3. Menguji Doktor

KODE K14

DESKRIPSI	:	Penyanggah Ujian Doktor Terbuka a.n. Etty Hary Kusumastuti, dr, Sp.PA(K), FIAC	Halaman
BUKTI	:	Undangan ……..	02
		SK Dekan FK No 124/Un3.11./HK/2022, tanggal 17 Maret 2022 ……..……..	03
		Bukti kinerja yaitu hal sampul, hal pengesahan dll……..	06

UNIVERSITAS AIRLANGGA
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B5.2.9

Nomor : 2216/UN3.1.1/DL/2020 8 Maret 2022
Lampiran :
Hal : Penyanggah Ujian Akhir Tahap 2 (Terbuka)

Kepada Yth,
Dr. Gondo Mastutik, drh., M.Kes
ditempat

Dengan hormat,

Dengan ini kami mengharap kehadiran Saudara sebagai **Penyanggah** Ujian Akhir Tahap 2 (Terbuka) Prodi Doktor Ilmu Kedokteran atas nama **Etty Hary Kusumastuti, dr., Sp.PA(K)., FIAC** yang akan diselenggarakan pada :

Hari, tanggal : Kamis, 17 Maret 2022
Pukul : 10.00 – 12.00 WIB
Tempat : Aplikasi Zoom
Meeting ID : 927 6339 2161
Passcode : fkunair

Demikian untuk diketahui dan atas perhatian Saudara kami sampaikan terima kasih.

a.n. Dekan
Wakil Dekan I,

Dr. Achmad C. Romdhoni, dr., Sp.THT-KL(K)., FICS
NIP. 197609022008011009

Catatan
- Dimohon hadir paling lambat 15 menit sebelumnya.
- Pakaian : Pria : Berjas dan berdasi
  Wanita : Menyesuaikan.

KEMENTERIAN PENDIDIKAN, KEBUDAYAAN,
RISET, DAN TEKNOLOGI
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SALINAN

PERATURAN
DEKAN FAKULTAS KEDOKTERAN
UNIVERSITAS AIRLANGGA
NOMOR 124/UN3.1.1/HK/2022

TENTANG

PENYANGGAH UJIAN DOKTOR TERBUKA PROGRAM DOKTOR
PROGRAM STUDI ILMU KEDOKTERAN FAKULTAS KEDOKTERAN
ATAS NAMA ETTY HARY KUSUMASTUTI, dr., Sp.PA(K).,FIAC

DENGAN RAHMAT TUHAN YANG MAHA ESA
DEKAN FAKULTAS KEDOKTERAN
UNIVERSITAS AIRLANGGA

Menimbang :

a. bahwa ujian disertasi tahap I Jenjang Doktor telah dilaksanakan, selanjutnya mahasiswa yang dinyatakan lulus dari ujian tahap I tersebut berhak mengikuti ujian tahap II yang disebut Ujian Doktor Terbuka;

b. bahwa nama-nama Penyanggah Ujian Doktor Terbuka yang tercantum dalam lampiran Keputusan ini dinyatakan memenuhi syarat dan bersedia untuk ditetapkan sebagai penyanggah Ujian Doktor Terbuka;

c. bahwa berdasarkan pertimbangan sebagaimana dimaksud pada huruf a dan huruf b, perlu menetapkan Keputusan Dekan Fakultas Kedokteran Universitas Airlangga tentang Penyanggah Ujian Doktor Terbuka Program Doktor Program Studi Ilmu Kedokteran Fakultas Kedokteran.

Mengingat :

1. Undang-Undang Nomor 20 Tahun 2003 tentang Sistem Pendidikan Nasional (Lembaran Negara Republik Indonesia Tahun 2003 Nomor 78, Tambahan Lembaran Negara Nomor 4301);
2. Undang-Undang Republik Indonesia Nomor 14 Tahun 2005 tentang Guru dan Dosen (Lembaran Negara Republik Indonesia Nomor 157, Tambahan Lembaran Negara Nomor 4586;
3. Undang-Undang Nomor 12 Tahun 2012 tentang Pendidikan Tinggi (Lembaran Negara Republik Indonesia Tahun 2012 Nomor 158, Tambahan Lembaran Negara Nomor 5336);

4 : ....

