also can be caused by the same reason that poorly differentiation adenocarcinoma, has greater ability to mitosis and proliferate, this increased malignant cell invasion and metastasis compared to moderately and well differentiation CRC [15].

## II. CONCLUSSION

There is a correlation between histophological grading and metastasis. Poorly differentiation adenocarcinoma is more likely to be found in advanced stage of CRC, while well differentiation adenocarcinoma it more prevalent in non metastasis CRC. Poorly differentiation it more common in advance stage based on Dukes classification (C1, C2, and D) and advanced stadium based on TNM classification (IIIA and above).

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# THE RELATIONSHIP BETWEEN HISTOPATHOLOGICAL GRADING AND METASTASIS: STUDY FROM COLORECTAL CANCER PATIENTS IN MAKASSAR INDONESIA

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The main reason we choose Bali as the conference venue is because of its strategic location (easy access with direct flight from prominent cities in the world and Visa on Arrival facilities for 64 countries) and its infrastructure. With the easy access we are confident the 23rd Asia Pacific Cancer Conference (APCC) will break a new record in term of participants' number. On the other hand the newly renovated spacious International airport, the direct new toll road from airport to Nusa Dua area, and the high-tech convention center will ensure the smooth organization of the meeting as well as the conveniences of all participants.
Please block the date and looking forward to meeting you soon in Bali.

Sincerely Yours,

**Aru W. Sudoyo, MD., Ph.D**
Congress Chairman of APCC 2015 and President of APFOCC

## IMPORTANT DATES AND TOPICS

| | |
|---|---|
| DATE | August 20th – 22nd, 2015 |
| VENUE | Grand Hyatt Hotel, Bali |
| ADDRESS | PO. BOX. Nusa Dua, Bali 80363, Indonesia |

**IMPORTANT DATES:**

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|---|---|
| • Pre – Congress Workshop | August 20th, 2015 |
| • Symposium | August 21st – 22nd, 2015 |
| • Poster & Free Paper | August 21st – 22nd, 2015 |
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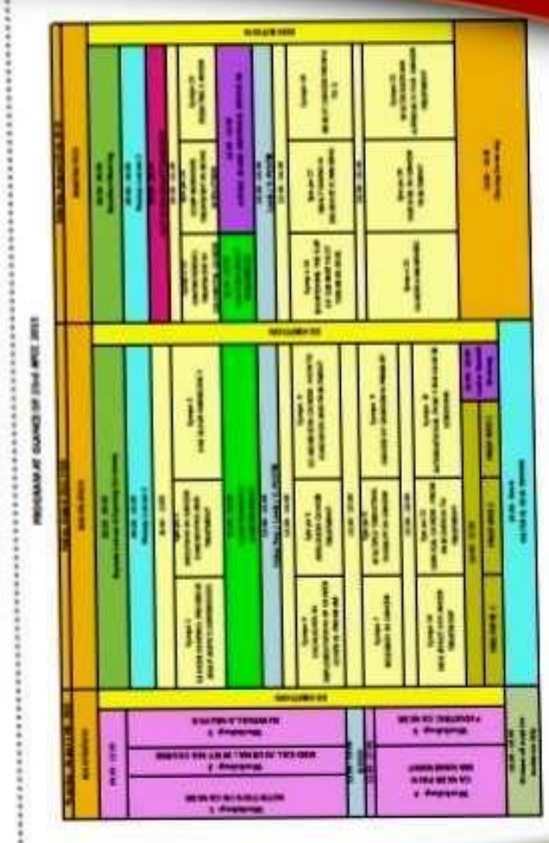

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This is to certify that

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rahmawati.minhajat@gmail.com
Cc: apcc2015@pharma-pro.com

Jakarta, 29 July 2015

Dear Rahmawati Minhajat, MD

On behalf the organizing committee we would like to thank you for your participation on the **The 23rd APCC 2015** Bali, We would liketo inform your time and number poster presentation as bellow:

1. **Session** **:** Poster Presenter

   **Title:** The Relationship Between HistopathologicalGrading and Metastasis in Colorectal Carcinoma Patients

   **Presentation schedule** : Saturday, August 22nd 2015

   **Number of Poster** : PO 141

2. **Session** **:** Poster Presenter

   **Title:** Angiogenesis and Lymphangiogenesis in Colorectal Cancer: Study Protein Expression of CD105, D2-40 dan VEGF

   **Presentation schedule** : Saturday, August 22nd 2015

   **Number of Poster** : PO 143

Please kindly stand by in front of your poster on Saturday, August 22nd 2015 during coffee break (10.00-10.30) and lunch time (13.00 – 14.00) incase some body will ask about your poster, and we will inform about size of the poster boards: 200cm (height) x 90 cm (wide) and poster printing 90cm (height)x60cm (wide). And with this email, we would like to inform you that you could put on your poster to poster boardson Friday (21st August 2015).

