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ABSTRACT

COGNITIVE OUTPUT OF NASOPHARYNGEAL CARCINOMA PATIENTS AFTER CHEMORADIATION THERAPY AT DR.SARDJITO GENERAL HOSPITAL YOGYAKARTA

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Background: Cognition is defined as all form of knowing and awareness. The decline of this function is called cognitive impairment, in which there would be a present of difficulty in thinking. Brain injury is known to be the risk factor of the condition and the cause of it including irradiation and toxic agents which might come from cancer therapy. NPC is one of the most prevalent cancer in Indonesia and it combines both chemo and radiation therapy in the management of the disease. Hence, the risk of developing cognitive impairment in patients increases. As cognition play great role in daily function, the presence cognitive impairment become an important issue to be aware of.

Objective: To determine the presence of cognitive impairment in NPC patients post chemoradiation therapy

Method: This study is an analytical observational study that uses cross-sectional study design. Data collection is done by interviewing NPC patients in Department of ENT dr.Sardjito General Hospital Yogyakarta. The cognitive result is determined based on the existing cut-off points.

Result: Among 21 NPC patients, 18 of them show Mild Cognitive Impairment, 2 of them show Normal Function, and 1 person show Moderate Cognitive Impairment. Meanwhile in healthy group, most of them show Normal Function (n=18) and the rest have Mild Cognitive Impairment (n=2). The analyzed result using Mann-Whitney test show p value of <0,001.

Conclusion: There is a significant association between the presence of cognitive output and chemoradiation therapy

Keyword: NPC, Chemoradiation, Cognitive Function, Cognitive Impairment

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CHAPTER I

INTRODUCTION

I.1 BACKGROUND

Cognition, the higher function of the brain, defined as modulated mental processes that will produce representational knowledge and mechanism in between stimulus and response, involved in gaining insight and comprehension. The cognitive processes are very complex. Each of the domains has its own mechanism and plays a role in critical functions. Therefore, cognitive function is an important aspect in managing daily activities and has an impact that influences one's quality of life. Although it is very complex, it is possible for cognitive processes to be imperfect as it could undergo a pitfall that causes a decline. This decline is defined as cognitive impairment. Cognitive impairment is a state where a person has trouble in remembering, learning, concentrating, and decision making that affect their daily lives.

In the United States, more than 16 million people live with cognitive impairment. Meanwhile, according to a previous study done in *Universitas Andalas*, a specific prevalence of cognitive impairment in Indonesia has not been available or published yet. Data available provided by *Kementrian Kesehatan* is related to the estimated number of people with dementia and Alzheimer that rises each year. According to WHO, there's an increase in incidence number of cognitive impairment and dementia globally. As age is known to be the greatest risk factor of cognitive decline, it is important to acknowledge a projection by WHO that

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indicates by the year 2050, population older than 60 years old will account for 22% of the world's population, thus the incidence number of cognitive impairment could also increase. Another risk factor of cognitive impairment including family history, brain injury, and the exposure of toxins. Exposure of toxins and brain injury might happen due to the chemotherapy and radiotherapy respectively as the treatment of cancers.

One of the cancers that is known to use chemotherapy along with radiotherapy as its treatment is the nasopharyngeal cancer. Nasopharyngeal carcinoma is a cancer that arises from epithelial cells lining the nasopharynx. It is the most common epithelial cancer in adults that is known to have association with Epstein-Barr virus. Other etiologies of this disease also include food consumption containing volatile carcinogenic nitrosamines (i.e : salted fish), and genetic susceptibility. Due to the genetic susceptibility factor, the incidence case of this tumor is high in several areas such as Southern China and Southeast Asia. In Indonesia, NPC has become one of the most frequent cancers, ranked as the fourth most common tumor after cervical cancer, breast cancer, and skin cancer, and the most common malignancy in the head and neck. According to Global Burden of Cancer 2020 there are 19.943 incidence cases of NPC in total and 13.399 deaths caused by NPC in Indonesia.

The staging of Nasopharyngeal Carcinoma is using tumor, node, metastasis (TNM) classification of the American Joint Committee on Cancer. There are 8 stages of NPC which are, stage 0, stage I, stage IIa, stage IIb, stage III, stage IVa, stage IVb, and stage IVc. The staging of NPC is used in determining the

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management. According to WHO, the standard care for the treatment of stage I NPC is radiotherapy, and for non-metastatic stage II-IV NPC is concurrent chemo-radiotherapy with or without adjuvant chemotherapy. As mentioned above, one of the adverse effects of both chemo-radiation therapy would affect the brain and causes cognitive decline. It is defined as chemotherapy induced cognitive impairment (CICI/chemo brain/chemo fog) and radiation induced cognitive impairment that works by disrupting the neurogenesis activity of the brain. As cognition would affect overall daily life, the presence of cognitive pitfalls would make a wide-range impact on the quality of life, thus cognitive impairment becomes an important issue to be aware of.