4. Undang-Undang Nomor 5 Tahun 2014 tentang Aparatur Sipil Negara (Lembaran Negara Republik Indonesia Tahun 2014 Nomor 06, Tambahan Lembaran Negara Nomor 5494);
5. Peraturan Pemerintah Republik Indonesia Nomor 57 Tahun 1954 tentang Pendirian Universitas Airlangga Di Surabaya sebagaimana telah diubah dengan Peraturan Pemerintah Nomor 3 Tahun 1955 tentang Pengubahan Peraturan Pemerintah Nomor 57 Tahun 1954. (Lembaran Negara Republik Indonesia Tahun 1954 Nomor 99 Tambahan Lembaran Negara Nomor 695 juncto Lembaran Negara Republik Indonesia Tahun 1955 Nomor 4 Tambahan Lembaran Negara Nomor 748);
6. Peraturan Pemerintah Nomor 4 Tahun 2014 tentang Penyelenggaraan Pendidikan Tinggi dan Pengelolaan Perguruan Tinggi. (Lembaran Negara Republik Indonesia Tahun 2014 Nomor 16, Tambahan Lembaran Negara Nomor 5500);
7. Peraturan Pemerintah Nomor 30 Tahun 2014 tentang Statuta Universitas Airlangga. (Lembaran Negara Republik Indonesia Tahun 2014 Nomor 100, Tambahan Lembaran Negara Nomor 5535);
8. Peraturan Rektor Universitas Airlangga Nomor 38 Tahun 2017 tentang Peraturan Pendidikan Universitas Airlangga;
9. Peraturan Rektor Universitas Airlangga Nomor 21 Tahun 2014 tentang Pedoman Pendidikan Program Doktor (S3) Universitas Airlangga;
10. Keputusan Rektor Universitas Airlangga Nomor 1947/H3/KR/2011 tentang Penetapan Ruang Lingkup Program Studi dalam Kategori Monodisiplin, Interdisiplin dan Multidisiplin untuk Pengelolaan Program Magister dan Program Doktor;
11. Keputusan Rektor Universitas Airlangga Nomor 762/UN3/KR/2020 tentang Pengangkatan Dekan Fakultas, Direktur Sekolah Pascasarjana, dan Direktur Rumah Sakit Periode 2020-2025.

MENETAPKAN :

PENYANGGAH UJIAN DOKTOR TERBUKA PROGRAM DOKTOR PROGRAM STUDI ILMU KEDOKTERAN FAKULTAS KEDOKTERAN ATAS NAMA ETTY HARY KUSUMASTUTI, dr., Sp.PA(K).,FIAC

BAB I

Menetapkan Penyanggah Ujian Doktor Terbuka Program Doktor Program Studi Ilmu Kedokteran Fakultas Kedokteran atas nama Etty Hary Kusumastuti, dr.,Sp.PA(K).,FIAC yang dilaksanakan pada tanggal, 17 Maret 2022 dengan susunan nama sebagai berikut:

1. Prof. Dr. I Ketut Sudiana, Drs.,M.Si
2. Dr. Muhtarum Yusuf, dr.,Sp.THT-KL(K).,FICS
3. Prof. Dr. H. Ambar Mudigdo, dr.,Sp.PA(K)
4. Prof. Dr. Ami Ashariati, dr.,Sp.PD.,K-HOM.,FINASIM
5. Dr. Afif Nurul Hidayati, dr.,Sp.KK(K).,FINSDV.,FAADV
6. Dr. Apriliawati, dr.,M.Kes.,Sp.GK
7. Dr. Hanik Badriyah Hidayati, dr.,Sp.S(K)
8. Dr. Gondo Mastutik, drh.,M.Kes.
9. Prof. Dr. Budi Santoso, dr., Sp.OG(K)

BAB II

Dalam menjalankan tugasnya sebagaimana dimaksud dalam diktum PERTAMA, berpedoman pada peraturan dan ketentuan yang berlaku serta mempertanggungjawabkan tugasnya kepada Dekan Fakultas Kedokteran.