Thank you for your kind attention and we are looking forward to meet you in Bali.

For more detail information please visit our website: www.apcc2015.com

**With best**

**regards,Gita**

**Handayani**

Komplek Perkantoran Duta Merlin Blok C/35-37

Jl. Gajah Mada 3-5, Jakarta

10130 Phone : +6221-6386-

9502, ext.115 Fax :

+6221-6386-9503/6386-9505

Mobile : +62812.9181.0522

Email : gita@pharma-pro.com

**Confirmation letter Poster Presenter -Rahmawati Minhajat.pdf**
294K

**Rahmawati Minhajat** <rahmawati.minhajat@gmail.com> 30 July 2015 at 04:21To: Gita <gita@pharma-pro.com>

Thank you

[Quoted text hidden]

**Rahmawati Minhajat** <rahmawati.minhajat@gmail.com> 30 July 2015 at 04:21To: emma minhajat <emmaminhajat@yahoo.com>

---------- Pesan Terusan----------
Dari: "Gita" <gita@pharma-pro.com>Tanggal: 29 Jul 2015 12.12
Subjek: Acceptance Letter Poster Presenter APCC 2015Kepada: <rahmawati.minhajat@gmail.com>
Cc: <apcc2015@pharma-pro.com>
[Quoted text hidden]

**Confirmation letter Poster Presenter -Rahmawati Minhajat.pdf**
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Gmail

5 messages

Abstract Acceptance Letter for 23rd APCC 2015

**Emma M <rahmawati.minhajat@gmail.com>**

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**APCC 2015** <apcc2015@pharma-pro.com> 9 July 2015 at 15:41
To: rahmawati.minhajat@gmail.com
Cc: APCC 2015 <apcc2015@pharma-pro.com>

**Dear Rahmawati Minhajat, MD**

First of all thank you for your participation towards the upcoming meetings **23rd Asia Pacific Cancer Conference(APCC) 2015, August 20th – 22nd at Grand Hyatt Nusa Dua Bali, Indonesia**.

Through this letter we would like to inform that your paper title, **The Relationship Between Histopathological Grading And Metastasis In Colorectal Carcinoma Patients; Angiogenesis and Lymphangiogenesis in ColorectalCancer: Study Protein Expression of CD105, D2-40 dan VEGF;** are accepted.

Please kindly find attached the acceptance letter.
Thank you and regards,

**Ms. Pusti Aisha**

**Secretariat APCC 2015**

Komplek Perkantoran Duta Merlin Blok C/35-36Jl. Gajah Mada 3-5, Jakarta 10130, Indonesia Phone : +6221-6386-9502, Ext. 108
Fax : +6221-6386-9503/6386-9505Mobile : +62856-9121-2850
Website: www.apcc2015.com
Email: apcc2015@pharma-pro.com

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**Abstract Acceptance Letter for 23rd APCC 2015- Rahmawati Minhajat.pdf**
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29K

Bali, July 8th, 2015

Subject: Abstract Acceptance Letter for 23rd Asia Pacific Cancer Conference (APCC)

2015Dear Rahmawati Minhajat, MD

First of all thank you for your participation towards the upcoming meetings **23rd Asia Pacific Cancer** Conference (APCC) 2015, August 20th – 22nd at Grand Hyatt Nusa Dua Bali, Indonesia.

Through this letter we would like to inform that your paper title, **The Relationship Between Histopathological Grading And Metastasis In Colorectal Carcinoma Patients; Angiogenesis and Lymphangiogenesis in Colorectal Cancer: Study Protein Expression of CD105, D2-40 dan VEGF;** are accepted.

We herewith would like to inform you the importance information below:

IMPORTANT NOTICE:

1. We need you to register soon (if you have not done it) and pay the registration fee before **July 30th, 2015.** Upon receiving the prove of registration payment, we will inform you the presentation format (oral / poster) and your schedule of presentation
2. Please inform us immediately after you paid your registration

Thank you for your kind attention.

Sincerely Yours,

Aru W. Sudoyo, MD, Ph.D
Congress Chairman of APCC 2015 and President of APFOCC

dr. Adityawati Ganggaiswari, M. Biomed
General Secretary APCC 2015

For further information please kindly contact the secretariat:

23rd APCC 2015 Secretariat
Ms. Pusti Aisha
Komplek Perkantoran Duta Merlin Blok C/35-36Jl. Gajah Mada 3-5, Jakarta 10130, Indonesia

Phone : +6221-6386-9502, Ext.108/ Mobile : +62856-9121-2850
Website: www.apcc2015.com
Email : apcc2015@pharma-pro.com

CONGRESS VENUE :

**GRAND HYATT BALI**
P.O. BOX 53, NUSA DUA - BALI, INDONESIA