I.2 PROBLEM FORMULATION

The importance of cognition in human daily life makes cognitive impairment an issue to be aware of. Several studies have proven that cognitive decline is present due to the intervention of cancer therapies. However, there is still a lack of availability in research related to cognitive impairment induced by chemoradiation therapy that is done to nasopharyngeal carcinoma patients, especially those in Indonesia. Meanwhile, the cognitive performance of a person is known to be affected by environmental factors such as place of residence and socioeconomic status, thus it is important to conduct this study in Indonesia to determine the presence of cognitive impairment in post-chemoradiotherapy nasopharyngeal carcinoma patients.

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I.3 STUDY OBJECTIVES

1.3.1 General Objective

To determine the presence of cognitive impairment in nasopharyngeal carcinoma patients post-chemoradiation therapy

1.3.2 Specific Objectives

To assess cognitive functions of non-cancer healthy people

To assess cognitive functions of NPC patients post-chemoradiation therapy

I.4 STUDY ORIGINALITY

There are several research related to the chemotherapy and radiation therapy induced cognitive impairment in nasopharyngeal carcinoma patients as listed below :

a. Long-term Disease-Specific and Cognitive Quality of Life after Intensity-Modulated Radiation Therapy: A Cross-Sectional Survey of Nasopharyngeal Carcinoma Survivors (Kiang *et al.*,2016)

Method : Cross sectional study design is conducted to surviving patients diagnosed and treated for NPC with curative-intent IMRT, with or without chemotherapy. QoL was measured using FACT-NP and FACT-Cog.

Result : 44 Patients completed all the questionnaires. Patients were categorized into 4 cohorts based on the duration since IMRT. All QoL measures were low during the initial recovery period (<2.5 years) and higher by 6 years post IMRT. At >10 years, lower scores were observed in the cognitive QoL.

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Similarity in the study : Both of the studies use cross sectional study design. The inclusion and exclusion criteria, such as including NPC patients treated with radiotherapy accompanied by chemotherapy and excluding people with known recurrent disease is also used in the proposed research, respectively.

Differences in the study : The type of study is differ from the proposed research. The dependent variables in this study is not only cognitive impairment, but also lower quality of life. The instruments used in this study are FACT-NP and FACT-Cog, meanwhile the proposed study uses MoCA.

b. **Effects of Intensity-Modulated Radiotherapy and Chemoradiotherapy on Attention In Patients with Nasopharyngeal Cancer (Wei *et al.*,2017)**

Method : Prospective study is used in evaluating attention performance in NPC patients before and within one week after completion of cisplatin concurrent chemoradiotherapy or IMRT alone. This study assesses attention using integrated visual and auditory continuous performance test (IVA/CPT).

Result : Attention declines observed in NPC patients as follows: IMRT alone had no negative short-term effects on attention in these patients, and auditory stamina improved within one week. Meanwhile, CCRT would decrease the response control in NPC patients and have poorer objective attention than those with RT alone.

Similarity in the study : This study assesses cognitive performance (attention) of NPC patients treated with chemoradiation therapy and comprises of two population similar with the proposed research.

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Differences in the study : The type of the study is differ from the proposed research. The study design used in this study is prospective study design, meanwhile the proposed study uses cross sectional study design. The domain of cognition that is evaluated in this study is only attention performance, meanwhile the proposed research would examine more cognitive domains that are covered by Montreal Cognitive Assessment as an instrument. The instrument used in this study is integrated visual and auditory continuous performance test (IVA/CPT).

In conclusion, there are differences between the proposed study and both of the previous studies, indicating the proposed study have never been done before. The instrument to assess cognitive function used in the proposed study differs from both of the studies. On top of that, study that specifies cognitive impairment as an output of chemoradiation therapy has not been published in and by an Indonesian author respectively, whereas cognitive performance of one's is affected by many factors including place of residence and socioeconomic status, thus it is important to conduct this study in Indonesia.

I.5 STUDY BENEFIT

1.5.1 Benefit For Researcher

This study is aimed to broaden the knowledge of the researcher and the result of this study is expected to provide additional insight related with cognitive impairment induced by chemoradiotherapy.

1.5.2 Benefit for Others

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The result of this study may contribute to the previous research regarding the cognitive output of chemoradiation therapy and may provide additional evidence on the cognitive impairment induced by chemoradiotherapy of nasopharyngeal carcinoma patients in Indonesia.

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CHAPTER II

LITERATURE REVIEW

II.1 LITERATURE REVIEW

II.1.1 COGNITIVE FUNCTIONS

According to American Psychological Association, cognition is defined as all forms of knowing and awareness, such as perceiving, conceiving, remembering, reasoning, judging, imagining, and problem solving. The performance of cognition is often conceptualized as domains or also called cognitive functions. These domains are in hierarchical order from the basic sensory and perceptual process to more complex cognitive control and related to each other (are not independent). The domains could be classified by the general process involved including memory, attention, language or executive functioning, or based on the region in the brain, for example functions that originate from frontal lobe, temporal lobe, hippocampus, or other structure. Each of the domains have subdomains that have a role in the assessment of cognitive function. There are 6 domains of cognition.