BAB III

Biaya untuk keperluan tersebut dibebankan pada dana Rencana Kegiatan dan Anggaran Tahunan (RKAT) Fakultas Kedokteran.

BAB IV

Peraturan ini mulai berlaku pada tanggal ditetapkan.

Ditetapkan di Surabaya
pada tanggal 17 Maret 2022

DEKAN,

ttd

Budi Santoso
NIP. 196302171989111001

Salinan sesuai dengan aslinya
Kepala Bagian Tata Usaha,

Basuni
NIP. 196501021987011001

SALINAN disampaikan Yth.
1. Rektor Universitas Airlangga
2. Yang bersangkutan

DISERTASI

PERBEDAAN DAN MEKANISME RESPON BAIK DAN BURUK TERHADAP KEMORADIASI PADA KARSINOMA NASOFARING MELALUI ANALISIS HIF-1α, CD133, SOD, HSP70, DAN APOPTOSIS PADA JARINGAN BIOPSI

ETTY HARY KUSUMASTUTI

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

PERBEDAAN DAN MEKANISME RESPON BAIK DAN BURUK TERHADAP KEMORADIASI PADA KARSINOMA NASOFARING MELALUI ANALISIS HIF-1α, CD133, SOD, HSP70, DAN APOPTOSIS PADA JARINGAN BIOPSI

DISERTASI

Untuk Memperoleh Gelar Doktor
Dalam Program Studi Ilmu Kedokteran Jenjang Doktor
Pada Fakultas Kedokteran Universitas Airlangga
dan dipertahankan di hadapan Panitia
Ujian Akhir Tahap 2 (Terbuka)

Oleh:

Etty Hary Kusumastuti
011617017337

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

LEMBAR PENGESAHAN

PERBEDAAN DAN MEKANISME RESPON BAIK DAN BURUK TERHADAP KEMORADIASI PADA KARSINOMA NASOFARING MELALUI ANALISIS HIF-1α, CD133, SOD, HSP70, DAN APOPTOSIS PADA JARINGAN BIOPSI

TELAH DISETUJUI

PADA TANGGAL 1 MARET 2022

Oleh:

Promotor

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

NIP. 19550705 198003 1 005

Kopromotor

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

NIP. 19620831 198903 1 010

Mengetahui

KPS Ilmu Kedokteran Jenjang Doktor

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

NIP. 19610817 2016016101

PENETAPAN PANITIA PENGUJI

Disertasi ini telah diuji dan dinilai
oleh Panitia Penguji Ujian Tahap 1 (Tertutup)
Pada Tanggal : 16 Pebruari 2022

PANITIA PENGUJI

Ketua : 1. Dr. Gondo Mastutik, drh., M. Kes

Anggota : 2. Prof. Dr. I Ketut Sudiana, Drs., M. Si
3. Dr. Muhtarum Yusuf, dr., Sp. THT KL (K), FICS
4. Prof. Dr. Bambang Suprijanto, dr., Sp. Rad (K)
5. Dr. Karyono Mintarum, dr., Sp. PA
6. Dr. Imam Susilo, dr., Sp. PA (K), FISCM
7. Dr. Desak Gede A. Suprabawati, dr., Sp. B (K) Onk
8. Dr. H. Budi Utomo, dr., M. Kes

Ditetapkan dengan Surat Keputusan
Dekan Fakultas Kedokteran Universitas Airlangga
Tentang Panitia Penguji Disertasi
Nomor : 88/ UN3.1.1/HK/2021
Tanggal : 16 Pebruari 2022

SUMMARY

THE DIFFERENCES AND MECHANISMS OF GOOD AND POOR CHEMORADIATION RESPONSES OF NASOPHARYNGEAL CARCINOMA THROUGH ANALYSIS OF HIF-1α, CD133, SOD, HSP70, AND APOPTOSIS IN TISSUE BIOPSIES

Nasopharyngeal carcinoma (NPC) is a common malignant tumor found in Southeast Asia, including Indonesia. Non keratinizing squamous cell carcinoma undifferentiated sub-type, however, is more common encountered in Dr. Soetomo Hospital. 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 in viable tumor cells after chemoradiation. Unfortunately, the molecular pathway that causes differences in the chemoradiation response in NPC is not yet clearly understood.

