

3. Menguji Doktor

KODE K10

DESKRIPSI	: Penguji Tertutup a.n Etty Hary Kusumastuti, dr., SpPA(K)	Halaman
BUKTI	: Undangan Wadek I	02
	ST WD I FK 1283/UN3.1.1/DL/ 2022, tanggal 3 Pebruari 2022	03
	Bukti kinerja yaitu hal sampul, hal pengesahan, dll	04



UNIVERSITAS AIRLANGGA

FAKULTAS KEDOKTERAN

Kampus A Jl. Mayjen. Prof. Dr. Moestopo, 47 Surabaya 60132 Telp. (031) 5020251 Fax (031) 5022472
Laman : <https://fk.unair.ac.id>, e-mail : info@fk.unair.ac.id

Nomor : 1282/UN3.1.1/DL/2022

3 Februari 2022

Lamp : 2 Berkas

Hal : Mohon Kesediaan untuk menjadi Panitia Penguji Disertasi

Yth.

1. **Dr. Gondo Mastutik, drh., M.Kes** (Ketua)
2. Prof. Dr. I Ketut Sudiana, Drs., M.Si
3. Dr. Muhtarum Yusuf, dr., Sp.THT-KL(K), FICS
4. Prof. Dr. Bambang Soeprijanto, dr., Sp.Rad(K)
5. Dr. Karyono Mintarum, dr., Sp.PA
6. Dr. H. Imam Susilo, dr., Sp.PA(K), FISCAM
7. Dr. H. Budi Utomo, dr., M.Kes
8. Dr. Desak Gede A. Suprabawati, dr, Sp.B(K)Onk

Dengan hormat,

Sehubungan dengan selesainya penulisan disertasi peserta Program Doktor angkatan tahun 2016/2017,

Nama : Etty Hary Kusumastuti, dr., Sp. PA(K), FIAC

ELPT : 520

NIM : 011617017337

Judul : PERBEDAAN DAN MEKANISME RESPON KEMORADIASI PADA KARSINOMA NASOFARING MELALUI ANALISIS HIF-1 α , CD133, SOD, HSP70 DAN APOPTOSIS

Promotor : Prof. Dr. I Ketut Sudiana, Drs., M.Si

Ko- Promotor : Dr. Muhtarum Yusuf, dr., Sp.THT-KL(K), FICS

Ujian Disertasi rencananya diselenggarakan :

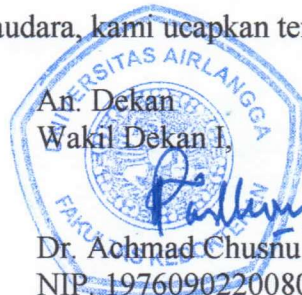
Hari, Tanggal : Rabu, 16 Pebruari 2022

Pukul : 13.00 – 16.00 WIB

Tempat : Menguji secara daring menggunakan aplikasi *Zoom*

Maka dengan ini mohon kesediaan Saudara untuk menjadi Ketua / Anggota panitia Penguji Disertasi tersebut, terlampir kami sampaikan pernyataan kesediaan untuk diisi dan dilampirkan pada kami dalam waktu yang tidak terlalu lama guna diproses lebih lanjut.

Demikian atas perhatian Saudara, kami ucapkan terima kasih.



Dr. Achmad Chusnu Romdhoni, dr., Sp.THT-KL(K), FICS

NIP. 197609022008011009

Tindakan :

- Kepala Sub. Bagian Keuangan



UNIVERSITAS AIRLANGGA

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Laman : <https://fk.unair.ac.id>, e-mail : info@fk.unair.ac.id

SURAT TUGAS

Nomor : 1283/UN3.1.1/DL/2022

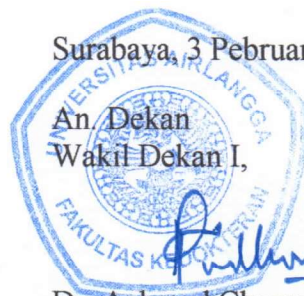
Wakil Dekan I Fakultas Kedokteran Universitas Airlangga dengan ini menugaskan :

- | | |
|--|---------|
| 1. Dr. Gondo Mastutik, drh., M.Kes | Ketua |
| 2. Prof. Dr. I Ketut Suidiana, Drs.,M.Si | Anggota |
| 3. Dr. Muhtarum Yusuf, dr.,Sp.THT-KL(K)., FICS | Anggota |
| 4. Prof. Dr. Bambang Soeprijanto, dr., Sp.Rad(K) | Anggota |
| 5. Dr. Karyono Mintarum, dr.,Sp.PA | Anggota |
| 6. Dr. H. Imam Susilo, dr., Sp.PA(K).,FISCM | Anggota |
| 7. Dr. H. Budi Utomo, dr., M.Kes | Anggota |
| 8. Dr. Desak Gede A. Suprabawati,dr,Sp.B(K)Onk | Anggota |

Sebagai Ketua / Anggota Panitia Ujian Tahap Pertama (Tertutup) Program Doktor Fakultas Kedokteran Universitas Airlangga atas nama Etty Hary Kusumastuti, dr.,Sp. PA(K).,FIAC peserta Program Doktor Program studi Ilmu Kedokteran angkatan tahun 2016/2017 yang diselenggarakan pada tanggal 16 Pebruari 2022.