A. Sensation and Perception

   The ability to detect a stimulus is called sensation, but the ability of a person to give meaning on the stimuli is called perception. Perception processes and integrates the sensory information, thus it is an ability to recognize an object, a sound, and also for the intactness of the perceptual field.

B. Motor Skills and Construction

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Motor skills is the ability to produce a movement, it includes fine motor abilities and other global skills such as balance. Meanwhile, construction skill is the ability to follow specific orders, for example to copy the drawings of common objects.

C. Attention and Concentration

Attention has two major subdomains which are the selective and sustained attention that include concentration. Selective attention is a process of the brain attending relevant information and ignoring the irrelevant information. Meanwhile, sustained attention that has been referred to as vigilance or the ability to focus on specific activity over a long period of time.

D. Memory

Memory is the most complex function of the human brain. It has several subdomains such as working memory, which is the ability to retain information for adaptive purposes, procedural memory or a memory of motor skills, semantic or long-term memory, and prospective memory, which is described as the ability to remember information to perform tasks in the future.

E. Executive Functioning

Executive Functioning is defined as cognitive processes that use cognitive abilities as resources to effectively and efficiently solve problems and future planning. It is commonly referred to as reasoning and problem solving.

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F. Language Skills

Language skills is the ability to understand language by having receptive and expressive abilities including the access to semantic memory to identify objects and respond to verbal instruction (Harvey, 2019).

II.1.2 BASIC CONCEPTS OF COGNITION

For over centuries it is known that the human brain plays a great role in cognition by modulating and processing signals. Those works are done by neurons that form the white and gray matter of the human brain. These neurons play a role in receiving information, processing, and producing firing signals to perform a specific act based on the specific activated area. Different areas of the human brain have different functions and specialization, for example, if the Broca area is activated, one individual would have the ability of motor language. Human brain also possesses plasticity, which is an adaptation process as a result of an experience. Plasticity is important in forming memory and learning processes that are parts of human cognition. One of the scientific fields that elucidate the cognitive processes is cognitive neuroscience. It is the combination of cognitive science and psychology that aims to explain the cognitive processes based on the brain based mechanisms that commonly use imaging techniques. (Ward, 2015; Mather, 2016)

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II.1.3 COGNITIVE IMPAIRMENT

Cognitive impairment is a state where there's an occurrence of cognitive decline that causes one to have difficulty in remembering, learning, and making decisions that affect their daily lives. Cognitive impairment ranges from mild to severe. In mild cognitive impairment, an individual will still be able to perform their daily activities, meanwhile in severe one, they will lose sense of things that are important and might lose the ability to talk and walk. The cognitive impairment could result in cognitive disorders such as dementia, amnesia, and delirium. Cognitive impairment holds a variety of risk factors including age, which is known to be the greatest risk factor, family history, education levels, brain injury, exposure of toxins, and lifestyle. There are common signs of cognitive impairment including memory loss, frequently repeating questions, failure to recognize familiar people or places, trouble in taking decisions, vision problems, and difficulty carrying out tasks. In the United States, more than 16 million people live with cognitive impairment (Centers For Disease Control and Prevention, 2011). Meanwhile, according to a previous study done in *Universitas Andalas*, a specific prevalence of cognitive impairment in Indonesia has not been available or published yet. Data available provided by *Kementrian Kesehatan* is related to the estimated number of people with cognitive disorders, such as dementia and Alzheimer's that rises each year (Kementerian Kesehatan Republik Indonesia, 2016). According to WHO, there's an increase in incidence number of cognitive impairment and dementia globally. As age is known to be the greatest risk factor of cognitive decline, it is important to acknowledge a projection by WHO that indicates by the year 2050 the

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population older than 60 years old will account for 22% of the world's population, thus the incidence number of cognitive impairment could also increase (World Health Organization, 2018). Related to brain injury and exposure to toxins as risk factors, specific groups of people such as cancer patients treated with chemoradiation therapy become one of the susceptible populations. Cancer patients that are treated with both chemoradiation therapy is prone to the occurrence of cognitive impairment, such as trouble in forming memory, attention decline, executive function, and processing speed due to the adverse effects of the treatment (Hardy *et al.,*2018)

II.1.4 ASSESSMENT OF COGNITIVE FUNCTIONS

Cognitive assessment is a multiple test essential to see the cognitive performance or to determine whether or not cognitive impairment is present. Many tools are established and carefully constructed to evaluate each domain of cognition. The variation of the tools range from the one that only assesses a single specific domain to multiple domains. Most clinicians are known to be prefer using mental status screening tools to assess the functions as it is short, efficient, and well-researched modalities. They often combined it with well conducted history taking, physical examination, labs, and imaging to establish a diagnosis. If the screening tool is inconclusive, a complete neuropsychological evaluation, which is noninvasive and involves a battery of assessment performed by trained professionals, could be carried out.