Oxygen deprivation is common in malignant solid tumors. Under hypoxia, hypoxia-inducible factors 1α (HIF-1α), a DNA binding transcription factors are undegraded and act as an activator to 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 that plays a role in reducing reactive oxygen species, and heat shock protein 70 (HSP70), a molecular chaperone that plays a role in protein folding, both of which act as cytoprotector against various types of injury, including radiation and chemotherapy agents. All of these biomarkers are thought to be able to inhibit apoptosis, leading cell to survive and affect the chemoradiation response.

The aim of the study is to elucidate the differences and mechanism of good and poor chemoradiation responses of NPC by studying the differences in the expressions of HIF-1α, CD133, SOD, HSP70, and cell survival before and after chemoradiation.

This research is an analytic observational study conducted on formalin-fixed paraffin embedded archives of tissue biopsy of NPC patients with an initial diagnosis of non-keratinizing squamous cell carcinoma undifferentiated sub-type in the Anatomical Pathology Unit of Dr. Soetomo General Hospital period January 2014 – December 2019. Samples are 34 pairs of 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-1α, CD133, SOD, and HSP70, while cell survivals were evaluated by TUNEL assay. The data were tested by comparative bivariate analysis to determine the difference between good and poor responses, before and after chemoradiation. Analysis using t-test 2-sample was chosen if the data distribution was normal and homogeneous. If the data had non normal distribution, analysis using the Mann Whitney Test was chosen. The results of delta before and after chemoradiation data were carried out by path analysis using Smart PLS3.

The result of this study showed that there were significant differences in expressions of HIF-1α 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). The majority of solid tumors are hypoxic. Tumor cells fight hypoxic conditions by delegating to HIF1α to regulate various functions to adapt to hypoxic conditions. HIF 1 is a transcription factor that induces a series of genes. Cyclin D1, p21 and p27 are the target genes of HIF-1α that can modify the cell cycle of tumor growth. HIF-1α is able to cause radioresistance through various ways including through glucose metabolism pathways, the epithelial-mesenchymal transitional pathway, as well as cell cycle control and autophagy. HIF-1α is able to regulate the increase in anti-apoptotic proteins such as Bcl-XL and Bcl-2, and decrease proteins that play a role in apoptosis such as Bak and Bax, thereby weakening the cytotoxic effect of chemotherapy. HIF-1α was able to upregulate the increase in anti-apoptotic proteins such as Bcl-XL and Bcl-2, and block proteins that play a role in apoptosis such as Bak and Bax, leading to a weakened cytotoxic effect of chemotherapy. HIF-1α accumulation is able to increase proangiogenic genes including VEGF, resulting in imperfect blood vessels. This causes disruption of drug flow thereby reducing the effect of chemotherapy.

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). The literature states that CD133 is correlated with the level of differentiation, stage, distant metastases, disease free interval and poor overall survival in malignancies of various organs. This is because CD133 can activate Wnt/β catenin which then interacts with transcription factors thereby accelerating the growth of cancer cells. CD133 is capable of promoting the PI3K-Akt signaling pathway, leading to promote tumor cell growth and inhibit apoptosis. Radiation exposure can also increase tumor cell stemness, through radiation causing gene instability and promoting the EMT pathway

There were significant differences in expression of SOD before chemoradiation in good and poor response (p= 0,002). The results of this study showed that the SOD before chemoradiation in NPC good response was higher than in NPC poor response. This is because the tumor is hypoxic, so it activates HIF-1α which can reduce c-Myc levels, thereby suppressing mitochondrial biogenesis and respiration. This prevents the production of ROS, resulting in low SOD as well. In this studi show that there was significant differences in expression of SOD after chemoradiation in good and poor response (p= 0,001) and delta before and after chemoradiation in good and poor response (p= 0,001). This indicates that chemoradiation plays a role in causing tumor cell death. However, tumors with high SOD expression were able to catalyze the dismutase of superoxide anion free radicals into oxygen and hydrogen peroxidase, thereby preventing tumor cell death.