Surat tugas ini diterbitkan sementara untuk menunggu keluarnya Surat Keputusan dari Dekan Fakultas Kedokteran Universitas Airlangga.

Surabaya, 3 Pebruari 2022



An. Dekan
Wakil Dekan I,
Dr. Achmad Chusnu Romdhoni,dr.,Sp.THT-KL(K).,FICS
NIP. 197609022008011009

DISERTASI

**PERBEDAAN DAN MEKANISME RESPON KEMORADIASI PADA
KARSINOMA NASOFARING MELALUI ANALISIS HIF-1 α , CD133, SOD,
HSP70, DAN APOPTOSIS**



ETTY HARY KUSUMASTUTI

**PROGRAM STUDI ILMU KEDOKTERAN JENJANG DOKTOR
FAKULTAS KEDOKTERAN UNIVERSITAS AIRLANGGA
SURABAYA
2022**

**PERBEDAAN DAN MEKANISME RESPON KEMORADIASI PADA
KARSINOMA NASOFARING MELALUI ANALISIS HIF-1 α , CD133, SOD,
HSP70, DAN APOPTOSIS**

DISERTASI

**Untuk memperoleh Gelar Doktor
dalam Program Studi Ilmu Kedokteran Jenjang Doktor
pada Fakultas Kedokteran Universitas Airlangga
dan ditetapkan di hadapan Panitia Ujian Akhir Tahap 1 (Tertutup)**

Oleh:

ETTY HARY KUSUMASTUTI

011617017337

**PROGRAM STUDI ILMU KEDOKTERAN JENJANG DOKTOR
FAKULTAS KEDOKTERAN UNIVERSITAS AIRLANGGA
SURABAYA**

2022

LEMBAR PENGESAHAN

DISERTASI

**PERBEDAAN DAN MEKANISME RESPON KEMORADIASI PADA
KARSINOMA NASOFARING MELALUI ANALISIS HIF-1 α , CD133, SOD,
HSP70, DAN APOPTOSIS**

**TELAH DISETUJUI
PADA TANGGAL 31 JANUARI 2022**

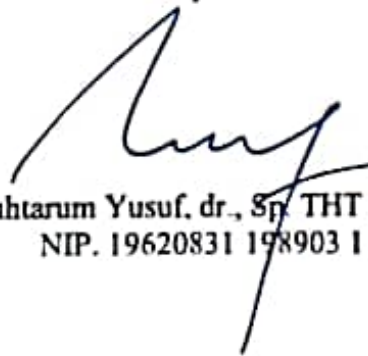
Oleh:

Promotor



Prof. Dr. I Ketut Sudiana, Drs., M. Si
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Kopromotor



Dr. Muhtarum Yusuf, dr., Sp. THT KL (K), FICS
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Mengetahui

KPS Ilmu Kedokteran Jenjang Doktor



Prof. Dr. Hendy Hendarto, dr. Sp OG (K)
NIP. 19610817 2016016101

PENETAPAN PANITIA PENGUJI DISERTASI

Disertasi ini telah disetujui untuk diuji dan dinilai
oleh panitia penguji pada Ujian Akhir Tahap I (Tertutup)
pada tanggal 16 Februari 2022

PANITIA PENGUJI

Ketua : Dr. Gondo Mastutik, drh., M. Kes
Anggota : Prof. Dr. I Ketut Suidiana, Drs., M. Si
Dr. Muhtarum Yusuf, dr., Sp. THT KL (K), FICS
Prof. Dr. Bambang Suprijanto, dr., Sp. Rad (K)
Dr. Karyono Mintarum, dr., Sp. PA
Dr. Imam Susilo, dr., Sp. PA (K), FISCM
Dr. Desak Gede A. Suprabawati, dr., Sp. B (K) Onk
Dr. H. Budi Utomo, dr., M. Kes

SUMMARY

THE DIFFERENCES AND MECHANISM OF CHEMORADIATION RESPONSES IN NASOPHARYNGEAL CARCINOMA THROUGH ANALYSIS OF HIF-1 α , CD133, SOD, HSP70, AND APOPTOSIS

Nasopharyngeal carcinoma (NPC) is a common malignant tumor found in Southeast Asia, including Indonesia. Although majority of NPC are sensitive to chemoradiation, characterized by absence of tumor cells on follow-up biopsies, there is a significant poor response that is still present of viable tumor cells after chemoradiation. The molecular pathway that causes differences in the chemoradiation responses in NPC is not yet clearly understood. Under hypoxia, hypoxia-inducible factors 1 α (HIF-1 α), a DNA binding transcription factors, activates a series of genes including promoter of cluster differentiation 133 (CD133), a cancer stem cells marker, which leads to inhibition of apoptosis. Superoxide dismutase (SOD), a metalloenzyme, and heat shock protein 70 (HSP70), a molecular chaperone, both acts as cytoprotector against various types of injury, including radiation and chemotherapy agents.

The aim of this study is to elucidate the differences and mechanism of chemoradiation responses in NPC by studying the differences in the expression of HIF-1 α , CD133, SOD, HSP70 and apoptosis.

This study is a quasi-experimental study with a pre-test post-test group design approach by a retrospective cohort. Samples are 34 pairs of non-keratinizing squamous cell carcinoma undifferentiated sub-type nasopharyngeal tissue biopsies on formalin fixed paraffin embedded pre and post-chemoradiation, composed of 18 pairs of good responses and 16 pairs of poor responses. Tissue samples were obtained from patients who received 70 Gy external radiation and combined platinum-based chemotherapy. Immunohistochemistry stain was performed to evaluate expressions of HIF-1 α , CD133, SOD and HSP70, while apoptosis was evaluated by TUNEL assay.

The result of this study showed there were significant differences in expression of HIF-1 α before chemoradiation in good and poor response $p= 0,002$, after chemoradiation in good and poor response $p= 0,001$, delta before and after chemoradiation in good and poor response $p= 0,001$. There were significant differences expression of CD133 before chemoradiation in good and poor response $p= 0,046$, after chemoradiation in good and poor response $p= 0,001$, delta before and after chemoradiation in good and poor response $p= 0,001$. There were significant differences in expression of SOD before chemoradiation in good and poor response $p= 0,002$, after chemoradiation in good and poor response $p= 0,001$, delta before and after chemoradiation in good and poor response $p= 0,001$. There were significant differences in expression of HSP70 before chemoradiation in good

and poor response $p= 0,044$, after chemoradiation in good and poor response $p= 0,001$, delta before and after chemoradiation in good and poor response $p= 0,001$. There was no significance differences of apoptosis which evaluated of cell tumor survive before chemoradiation in good and poor response $p= 0,088$. There were significant differences after chemoradiation in good and poor response $p= 0,001$, and delta before and after chemoradiation in good and poor response $p= 0,001$. The result of path analysis showed that there was a significant effect of HIF-1 α on CD133 $p= 0,001$. But there was no significant effect of CD133 on apoptosis $p= 0,972$. There were significant effects of SOD and HSP70 on apoptosis $p= 0,047$ and $p= 0,001$, and there was significant effect of apoptosis on chemoradiation responses $p= 0,001$.

In this study, it was proven that there were significant differences among HIF-1 α , CD133, SOD, HSP70 and apoptosis before and after chemoradiation in good and poor response of NPC. The mechanisms of chemoradiation responses in NPC are determined by SOD, HSP70 and apoptosis pathway.

ABSTRACT

THE DIFFERENCES AND MECHANISM OF CHEMORADIATION RESPONSES IN NASOPHARYNGEAL CARCINOMA THROUGH ANALYSIS OF HIF-1 α , CD133, SOD, HSP70, AND APOPTOSIS

Background: Nasopharyngeal carcinoma (NPC) is a common malignant tumor founded in Southeast Asia. Although majority of NPC are sensitive to chemoradiation, but there is a significance poor response.

Objective: To elucidate the differences and mechanism of chemoradiation responses in NPC by studying the differences in the expression of HIF-1 α , CD133, SOD, HSP70 and apoptosis.

Methods: A quasi-experimental study with a pre-test post-test group design approach by a retrospective cohort. Samples are 34 pairs of non-keratinizing squamous cell carcinoma undifferentiated sub type tissue biopsies pre and post chemoradiation, composed of 18 good and 16 poor responses. Immunohistochemistry stain was performed to evaluate expression of HIF-1 α , CD133, SOD and HSP70. Apoptosis was evaluated by TUNEL assay.

Result: There were significance differences in the expression of HIF-1 α , CD133, SOD and apoptosis before and after chemotherapy in good and poor responses, each of which has p value 0,001. The result of path analysis showed that there was a significance effect of HIF-1 α on CD133 $p= 0,001$, but no significance effect of CD133 on apoptosis $p= 0,972$. There were significance effect of SOD and HSP70 on apoptosis $p= 0,047$ and $p= 0,001$, and there was significance effect of apoptosis on chemoradiation response $p= 0,001$.

Conclusion: There were significance differences expression among HIF-1 α , CD133, SOD, HSP70 and apoptosis before and after chemoradiation in good and poor responses of NPC. The mechanisms of chemoradiation responses in NPC is determined by SOD, HSP70 and apoptosis pathway.

Keyword: Nasopharyngeal carcinoma, chemoradiation response, HIF-1 α , CD133, SOD, HSP70, apoptosis.