There were significant differences in expression of HSP70 before chemoradiation in good and poor response (p= 0,044), after chemoradiation ingood and poor response (p= 0,001), delta before and after chemoradiation in good and poor response (p= 0,001). HSP70, a chaperone molecule that plays a

role in regulating protein folding, is able to prevent protein degradation and ensure the achievement of functional stabilization of various proteins in cells under stress conditions, for example in cancer growth. HSP70 acts as an anti-apoptotic protein in both the intrinsic and extrinsic pathways.

The result of this study showed that there was no significant difference of apoptosis which was evaluated from cell tumor survival before chemoradiation in good and poor response (p= 0,088). This was because the two groups had not received radiation induction or chemotherapy. But 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). This shows that chemoradiation is beneficial in causing tumor cell death, resulting in a good NPC response. Whereas in NPC poor response, a progressive tumor, is often containing tumor cells with p53 mutations, thus they lose their function as tumor suppressor genes. This leads to tumor cell survival, inhibits apoptosis and causes a poor response.

The result of path analysis showed that there was a significant effect of HIF-1α on CD133 (p= 0,001), but there was no significant effect of CD133 on apoptosis (p= 0,972). This is because CD133 modulation is influenced by hypoxia and mitochondrial dysfunction. Hypoxia leads to activation of the CD133 promoter by HIF-1α. CD133 activity depends on the activation of its promoters, namely OCT4, SOX2 Notch1, in addition to HIF-α-1. CD133 activation is also affected by phosphorylation of tyrosine 828 in the c-terminal domain. There were significant effects of SOD and HSP70 on cell survival (p= 0,047 and p= 0,001), and there was a significant effect of cell survival on chemoradiation responses (p= 0,001).

In this study, it was proven that there were significant differences in expressions among HIF-1α, CD133, SOD, HSP70, and cell survival delta before and after chemoradiation in good and poor responses of NPC. The mechanisms of chemoradiation responses in NPC are determined by SOD, HSP70, and cell survival, which in poor responses showed increases in expressions of SOD, HSP70, and cell survival.

ABSTRACT

THE DIFFERENCES AND MECHANISMS OF GOOD AND POOR CHEMORADIATION RESPONSES OF NASOPHARYNGEAL CARCINOMA THROUGH ANALYSIS OF HIF-1α, CD133, SOD, HSP70, AND APOPTOSIS IN TISSUE BIOPSIES

Background: Nasopharyngeal carcinoma (NPC) is commonly sensitive to chemoradiation, but it has a significant poor response. In addition, the molecular pathway in the chemoradiation responses in NPC is not yet clearly understood.

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

Methods: This study was conducted on FFPE tissue biopsy of non-keratinizing squamous cell carcinoma undifferentiated sub-type of NPC patients in Dr. Soetomo Hospital period 2014 – 2019. Samples are 34 pairs of pre and post-chemoradiation, composed of 18 pairs of good and 16 pairs of poor responses. All patients received 70 Gy external radiation and combined platinum-based chemotherapy. Immunohistochemistry was performed to evaluate HIF-1α, CD133, SOD and HSP70, while cell survivals were evaluated by TUNEL assay. The data were tested by comparative bivariate and path analysis.

Result: There were significant differences in the delta expression of HIF-1α, CD133, SOD, HSP70, and cell survival before and after chemotherapy in good and poor responses, each of which has a p-value of 0,001. There was a significant effect of HIF-1α on CD133 (p-value 0,001), but no of CD133 on cell survival (p-value 0,972). There were significant effects of SOD and HSP70 on cell survival (p-value of 0,047 and 0,001), and of cell survival on chemoradiation response (p-value of 0,001).

Conclusion: There were significant differences in the delta expressions among HIF-1α, CD133, SOD, HSP70, and cell survival in good and poor chemoradiation responses of NPC. The mechanisms of chemoradiation responses in NPC are determined by SOD, HSP70, and cell survival, in which poor response showed increased expressions of SOD, HSP70, and cell survival.

Keyword: Nasopharyngeal carcinoma, chemoradiation, and chemoradiation response.